Non-communicable diseases in people living with HIV in rural Africa: tackling the double burden

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Herry Mapesi

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Prof. Dr. Daniel Henry Paris, first supervisor

Prof. Dr. Manuel Battegay, second supervisor

Prof. Dr. Robert Peck, external expert

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Prof. Dr. Primo Leo Schär

Dekan der Medizinischen Fakultät

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'I can do all this through him who gives me strength, (Philippians 4:13)'

Summary

In 2019, there were around 38 million people living with HIV (PLHIV) worldwide. For the past decade, new HIV infections have been reduced by 23% and AIDS-related deaths have been reduced by 39% worldwide. All these achievements were possible mainly due to discovery and global rollout of antiretroviral therapies (ART), reduction in stigma and a global effort for funding to tackle the HIV epidemic. Sub-Saharan Africa is the most affected WHO region with around 20.7 million (54%) PLHIV. Since 2010, in the region, new HIV infections have been reduced by 38% and AIDS-related deaths have been reduced by 49%. This accomplishment was possible mostly due to extensive vertical HIV testing and treatment programs.

Each year, more than 41 million people die from non-communicable diseases (NCDs) worldwide. More than 15 millions of these deaths are premature deaths (people aged between 30-69 years) and 85% occur in lower- and middle-income countries. The most common NCDs that cause deaths are cardiovascular diseases, cancers, respiratory diseases, and diabetes mellitus. The risk factors for most NCDs can be grouped as behaviour or metabolic risk factors. The most common modifiable behaviour risk factors are harmful tobacco use, excessive alcohol consumption, eating unhealthy diet, physical inactivity, overweight and obesity. Other metabolic risk factors are raised blood cholesterol, and raised fasting blood glucose.

In sub-Saharan Africa, with the rapid demographic changes, an epidemiological transition from infectious diseases to non-communicable and chronic diseases can be observed. By 2030, mortality due to NCD is projected to surpass the mortality from combined infectious, neonatal, maternal and nutritional diseases. Therefore, there is an urgent need for innovative ways to tackle this double burden of diseases on the African continent.

The overall goal of this doctoral thesis was to summarise the burden of non-communicable diseases in sub-Saharan Africa. Additionally, data from rural Tanzania was used to estimate the burden of renal impairment, excessive weight gain and different comorbidities among HIV-infected patients receiving antiretroviral treatment.

The first study described the burden of the most relevant etiologies for NCDs in sub-Saharan Africa, which are arterial hypertension, heart diseases, diabetes mellitus and chronic kidney diseases. The review emphasized the importance of using a multifactorial approach, with emphasis on strengthening the existing health care systems to facilitate early diagnosis, treatment and management of NCDs. Furthermore, the review highlighted an urgent need for robust high-

quality evidence directed at informing national stakeholders on the key drivers of NCDs across Africa.

The second study assessed the prevalence, incidence and predictors of renal impairment among PLHIV receiving ritonavir-boosted protease inhibitors (bPI). Renal impairment was present in 7.6% of participants at the switch from first-line to bPI. Among participants with normal kidney function at the time of switch, 7.4% developed renal impairment after a median time of 3.5 years. The study reported risk associated with renal impairment at switch to be older age, low body mass index (BMI) <18.5 kg/m^2 and arterial hypertension. Hence, this study highlighted the high burden of renal impairment among patients who are switched from first-line to bPI in rural sub-Saharan Africa and stress the importance of clinical monitoring of renal function for patients using ART.

The third study evaluated the weight change among newly diagnosed PLHIV starting treatment with either dolutegravir-based or efavirenz-based regimen in rural Tanzania. Additionally, it assessed risk factors associated with increased body weight ≥10% after 12 months of treatment. Initiating a dolutegravir-based ART regimen was associated with more weight gain compared to efavirenz-based regimens during the first 12 months of treatment, confirming observations from industrialized settings. Weight gain of ≥10% was associated with use of dolutegravir, level of immunosuppression, BMI at ART initiation and being female.

The fourth article is a letter to the editor that discussed the rollout of dolutegravir-based antiretroviral therapy in sub-Saharan Africa and its public health implications. The letter highlighted the lack of studies to evaluate long-term side effects of dolutegravir-based regimens among PLHIV living in sub-Saharan Africa. At the time, it was vital since there were studies that demonstrated excessive weight in PLHIV either starting treatment with dolutegravir-based regimens or those who were switched from other regimens to dolutegravir-based regimen. Therefore, this letter set the basis for the third study to evaluate weight gain in patients starting ART in rural Tanzania.

The fifth study investigated the age-related causes of morbidity and mortality of people living with HIV in rural Tanzania. Prevalence and incidence of different comorbidities in patients starting antiretroviral treatment was evaluated. The results showed that anaemia, arterial hypertension and undernutrition are the most relevant comorbidities with different age-associated frequencies and impact on death/LTFU in this population.

The sixth study is a study protocol for an open-label, three-arm, parallel randomized controlled trial conducted at two rural hospitals in Lesotho and Tanzania. The clinical trial compares the

efficacy and cost-effectiveness of three antihypertensive treatment strategies among HIV-positive and negative participants. The primary endpoint is the proportion of participants reaching the target blood pressure at 12 weeks. The results from this trial will help to identify the most effective and cost-effective treatment strategies for uncomplicated arterial hypertension among people of African descent living in rural sub-Saharan Africa.

The seventh article is an editorial that discussed the challenges for HIV-infected adolescents during transition from paediatric to adult HIV clinics in Africa. The editorial addressed the challenge of high HIV prevalence and incidence among adolescents and young adults in sub-Saharan Africa. The editorial stressed an urgent need to ensure that the transition policy from paediatric to adult-centred clinics is part of health care management for HIV-infected adolescents and young adults in Africa.

In conclusion, the studies included in this thesis highlight the double burden of infectious diseases and non-communicable diseases in sub-Saharan Africa. The lessons learnt will help to inform future guidelines on the importance of clinical monitoring of people living with HIV once they start antiretroviral treatment. The results highlighted the urgent need to improve pharmacovigilance systems in the region to monitor side effects of new drugs. Finally, the results from this thesis stress the importance that future research from local context to tackle the double burden of diseases in the region.

Muhtasari

Mnamo mwaka wa 2019, kulikuwa na takribani watu milioni 38 wanaoishi na Virusi vya Ukimwi (VVU) ulimwenguni. Kwa muongo uliopita, maambukizi mapya ya VVU yamepungua kwa 23% na vifo vinavyohusiana na UKIMWI vimepungua kwa 39% duniani kote. Mafanikio haya yote yaliwezekana hasa kutokana na ugunduzi na usambazaji wa kimataifa wa tiba za kurefusha maisha, kupunguza unyanyapaa na jitihada za kimataifa za ufadhili wa kukabiliana na janga la VVU. Kusini mwa Jangwa la Sahara ndiyo kanda iliyoathiŕika zaidi ikiwa na karibu watu milioni 20.7 (54%) wanaoishi na VVU. Tangu mwaka 2010, katika ukanda huo, maambukizi mapya ya VVU yamepungua kwa 38% na vifo vinavyotokana na UKIMWI vimepungua kwa 49%. Mafanikio haya yaliwezekana zaidi kutokana na kuongezeka kwa shughuli za upimaji pamoja na kuongezeka shughuli za matibabu kwa atu wanaoishi na VVU.

Kila mwaka, zaidi ya watu milioni 41 hufa kutokana na magonjwa yasiyo ya kuambukiza duniani kote. Zaidi ya milioni 15 ya vifo hivi ni vya mapema (watu wenye umri kati ya miaka 30-69) na 85% hutokea katika nchi za kipato cha chini na cha kati. Magonjwa yasiyo ambukiza ambayo husababisha vifo ni pamoja na magonjwa ya moyo na mishipa ya damu, saratani, magonjwa ya kupumua, na kisukari. Tabia hatarishi ambazo zinaweza zikasababisha magonjwa yasiyo ambukizwa ni kama matumizi mabaya ya tumbaku, unywaji pombe kupita kiasi, ulaji usiofaa, kutofanya mazoezi ya mwili, uzito na kunenepa kupita kiasi. Sababu zingine za hatari ni pamoja na kuongezeka kwa cholesterol na sukari ya damu.

Kusini mwa Jangwa la Sahara, pamoja na mabadiliko ya haraka ya idadi ya watu, kuna mabadiliko ya epidemiolojia kutoka magonjwa ya kuambukiza kwenda kwa magonjwa yasiyo ya kuambukiza. Ifikapo mwaka wa 2030, inakadiliwa kwamba vifo vinavyotokana na mangonjwa yasiyoambukizwa vitakuwa vimezidi vifo vinavyotokana na magonjwa ya kuambukiza, magonjwa ya watoto wachanga, pamoja na vya uzazi na lishe duni. Kwa hiyo, kuna hitaji la dharura la njia za kibunifu za kukabiliana na mzigo huu wa magonjwa yanaoambukiza na yasiyoambulizwa katika bara la Afrika.

Lengo la jumla la tafiti katika shahada hii ya uzamifu lilikuwa ni kuangalia ukubwa wa mzigo wa magonjwa yasiyo ya kuambukiza kusini mwa jangwa la Sahara. Zaidi ya hayo, takwimu kutoka Tanzania zilitumika kukadiria magonjwa kuharibika kwa figo, kuongezeka uzito kupita kiasi na magonjwa mbalimbali miongoni mwa wagonjwa walioambukizwa VVU wanaopokea matibabu ya kurefusha maisha.

Utafiti wa kwanza ulielezea mzigo wa magonjwa yasiyoambukizwa Kusini mwa Jangwa la Sahara, ambayo ni shinikizo kubwa la damu, magonjwa ya moyo, kisukari na magonjwa ya figo. Matokeo ya utafiti huu yalisisitiza umuhimu wa kutumia mbinu mbalimbali, kwa kutilia mkazo katika kuimarisha mifumo iliyopo ya huduma za afya ili kuwezesha utambuzi wa mapema, matibabu na usimamizi wa magonjwa yasiyoambukiza. Majibu ya utafiti huo yalisisitiza umuhimu wa kufanyika tafiti ambazo zitaweza kuwapa taarifa washikadau wa afya jinsi ya kupambana na magonjwa yasiyoambukizwa barani Afrika.

Utafiti wa pili ulitathmini kiwango cha kuharibika kwa figo miongoni mwa watu wanaoishi na VVU na wanapokea dawa za daraja la pili za kurefusha maisha. Kutokufanya kazi vizuri kwa figo kulikuwepo katika 7.6% ya washiriki katika muda kubadili kutoka dawa za daraja la kwanza kwenda daraja la pili. Miongoni mwa washiriki waliokuwa na figo nzima wakati wa kubadili dawa, 7.4% walipata matatizo ya figo kutofanya kazi vizuri baada ya muda wa wastani wa miaka 3.5. Utafiti huo uliripoti uhusiano kati ya matatizo ya figo na umri mkubwa, uzito mkubwa, na shinikizo kubwa la damu. Kwa hivyo, utafiti huu ulionyesha kuna tatizo kubwa la kupungua kwa ufanisi wa kufanya kazi kwa figo kwa wagonjwa ambao hubadilishwa kutoka daraja la kwanza kwenda daraja la pili kusini mwa Jangwa la Sahara. Pia, majibu ya utafiti huu yanasisitiza umuhimu wa ufuatiliaji wa kimatibabu wa utendaji kazi wa figo kwa wagonjwa wanaotumia dawa za kufubaza VVU.

Utafiti wa tatu ulitathmini mabadiliko ya uzito miongoni mwa watu wanaoishi na VVU wanaoanza matibabu kwa kutumia dawa za dolutegravir au efavirenz nchini Tanzania. Zaidi ya hayo, utafiti huu ulichunguza mambo ya hatari yanayohusiana na kuongezeka kwa uzito wa mwili ≥10% baada ya miezi 12 ya matibabu ya VVU. Majibu ya utafiti huu yanaonyesha washiriki walioanza dawa na dawa zenye dolutegravir walikuwa na ongezeko la uzito zaidi ikilinganishwa na washiriki walioanza dawa zenye efavirenz wakati wa miezi 12 ya kwanza ya matibabu, kuthibitisha uchunguzi kutoka katika nchi zilizoendelea. Kuongezeka kwa uzito wa ≥10% kulihusishwa na matumizi ya dawa zenye dolutegravir, kuanza dawa na na uzito wa kawaida pamoja na kuwa mwanamke.

Makala ya nne ni barua kwa mhariri ambayo ilijadili kuanzishwa kwa tiba ya kurefusha maisha zenye dawa ya dolutegravir katika eneo la kusini mwa Jangwa la Sahara na athari zake kwa afya ya umma. Barua hiyo iliangazia ukosefu wa tafiti za kutathmini madhara ya muda mrefu ya dawa zenye dolutegravir miongoni watu wanaoiushi na VVU wanaoishi kusini mwa Jangwa la Sahara. Wakati huo, kulikuwa na tafiti ambazo zilikuwa zimeshaonyesha uzito wa kupindukia kwa watu wanaoishi na VVU wanaoanza matibabu kwa kutumia dawa zenye dolutegravir au wale ambao walibadilishwa kutoka kwa dawa zingine kwenda kwenye dawa zenye dolutegravir. Kwa hiyo,

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Acronyms and abbreviations

3TC	Lamivudine
ABC	Abacavir
ACE	Angiotensin-converting enzyme
AE	Adverse Events
aHT	Arterial hypertension
ART	Antiretroviral treatment
ATV/r	Atazanavir/ritonavir
AZT	Zidovudine
BMI	Body Mass Index
BP	Blood pressure
AIDS	Acquired Immunodeficiency Syndrome
ARB	Angiotensin II receptor blockers
CCB	Calcium channel blockers
CDCI	Chronic Diseases Clinic of Ifakara
CI	Confidence intervals
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CoArtHA	Control Arterial Hypertension in sub-Saharan Africa
CTCAE	Common terminology criteria for adverse events
CVDs	Cardiovascular diseases
DALYs	Disability adjusted life-years
DASH	Dietary Approaches to Stop Hypertension
DM	Diabetes Mellitus
DTG	Dolutegravir
ECG	Electrocardiogram
eCRF	Electronic case report forms
eGFR	Estimated glomerular filtration rate
ESC	European Society of Cardiology
ESH	European Society of Hypertension
HIV	Human Immunodeficiency Virus
HIVAN	HIV-associated nephropathy
IDMC	Independent data monitoring committee
INSTI	Integrase-strand-transfer inhibitors

IHI	Ifakara Health Institute
IHI-IRB	Ifakara Health Institute – Institutional Review Board
ITT	Intention-to-treat
JAMA	Journal of the American Medical Association
KDOQI	National Kidney Foundation's Kidney Disease Outcomes Quality Initiative
KIULARCO	Kilombero and Ulanga Antiretroviral Cohort
LPV/r	Lopinavir/ritonavir
NCDs	Non-communicable diseases
NVP	Nevirapine
NNRTIs	Non-Nucleoside Reverse Transcriptase Inhibitors
NIMR	National Institute for Medical Research
PEN	Package of Essential Non-communicable
PLHIV	People Living with HIV
RAAS	Renin angiotensin aldosterone system
SAE	Serious adverse Event
SBP	Systolic blood pressure
Swiss TPH	Swiss Tropical and Public Health Institute
SSA	Sub-Saharan Africa
TDF	Tenofovir Disoproxil Fumarate
TMDA	Tanzania Medicines and Medical Devices Authority
T2DM	Type 2 diabetes mellitus
TZD	Thiazide diuretic
WHO	World Health Organization

Introduction

Burden of HIV/AIDS

The Centre for Diseases Control reported the first five cases with AIDS defining illness (pneumocystis pneumonia) among young active homosexuals in 1981[3]. Since then, the disease has been reported across all regions of the world, and by the end of 2019 approximately 32.7 million people died from AIDS-related illnesses since the start of the epidemic [4]. In 2019, there were 38 million people living with HIV (PLHIV) worldwide [5]. Since 2010, new HIV infections have been reduced by 23% and AIDS-related deaths have need reduced by 39% **(Figure 1)** [6]. All these achievements were possible mainly due to discovery and global rollout of antiretroviral (ART), reduced stigma and increased global funding to tackle the HIV epidemic [5,6].

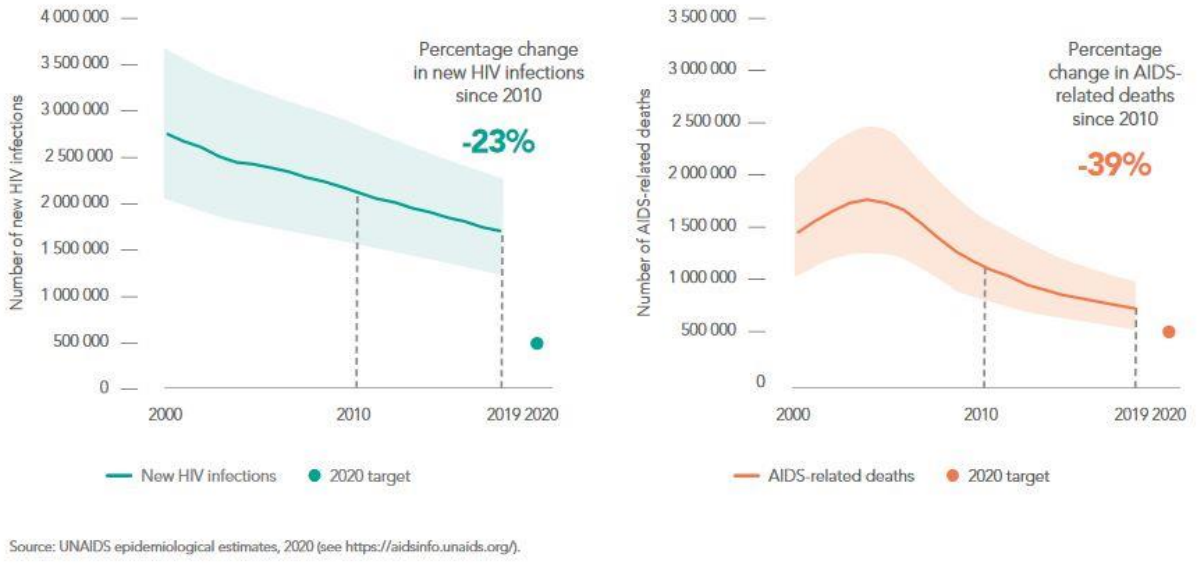

Figure 1. Number of new HIV infections and AIDS-related deaths, global, 2000-2019[6]

Before the discovery of ART, AIDS-related illnesses were the leading cause of deaths in sub-Saharan Africa [7,8]. Previously randomized trials, showed that early ART start not only reduces AIDS-related morbidity and mortality but also prevents transmission of HIV [9–12]. Over the years, the WHO was changing its guidelines on when to start ART among HIV-infected asymptomatic adults [13,14]. Since 2015, WHO recommends to offer ART to anyone with HIV regardless of the CD4 cell count due to evidence from clinical trials confirming that early initiation of ART leads to improved clinical outcomes compared to a later start [15–17]. Currently, PLHIV

who are using ART with suppressed viral loads have almost the same life expectancy compared to HIV-negative individuals [18–21].

Sub-Saharan Africa is the WHO region most affected with around 20.7 million (54%) PLHIV [5]. Since 2010, new HIV infections have been reduced by 38% and AIDS-related deaths have been reduced by 49% in the region [5,22]. This accomplishment was possible mostly due to extensive HIV testing and treatment programs in the region [5].

UNAIDS launched the 90-90-90 targets by 2020 [23] in order to be able to end the HIV/AIDS epidemic by 2030 based on the modelling study by Stover *et al* [24]. These targets are; 90% of all PLHIV should know their HIV status; 90% of all people diagnosed should receive sustained ART; of these, 90% should achieve a suppressed HIV RNA viral load. In sub-Saharan Africa, approximately, 87% of PLHIV know their HIV status, 72% have access to ART and 65% have suppressed viral loads [5].

Burden of HIV in Tanzania

In Tanzania, according to the latest National Survey there were 1.7 million PLHIV in 2019 which corresponds to the prevalence of 4.8% among adult population **(Figure 2)** [25]. This is a significant improvement compared to the previous survey in 2007-08 which showed the prevalence of 6% [26]. Since 2010, the number of new HIV infections and AIDS-related deaths have been reduced by 19% and 47% respectively **(Figure 3)** [22]. As of December 2018, the number of healthcare facilities offering free ART services in the country had increased from 96 in 2005 to 6,206 [27]. Tanzania has made substantial progress towards achieving the Global targets of 90-90-90 by 2020 and 95-95-95 by 2030 [23,28]. Approximately, 83% of PLHIV people know their status, 75% are on ART, and 69% have undetectable viral load [5].

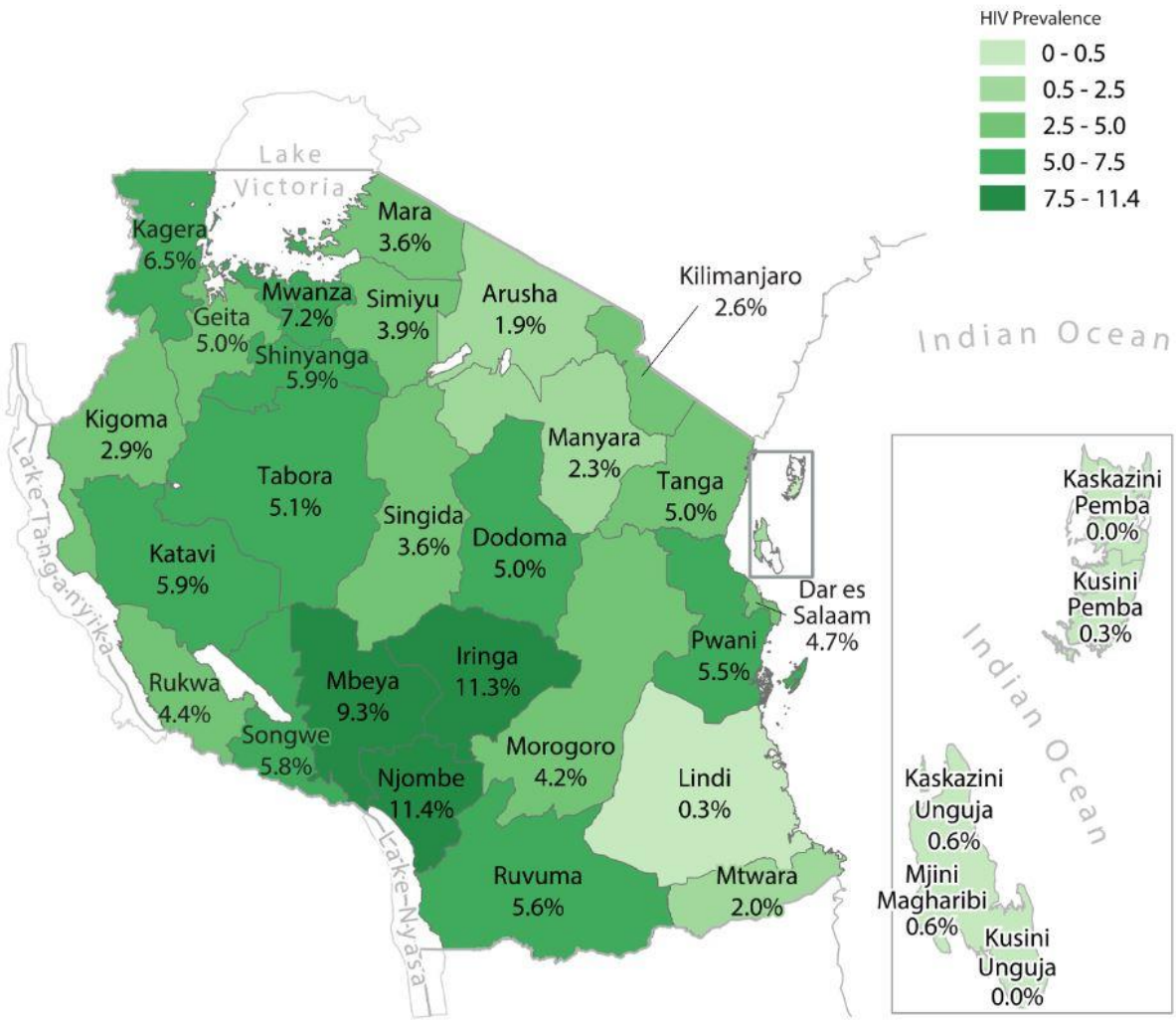

Figure 2: HIV prevalence among adults aged 15 years and older, by region, THIS 2016-2017 [25].

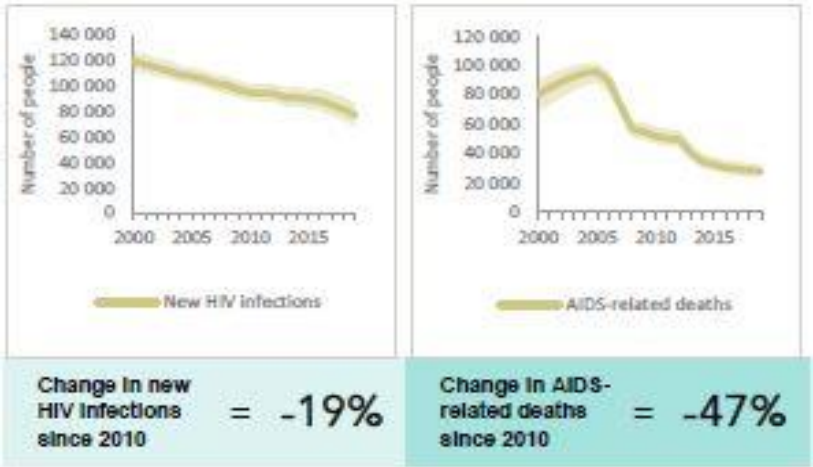

Figure 3: Change in new HIV infection and AIDS-related deaths, 2010-2019[22]

First, second and third-line ART regimens in Tanzania

In October 2016, the Tanzania HIV treatment guidelines adopted test and treat strategy following the recommendations of the WHO treatment guidelines [27,29]. These recommend the use of a triple therapy with the following combinations: 2 Nucleos(t)ide Reverse Transcriptase Inhibitors (NRTIs) + 1 Integrase Strand Transfer inhibitors (INSTI); 2 NRTI + 1 Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI); 2NRTI + 1 ritonavir-boosted Protease inhibitors (PI).

The default first-line regimen for adults and adolescents since 2019 consists of tenofovir disoproxil fumarate (TDF) in combination with lamivudine (3TC) and dolutegravir (DTG). Other alternative first-line regimen includes DTG with 3TC in combination with either abacavir (ABC) or zidovudine (AZT). Furthermore, TDF with efavirenz (EFV) in combination with either 3TC or emtricitabine (FTC) can used as first-line as well as AZT in combination with 3TC and nevirapine (NVP) [27].

For second-line regimens, the NRTI choice depends on the backbone of NRTI a patient was receiving as first-line. For patients who received TDF-based regimen as first-line the preferred second-line regimen should consists AZT plus 3TC and either ATV/r or LPV/r. For patients who started treatment with AZT-based regimen the preferred second-line regimen is TDF or ABC with FTC or 3TC in combination with either ATV/r or LPV/r.

For the third-line regimen, the national guideline recommends the use of second-generation drugs used in the first and second-line regimens hence minimum cross-resistance. The preferred third-line regimen consist of DTG or darunavir/ritonavir (DRV/r) in combination with AZT/3TC. The alternative third-line regimen consist of raltegravir (RAL) or DRV/r in combination with AZT/3TC.

Rollout of dolutegravir

Most of the low and middle-income countries' (LMIC) HIV treatment guidelines recommend the use of Integrase-strand-transfer inhibitors (INSTI)-based regimens as first-line treatment against HIV infection [27,30–33]. Additionally, most of the treatment guidelines recommend PLHIV receiving NNRTI-based regimens to be switched to dolutegravir-based regimens ART [27,30–33].

Dolutegravir is the most used INSTI since several previous phase 3 clinical trials have demonstrated its superiority or non-inferior compared to the most current used ART regimens [30,34–38]. Several phase 3 clinical trials have demonstrated excellent safety profile of

dolutegravir with few severe adverse events compared to the mostly current used ART regimens [34–38]. Moreover, previous resistance data has demonstrated dolutegravir to have high genetic barrier hence a low proportion of patients developed treatment-emergent resistance compared to the most currently used ART [34–39].

Dolutegravir and weight gain

Once starting ART, PLHIV usually experience weight gain. This is most pronounced in those patients with advanced HIV disease (low CD4 cell count or WHO Stage III/IV), patients with a high RNA HIV viral load and lower pre-ART BMI [40–46]. Short-term weight gain may be considered as a positive prognostic indicator showing a 'return to health effect' [45,47–50]. However, excessive weight gain among patients with normal weight, overweight or obesity have been associated with an increased risk of cardio-metabolic disorders [41,51,52]. Previous studies have demonstrated excessive weight gain among PLHIV starting treatment with INSTI (such as dolutegravir and bictegravir) compared to NNRTI, PIs and NRTI [46,53–57]. Several studies reported excessive weight gain among ART-naïve PLHIV who start ART with dolutegravir-based regimen compared to patients starting treatment with other NNRTIs and PIs [46,54,56,58]. Additionally, PLHIV who are switched from NNRTI or PIs to dolutegravir-based regimen have demonstrated excessive weight gain among PLHIV who are switched from other ART regimens to dolutegravir-based regimen [55,59]. The risk factors associated with excessive weight gain includes black ethnicity, female sex, lower CD4 count, and high HIV RNA viral load [40,43,45,46,56,57,60,61]. Consequently, the current WHO HIV treatment guideline cautioned about the possible side effect of weight gain among patients receiving dolutegravir-based regimens [62].

Non-communicable diseases

Global Burden of Non-communicable diseases

According to the WHO, each year more than 41 million people, which is equivalent to 71%, die from non-communicable diseases (NCDs) worldwide [63]. Among people aged between 30-69 years, more than 15 million die from NCDs and 85% of these deaths occur in LMIC [63]. The most common NCDs causes of deaths annually are cardiovascular diseases (17.9 million), cancers (9.3 million), respiratory diseases (4.1 million) and diabetes mellitus (1.5 million) [63].

The risk factors for most of the NCD are modifiable behaviour and metabolic risk factors. The most common modifiable behaviour risk factors are harmful tobacco use, excessive alcohol

consumption, eating unhealthy diet, physical inactivity, overweight and obesity [1,64]. Other important risk factors are arterial hypertension, and metabolic conditions such as raised blood cholesterol, and raised fasting blood glucose [1,2].

During the UN General Assembly high-level meeting on prevention and control of NCD in 2011, the World Leaders committed to reduce the mortality from four NCD (cardiovascular diseases, cancer, diabetes and chronic respiratory diseases) among people aged 30-70 years [65,66]. In 2016, NCD were added in the Sustainable Development Goal (SDG) target 3.4, aiming at "reducing by one third from non-communicable diseases through prevention and treatment and promote mental health and well-being by 2030" [65,67,68].

In order to tackle NCDs in low-resource settings, the WHO Package of Essential Non-communicable (PEN) diseases interventions for primary health care was established. The aim was to improve treatment and care of people suffering from NCD in the attending primary health care facilities in low-resource settings by prioritizing cost-effective interventions to improve quality of care [69]. The WHO Global NCD Action Plan 2013-2020, recommends countries to strengthen their healthcare systems to provide equitable access to universal health coverage, promote affordable prevention, screening, treatment, and care to NCD [70]. However, most of the countries have not been able to reach this target, particularly, most of the LMIC [68]. One major reason is that LMIC do not have structures for chronic disease management outside of secondary and tertiary healthcare facilities.

Double burden of NCD and infectious diseases in sub-Saharan Africa

The WHO African region, like most of the LMIC is one of the most affected region with NCD globally **(figure 4)** [71]. For decades, the leading cause of deaths in sub-Saharan Africa has been infectious diseases such as HIV, Tuberculosis and Malaria [72]. In sub-Saharan Africa, just like most of the LMIC there is a rapid demographic and epidemiological transition from the burden of infectious diseases to non-communicable diseases or chronic diseases [71,73,74]. By 2030, mortality due to NCD is projected to surpass the morality from combined infectious, neonatal, maternal and nutritional diseases [75,76]. Studies from sub-Saharan Africa, indicated the rise burden of NCD such cardiovascular diseases, diabetes mellitus, respiratory disorders and cancer and mental and substance use disorders [71,73,76]. According to the 2017 Global Burden of Diseases study, from 1999 to 2017, the total number of disability-adjusted life-years (DALYs) due to NCD in sub-Saharan Africa has increased from approximately 90.6 million to 151.3 million, representing 67% increase [71]. Additionally, from 1999 to 2017, the total number of DALYS caused by NCD increased from 18.6% to 29.8% **(figure 4)** [71].

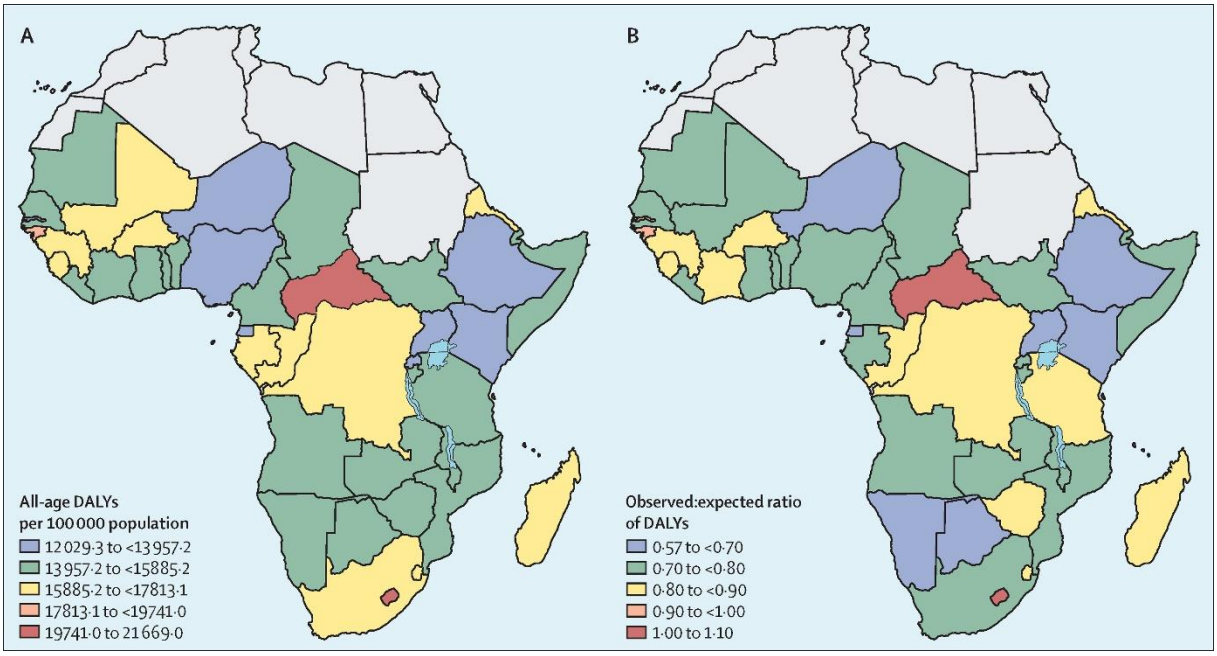

Figure 4. Burden of non-communicable diseases by country in sub-Saharan Africa, 2017[71]

(A) All-age rates for non-communicable diseases (per 100 000 population). (B) Ratio of observed to expected DALYs (according to the Socio-demographic Index) for all non-communicable diseases. DALY; disability-adjusted life-year

In order to be able to collect information on key risk factors for NCD in all Member States, the WHO established the STEPwise surveys (STEPS). The eight key risk factors collected during the surveys include tobacco use, harmful alcohol consumption, eating unhealthy diet, physical inactivity, overweight and obesity, arterial hypertension, raised blood cholesterol, and raised fasting blood glucose [77]. According to the 2015 report from WHO Africa region, most of the adults are exposed to at least one of these risk factors [77]. Furthermore, in half of African countries, at least one quarter of adults had at least three of the risk factors recorded hence increased risk of developing NCD over the course of their lives [77].

The rapid rise of the NCD burden is a challenge to the health care systems in sub-Saharan Africa, which are already overwhelmed with the high burden of infectious diseases [73,78,79]. This lack of preparedness of the healthcare system in sub-Saharan Africa to combat non-communicable diseases is expected to lead to an increase in NCD-related morbidity and mortality[79–81]. All the 47 countries in the WHO African region face challenges including lack of screening and diagnosis of NCD, use of out-of-pocket expenses while attending the healthcare facility [82,83], lack of access to essential medicines [84] and lack of NCD services in primary healthcare facilities [85]. Additionally, there is lack of health care workers, lack of knowledge and experience of NCD management among healthcare workers, workers working in the clinics compared to the developed countries [79].

In the WHO Africa region, the progress to achieve the sustainable development goal 3.4 has been recorded to be slow compared to other WHO regions [1]. More than half of the member states did not reach their interim targets for 2015 [86]. Several targets have to be achieved by the member States by 2030 [85]:

(1) Adaption of the WHO PEN and WHO guidelines for prevention and control of NCD using evidence-based different guidelines that are suitable to their respective national contexts
(2) Capacity building by conducting trainings to the healthcare workers in order to be able to deliver high quality NCD treatment and prevention services to the primary healthcare facilities
(3) To ensure the availability of essential medicines for NCD management as well as new technology and innovation for NCD diagnosis and management
(4) Improve surveillance system to collect all the information on morbidity, mortality and risk factors of NCD in order to be able to monitor the burden of NCD overtime

Chronic Kidney Diseases

Global burden of chronic kidney diseases

Chronic Kidney Disease (CKD) is among the leading causes of morbidity and mortality worldwide affecting around 9% - 13% of people [87–89]. Between 1990 and 2016, the global DALYS caused by CKD increased by 62% worldwide [90]. In 2017, it was estimated around 698 million people were diagnosed with CKD worldwide [87]. From the same report, CKD caused around 1.2 million deaths worldwide [87]. However, by 2040, this number has been projected to be around 2.2 million in a best-case scenario and 4 million in a worst case scenario [91].

According to the Kidney Disease Improving Global Outcome (KDIGO) guidelines, CKD is defined as 'changes in the kidney structures or functions, presented for more than 3 months, with implications to health' [92]. CKD can be categorised based on presence or absence of systemic disease that affect the kidney function, estimated glomerular filtration rate (eGFR) categories or albuminuria category [92]. Categories based on eGFR categories measured in ml/min/1.73m^2 are (>90, normal), (60-89, mild decreased), (45-59, mild to moderately decreased), (30-44, moderately to severely decreased), (15-29, severely decreased) and (<15, kidney failure) [92]. The Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) equation is the most recommended equation for calculation of eGFR in population where the burden of CKD is unknown and it is more accurate for patients with eGFR ≥60 ml/min/1.73m^2 ([93–96]. Categories

based on the albumin excretion rate measured in mg/24 hours are (<30, normal to mild increased), (30-300, moderately increased) and (>300, severely increased) [92].

Several risk factors have been reported previously to be associated with development of CKD. These factors include older age, having other comorbidities such as obesity, arterial hypertension, heart failure, anaemia and diabetes mellitus [97–99]. Importantly, infectious diseases such as HIV/AIDS, tuberculosis and schistosomiasis have been previously reported to be associated with increased frequencies of CKD [100–104].

Summary of the burden of CKD in sub-Saharan Africa

Sub-Saharan Africa is one of the most affected region with high prevalence of CKD in the general population which is estimated to range from 11% - 41% [93,100,105]. Among Africans, CKD has been reported to affect a much younger population (20-50 years) compared to other regions [106–110]. The reasons for this disproportional burden could be explained due to lack of community awareness of the disease, late presentation to the hospitals and limited capacity of healthcare workers in management of kidney diseases and the use of traditional medicines [111–114]. Additionally, other risk factors such as arterial hypertension and diabetes mellitus type 2 that are strong risk factors for CKD are more prevalent and hence increase the high cardiovascular diseases burden [115,116]. Furthermore, the burden of infectious diseases such as HIV, Malaria, Schistosomiasis and tuberculosis contribute to the high burden of CKD in the region [117–119]. Hodel *et al* recently reported around 85% of patients with CKD in urban Tanzania had at least one of the following risk factors; hypertension, diabetes mellitus, anemia, schistosomiasis or history of tuberculosis [100].

Chronic kidney disease and HIV

Before the rollout of ART, HIV-associated nephropathy (HIVAN) was one of the leading causes of comorbidity and mortality among PLHIV [104,120,121]. Since the widespread use of ART, the incidence of HIVAN has decreased greatly [122–124]. Kidney dysfunction due to HIV (HIVAN) has been hypothesized to be caused by immune complex formation and thrombotic microangiopathy [104,122]. Factors that predispose HIV-infected patients to develop kidney dysfunction includes increases susceptibility for pyelonephritis, anti-HIV immune complex mediated glomerulonephritis, nephrotoxic ART and direct kidney damage through HIVAN [104,123]. Other non-HIV related risk factors are arterial hypertension, diabetes mellitus, and medications that have been reported to be associated with kidney dysfunction among HIV patients [104,125].

The use of tenofovir and chronic kidney disease

Most of the HIV treatment guidelines recommend the use of TDF as a first-line ART due to its high efficacy and low side effects when used in combination with other antiretroviral agents [27,62,126]. Additionally, the use of TDF had in addition to its effect against Chronic Hepatitis B infection which is also highly prevalent in sSA [127–130]. Despite its wide use, there is still contradictory information in the literature whether long-term use of TDF use can cause kidney dysfunction, several studies have reported a strong association between TDF use and declining eGFR [101,131] and development of CKD [101,132–134]. However, a recent study by Hsu *et al* conducted in the United States has reported that the long-term use of TDF was not associated with an increased risk of developing CKD [135]. Tenofovir Alafenamide (TAF) has a favourable safety profile compared to TDF, and several guidelines recommend it to be used among PLHIV [126,136]. However, WHO treatment guidelines does not recommend the general use of TAF due safety concerns after reports that showed rising of blood lipids levels and excessive weight gain among compared to patients initiating treatment with TDF, particularly, when combined with dolutegravir [57,137,138].

The use of protease inhibitors and chronic kidney disease

The current WHO HIV treatment guidelines recommend the use of PI such as LPV/r, ATV/r and DRV/r as second-line treatment [62]. Accordingly the Tanzania HIV treatment guidelines, just like most of the treatment guidelines from sub-Saharan Africa, also have implemented PI as second-line treatment once patients develop treatment failure [27]. The long-term use of PI among PLHIV has been previously reported to be associated with increased risked risk of CKD incident or progression of CKD [134,139]. LPV/r has been linked with development of crystalluria, urolithiasis, and interstitial nephritis [140]. The long-term use of ATV/r has been associated with an increased incidence of urolithiasis that increased the risk of CKD incident [131,141–146]. Furthermore, the risk of kidney dysfunction increases when patients receive TDF in combination with protease inhibitors [134,147–149].

Cardiovascular diseases

Global burden of cardiovascular diseases

Cardiovascular diseases (CVD) are conditions that affect the heart and different blood vessels [150]. The most clinically most relevant blood vessels are the ones supplying the brain (cerebrovascular diseases), heart (coronary heart diseases) and those supplying peripheral parts of the body such as legs and arms (peripheral arterial diseases)[150,151]. Globally, almost 18 million people die each year from cardiovascular diseases complications (CVD) [90,151,152]. This

accounts for more than 32% of all global deaths and majority (85%) are due to coronary heart diseases(heart attack) and cerebrovascular diseases(stroke) [71,151].

Cardiovascular diseases in sub-Saharan Africa

During the past three decades, the number of deaths due to CVD has increased for more than 50% in sub-Saharan Africa [153]. Approximately 37% of all deaths happening in the region are due to NCD [154]. In 2017, CVD contributed around 22.9 million DALYS in sub Saharan region, which is more than 15% of all DALYS caused by NCD in the region [71]. The most common CVD conditions in the region are ischemic and hypertensive heart disease and stroke [71]. Additionally, compared to other countries in the developed world, sub-Saharan Africa still faces a high burden of congenital heart diseases and rheumatic heart diseases that increase the risk of CVD events [71,155].

Burden of arterial hypertension in sub-Saharan Africa

For the past decades, the burden of high blood pressure which is the leading risk factor for cardiovascular diseases has been on the rise in sub-Saharan Africa [156]. Arterial hypertension is the most frequent modifiable risk factor for stroke causing 11% of all deaths in the region [157]. The prevalence of arterial hypertension among adults (age > 25 years) is approximated to be around 25 - 46% in the WHO sub-Saharan Africa region [158–165] compared to around 35% to 40% in other WHO regions [160]. By 2030, it is projected that there will be 216.8 million persons with arterial hypertension compared to 54.6 million cases in 1990 and 130.2 million in 2010 [165].

Despite the high burden of arterial hypertension in the region, there is still little knowledge about frequency of complications and associated morbidity/mortality – partly due to low access to diagnostic services and treatment [166–168]. Atahlte *et al* reported in a systematic review involving 110,414 participants that only 27% of people were aware of their diagnosis, only 18% were receiving treatment and only 7% had a controlled blood pressure [160]. Additionally, there is a few data on best hypertension treatment for people living in sub-Saharan Africa and a lack of healthcare workers with the ability of treating hypertension [78,79,166]. On the other hand, people with black ethnicity have an increased risk of arterial hypertension that is hypothesized might be due to other genetic factors and susceptibility to salt intake [169–172].

Global burden of overweight and obesity

According to the WHO, overweight and obesity are defined as 'abnormal or excessive fat accumulation that may impair health' [173]. Overweight and obesity are modifiable risk factors

for NCDs and in 2016 there were more than 1.9 billion people over the age of 18 years were overweight and among them 650 million people were obese [173,174]. The burden of obesity worldwide almost tripled from 1975 to 2016 [174] and by 2030, around 38% of the adult world population will be overweight and 20% will be obese [175,176]. The same study reported more than 340 million children and adolescents (5-19 years) were also either overweight or obesity worldwide [174]. This is worrisome since childhood obesity can persist to adulthood hence increase the risk of NCD later in life such as diabetes mellitus [177–181].

Body mass index (BMI) is a commonly used measurement to categorise overweight and obesity among the adult population. The BMI is calculated by dividing the body weight in kilogram divided by height in meters squared [182]. The categories are underweight or wasting (<18.5 kg/m^2), normal weight (≥18.5-24.9 kg/m^2), overweight (≥25-29.9 kg/m^2) and obesity (≥30 kg/m^2) [183]. Obesity increases the risk of developing cardiovascular disease such as cardiovascular diseases, diabetes mellitus and dyslipidaemias [184–186]. Another measurement is the waist circumference which is the measure of abdominal adiposity and has been associated with increased risk of developing cardiovascular disease [187,188].

The burden of overweight and obesity in sub-Saharan Africa

The prevalence of overweight or obesity in sub-Saharan Africa is estimated to range from 20% to 50% [78,189]. In addition, LMIC often have a double burden of malnutrition, with both under- and overweight occurring in the same population [190]. There are several reasons for this epidemiological transition such as rapid urbanization and different lifestyle factors such as excessive use of alcohol and tobacco [191,192], high prevalence of physical inactivity [78,193] and consumption of poor diet [78,194].

Summary from WHO Tanzania country report

In 2016, according to the WHO non-communicable diseases country report, there were more than 409,000 deaths in Tanzania [195]. This is equivalent to 33% of the total deaths in the country; 13% from cardiovascular diseases, 7% cancers, 2% chronic respiratory diseases, 2% diabetes mellitus and 10% other NCD [195]. Despite this high burden of NCD, the proportion of primary health care centres reported as offering CVD risk stratification was <25% [195].

A recent study from urban Tanzania (Dar es Salaam) has demonstrated that over two-thirds of the population consume alcohol [78]. The total daily alcohol consumption per capita (litres of alcohol) was reported to be 9, the mean population salt intake (g/day) was 7 and prevalence of physical inactivity was 6% [195]. Approximately, 14% of adult population were current tobacco smokers, 7% were obese and 21% had a raised blood pressure (**Figure 5**) [195].

In Tanzania, the prevalence of overweight and obesity is estimated to be around 19% - 35% [166,196–198]. Hypertension affects around 18%-29% of the adult population [74,78,166] and the prevalence of CKD is around 13% [100]. Despite this high burden of NCD in the country, there is still low awareness in the community, low number of healthcare workers with capacity to manage NCD and lack of essential medicine and technology for diagnosis of NCDs [78,79,114,166].

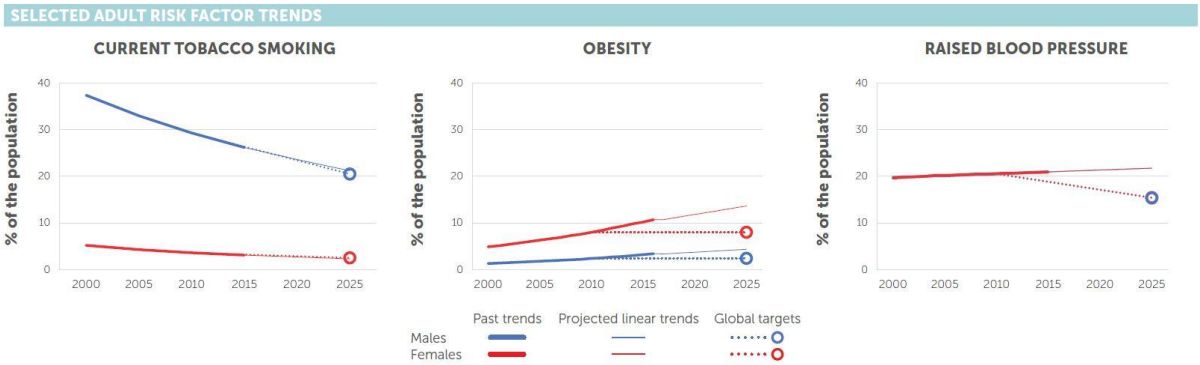

Figure 5. Selected adult risk factors trends for NCD in Tanzania[195]

Study aims

This doctoral thesis aimed to summarize the burden of different NCDs in sub-Saharan Africa. Additionally, the studies in this thesis aimed to estimate the burden of renal impairment, weight change and comorbidities once HIV-infected patients start their treatment in rural Tanzania.

Manuscript 1: The first study summarized the current literature on the burden of NCDs in sub-Saharan Africa. The review highlighted the clinical implications of the most relevant etiologies, i.e. hypertension, heart diseases, diabetes mellitus and chronic kidney diseases.

Manuscript 2: The second study investigated the prevalence and associated factors of renal impairment in people living with HIV at the time of switch from NNRTI to bPI, and renal impairment incidence. Additionally, it assessed and associated factors among those who had normal kidney function at the time of switch from NNRTI to bPI.

Manuscript 3: The third study evaluated the weight change among newly diagnosed PLHIV starting treatment with either dolutegravir-based or efavirenz-based regimen in rural Tanzania. Additionally, it assessed risk factors associated with increased body weight ≥10% after 12 months of treatment.

Manuscript 4: The fourth manuscript is a letter to the editor discussing the rollout of dolutegravir-based antiretroviral therapy in sub-Saharan Africa and its public health implications. The letter highlighted the lack of studies to evaluate long-term side effects of dolutegravir-based regimens among PLHIV living in sub-Saharan Africa.

Manuscript 5: The third study analyzed the prevalence and incidence of different comorbidities in different groups of HIV-infected patients on ART in rural Tanzania. Furthermore, the study assessed association between these different comorbidities and mortality overtime.

Manuscript 6: the sixth study is a study protocol for the control Arterial Hypertension in sub-Saharan Africa (coArtHA) trial that aims at comparing three treatment strategies to achieve rapid BP control with widely available drugs within 12 weeks in participants of African descent in rural sub-Saharan Africa. Additionally, the clinical trial will assess hypertension-mediated organ damage and compares the cost-effectiveness of the three treatment strategies considered.

Manuscript 7: the seventh manuscript is an editorial that discussed the challenges for HIV-infected adolescents during transition from paediatric to adult HIV clinics in Africa. It aimed to address the challenge of high HIV prevalence and incidence among adolescents and young adults in sub-Saharan Africa.

Manuscripts

Manuscript 1. Non-communicable diseases on the rise in sub-Saharan Africa, the underappreciated threat of a dual disease burden

Herry Mapesi[1, 2, 3], Daniel Henry Paris[2, 3]

[1]Ifakara Health Institute, Ifakara branch, Ifakara,Tanzania

[2]Swiss Tropical and Public Health Institute, Basel, Switzerland

[3]University of Basel, Basel, Switzerland

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Abstract (English)

In sub-Saharan Africa (SSA), the burden of non-communicable diseases (NCDs) remains under appreciated, but emerging evidence suggests it to be substantial. NCDs such as arterial hypertension, heart diseases, diabetes mellitus and chronic kidney diseases are especially relevant, and put additional strain on the already challenged health systems in this region. Moreover, NCDs appear to be associated with higher mortality and morbidity rates and are more common in younger population groups, in people from SSA when compared to more developed countries. In this review, we summarize the current literature on the burden of NCDs in SSA, and highlight the clinical implications of the most relevant etiologies, i.e. hypertension, heart diseases, diabetes mellitus and chronic kidney diseases.

Keywords: Non-communicable diseases, sub-Saharan Africa, dual disease burden, arterial hypertension, kidney diseases

Abstract (German)

Zusammenfassung: In Subsahara-Afrika bleibt die Belastung durch nicht übertragbare Krankheiten (NCDs) unterbewertet, aber es gibt neue Erkenntnisse, die darauf hindeuten, dass sie erheblich sind. Nicht übertragbare Krankheiten wie arterielle Hypertonie, Herzerkrankungen, Diabetes mellitus und chronische Nierenerkrankungen sind besonders relevant und belasten die bereits geforderten Gesundheitssysteme in dieser Region zusätzlich. Darüber hinaus scheinen nicht übertragbare Krankheiten mit einer höheren Sterblichkeits- und Morbiditätsrate verbunden zu sein und sind in jüngeren Bevölkerungsgruppen in Subsahara-Afrika häufiger anzutreffen als in weiter entwickelten Ländern. In diesem Beitrag fassen wir die aktuelle Literatur über die Belastung durch nicht übertragbare Krankheiten in Afrika südlich der Sahara zusammen und heben die klinischen Auswirkungen der wichtigsten Ätiologien hervor, d.h. arterielle Hypertonie, Herzkrankheiten, Diabetes mellitus und chronische Nierenerkrankungen.

Schlüsselwörter: Nicht übertragbare Krankheiten, Subsahara-Afrika, doppelte Krankheitsbelastung, arterielle Hypertonie, Nierenerkrankungen.

Abstract (French)

En Afrique subsaharienne, le fardeau des maladies non transmissibles (MNT) reste sous-estimé, mais de nouvelles données indiquent qu'il est considérable. Les maladies non transmissibles telles que l'hypertension artérielle, les maladies cardiaques, le diabète sucré et les maladies rénales chroniques sont particulièrement pertinentes et exercent une pression supplémentaire sur les

systèmes de santé déjà en difficulté dans cette région. En outre, les maladies non transmissibles semblent être associées à des taux de mortalité et de morbidité plus élevés et sont plus fréquentes dans les groupes de population plus jeunes, chez les populations d'Afrique subsaharienne que dans les pays plus développés. Dans cette revue, nous résumons la littérature actuelle sur le fardeau des maladies non transmissibles en Afrique subsaharienne et soulignons les implications cliniques des étiologies les plus pertinentes, à savoir l'hypertension artérielle, les maladies cardiaques, le diabète sucré et les maladies rénales chroniques.

Mots-clés: Maladies non transmissibles, Afrique subsaharienne, double charge de morbidité, hypertension artérielle, maladies rénales

Introduction

During the year 2016, a total of 57 million deaths were recorded worldwide and among them 41 million (71%) were attributable to NCDs [199]. The most prevalent NCDs include cardiovascular diseases, respiratory diseases, cancers and diabetes mellitus which account for over 80% of deaths [199,200]. Further, there were 15 million premature deaths, involving individuals aged between 30 and 70 years. The highest burden of NCDs were documented in low-and middle-income countries, where not only 78% of all deaths occurred, but also 85% of all premature deaths – due to diagnostic limitations and limited awareness these are likely underestimations [199]. It is projected that by the year 2020, NCDs will contribute to 65% and 60% of overall morbidity and mortality in sub-Saharan Africa (SSA), respectively [201].

In SSA there is rapid but sub optimally organized growth of cities, urbanization and industrialization – all of which increasingly expose the population to risk factors for NCDs [202]. There is a documented increase in prevalence of obesity and overweight in SSA, as in other low and middle-income countries. Life-style factors such as nutritional behavior with increased consumption of highly processed foods, tobacco use and physical inactivity play important roles [203,204]. These are major risk factors for development of metabolic disorders such as diabetes mellitus, hypertension, cancer and cardiovascular disorders.

SSA is facing an era of dual disease burden – the combined burden of infectious diseases with rapid increase of NCDs across the region – posing multifactorial challenges. In this review, we discuss about the burden and clinical implications of the most prevalent NCDs in SSA, which are hypertension, cardiac diseases, diabetes mellitus and chronic kidney diseases.

Hypertension

The worldwide prevalence of hypertension is estimated around 40% among adults aged 25 years and above [205]. Populations of African ethnicity have been previously reported to be associated with higher age-standardized blood pressure than other ethnicities, and black ethnicity is a risk factor for elevated blood pressure (BP) and associated cardiovascular events [206]. In SSA, age-standardized mean systolic blood pressure (SBP) is about 5 - 20mmHg higher compared to North America or Europe [207] with a prevalence of arterial hypertension (aHT) 30-46% in the population aged 30 to 60 years [160,165,205]. Reasons might be genetic factors, e.g. as a consequence of adaptation to climate [169,170] and increased susceptibility to salt intake [171,172]. In high-income countries, complications of aHT (stroke, myocardial infarction, kidney failure) have been shown to be higher in individuals with African descent compared to Caucasians – e.g. stroke is 2 – 3 times more common among African than Caucasian ethnicities [208].

The treatment cascade for aHT in SSA remains poor with less than 40% of hypertensive patients being diagnosed, less than 30% of those being diagnosed receiving medical treatment, and less than 20% of those being treated achieving good BP control [164]. On these grounds, the WHO released a Global Action Plan to address aHT in 2013 aiming to reach the following goals by 2020: (1) a relative reduction of raised BP prevalence by 25%; (2) improved salt/sodium intake, drug therapy and counselling to prevent stroke and ischemic heart disease in 30% and 50% respectively; (3) increased availability of basic technologies and medicines for 80% of NCDs cases [209].

Adequate long-term management of aHT is crucial to prevent end organ damage and should involve both non-pharmacological and pharmacological interventions [210,211]. Non-pharmacological interventions include the use Dietary Approaches to Stop Hypertension (DASH) which comprises intake of more vegetables, fruits, low-fat dietary products combined with moderate physical exercises [212], and a restricted consumption of table salt (sodium chloride) [213]. Of the three first-line drug classes: Thiazide diuretics (TZD); long-active calcium channel blockers (e.g. amlodipine) (CCB); and renin angiotensin system inhibitors (RAS-I), [angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II receptor blockers (ARB)], no unequivocal superiority is attributable to a drug class to control aHT [214–220]. A recent Cochrane Analysis on first-line aHT treatment showed evidence for best reduction in morbidity and mortality for TZD, although CCB and RAS-I were similarly effective, the evidence was of lower quality [221]. Most patients eventually need a combination of at least two antihypertensive drugs to achieve BP control [216,222]. Thus, for patients with aHT stage II (≥140/90mmHg) new guidelines recommend combination pharmacologic treatment with at least two classes of hypertensive drugs from the start [211]. Choice of antihypertensive drug combination is guided by comorbidities and side-effects [211].

In patients of African descent aHT appears less responsive to ACE-I and Beta-blockers when compared to Asian or Caucasian patients [211,223], likely due to a minor role of angiotensin-II dependency of BP [224]. Thus, international guidelines recommend TZD or CCB in patients of African descent [206,225–227], and international guidelines recommend the use of at least two medications from two different groups. Recent evidence suggests that CCB (amlodipine) plus either diuretic (hydrocholothiazide) or ARB (perindopril) is more potent in controlling hypertension in Africans control at six months than the use of TZD (hydrocholothiazide) plus ARB (perindopril) [228].

Diabetes Mellitus

The steady increase in global diabetes mellitus (DM) prevalence is worrisome. The International Diabetes Federation has projected an increase in DM prevalence among adults worldwide by 55%, from 425 million in 2019 to 642 million by 2040 [229]. The prevalence of DM in SSA is estimated at 3.1% (20 to 79 years old), and 15 million people are suffering from DM with an expected increase to 34 million by 2040. The most common form is type 2 diabetes mellitus (T2DM) which accounts for 90 – 95% of all cases, while Type 1A (autoimmune), (ketosis-prone, idiopathic) diabetes, and gestational diabetes account for <10% of all cases [230].

Similar to other NCDs, the rapid social-cultural and economic changes parallel the growing prevalence of DM in SSA. As elsewhere DM is linked to decreased life expectancy, physical inactivity and poor nutritional behavior [231]. Modifiable risk factors for DM include physical inactivity, obesity, and consumption of highly refined foods (high glycemic index) require targeted approaches, in contrast to non-modifiable risk factors for diabetes mellitus such as older age, family history and genetic susceptibility of the disease.

The end-organ complications of both macrovascular (cerebrovascular disease and coronary heart disease) and microvascular (retinopathy, neuropathy and nephropathy) etiologies are more common among Africans compared to patients from Western countries [232,233]. Also, diabetic cardiomyopathy has been associated with an increased risk of developing aHT, coronary heart disease and progression of heart failure among T2DM patients [234–236]. Furthermore, 40% of Africans who are diagnosed with a type 1 diabetes are more likely to die within 5 years compared to patients diagnosed from the UK who survive up to an average of 40 years post-diagnosis [232,237].

Early diagnosis and management of DM are of paramount importance to diminish the progression of DM complications. Preferably, preprandial blood glucose should be maintained at levels between 90 – 130 mg/dl and haemoglobin A1C (HB1Ac) below 7%. Clinical trials suggest benefits in the “polypill” approach in reducing CVD complications among T2DM patients [238–242]. A polypill formulation contains a fixed dose combination with an anti-platelet, anti-hypertensive and a statin. The use of polypills in high-risk patients has been proven a highly cost-effective way of reducing CVD complications in T2DM patients.

Cardiac diseases

Cardiovascular diseases (CVDs) represent a major global public health problem, resulting in the highest disability adjusted life-years (DALYs) worldwide [152]. Low and middle income countries are most affected with 85% of all deaths worldwide [191]. In Africa, approximately 1.2 million people died of CVDs in 2015 [243]. Heart failure is a major contributor of morbidity and mortality

in Africa, and in contrast to other regions of the world where ischemic heart disease is the major etiology for heart failure, hypertensive heart disease in Africa contributes to 39% of all patients with heart failure and mostly affects young and economically active adults [244–246].

We recently investigated the etiologies of heart diseases using echocardiography in patients from the rural Tanzania. Among 815/1184 adult patients with abnormal echocardiography who were included in the study, 66% (537/815) were hypertensive, of which only 42% (230/537) were on antihypertensive medications. Hypertensive heart disease was most common, followed by valvular heart disease and coronary heart disease [247]. Our results concur with other studies done in African settings showing high prevalence of hypertensive heart diseases, low uptake of hypertensive medications as well as poor controlled aHT [244,248].

Arterial hypertension is the leading etiology of heart diseases in Africa both rural and urban settings (table 1). More than two third of patients presenting with advanced stages of heart disease are without regular medications [247]. In SSA, there is an urgent need for increased awareness, expertise and infrastructure to detect and manage aHT and heart failure.

Chronic Kidney Disease

Chronic kidney disease (CKD) is defined as an impaired kidney function with glomerular filtration rate (eGFR) < 60 ml/min and/or raised proteinuria, measured at least two times three months apart. CKD is an independent risk factor for CVD and its prevalence is estimated to range between 11% – 13% worldwide [249]. Although the reported prevalence of CKD in the general population of Tanzania is around 14% [100] there is a scarcity of useful epidemiological data from SSA. The burden is even higher among HIV-infected patients and CKD is associated with increased mortality in this population [102,250]. The expected increase of NCDs in SSA during the next decade will include an increase in CKD as well [93,251]. Importantly, SSA continues to face a high burden of (chronic) communicable diseases like tuberculosis, schistosomiasis and HIV/AIDS which are associated with development of CKD [100,102,252].

Most risk factors for CKD are similar to other NCDs such as aHT and obesity - highly prevalent in SSA [100,102]. A recent study in Tanzania found at least one of the following risk factors among 85% of patients with CKD; aHT, DM, anemia, schistosomiasis or history of tuberculosis (table 2) [100]. These results concur with previous studies in SSA showing that the 'double burden' of disease in SSA is a major contributor to CKD. Additionally, albuminuria which is a strong predictor for development of CKD is very prevalent in SSA [100,253]. Unfortunately, the impact of the double burden of communicable and NCDs on the development of CKD has been poorly investigated [254,255] – clearly this preventable disease entity requires further attention.

Early diagnosis and management of CKD is important to prevent end-stage renal disease (ESRD) which has been associated with very high mortality and morbidity [107]. According to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) BP should be less than 130/80 mmHg in order to delay progression of CKD [256], and recommend the use of a renin angiotensin aldosterone system (RAAS) blocker, an ACE-I, or ARB for aHT and albuminuria control. Additionally, it is crucial to control DM as well as metabolic acidosis [256].

Discussion

The major contributors to the growing burden of NCDs in SSA include arterial hypertension, diabetes mellitus, heart failure and chronic kidney diseases – and there is a great need to improve awareness, diagnostics and management for NCDs in this region. The rapid rise in NCDs incidence adds to the existing burden of infectious diseases resulting in the devastating dual burden of diseases (figure 1). In contrast to other regions, NCDs in SSA disproportionally affect a much younger population compared to more developed countries hence and thus has very big impact on the economic growth [257]. People from African ethnicity are more likely to develop aHT due to increased genetic and salt intake susceptibility compared to other races [169–172]. They are more prone to develop other CVDs as well as complications such as ischemic heart disease, cardiomyopathies and stroke [244]. Furthermore, the co-existence of chronic infectious diseases such as HIV/AIDS, tuberculosis, schistosomiasis can increase the risk of developing NCDs (e.g. CKD) possibly with more rapid progression and complications (figure 1). Therefore, tackling the burden of NCDs in Africa requires multifactorial approaches with strengthening of existing health care systems to facilitate early diagnosis, treatment and management.

These data reflect the important rise of NCDs in the past decade with ischemic heart disease moving from 8th to 4th position and diabetes moving into the top ten (from 13th to 10th position) [258].

Rapid and unplanned urbanization in SSA has affected the consumption of highly processed foods, physical inactivity, excessive alcohol intake, cigarette smoking and obesity, which are main risk factors for development of NCDs. Educational measures are relevant at this stage to increase community awareness about risk factors of NCDs through outreach programs [259]. In most of SSA countries there is lack of regulations for control of foods and sugary soft drinks that increase the risk of obesity, aHT and DM. Around 13% of people with either DM or aHT are active tobacco smokers in Africa [260]. The WHO Framework Convention on Tobacco Control Guidelines which include controlled labelling, advertising and sponsorship are poorly implemented across SSA [261]. The most cost-effective way of controlling tobacco use is raising taxes for related products;

which is also poorly implemented [262]. Therefore, considering the major impact of tobacco consumption in this setting, it is important for African countries to implement strict legislation for tobacco use across the continent.

Until today, the majority of donors and SSA governments see their priorities in three communicable diseases (Malaria, HIV/AIDS and tuberculosis) rather than NCDs. Between the year 2001 and 2008 the Global development assistance for health contributed only $0.78/DALY attributed to NCDs compared to $23.9/DALY attributed to tuberculosis, HIV/AIDS and Malaria – this is over 30-times more [263]. Therefore, there is a need for more donor funding to support the existing health systems to combat NCDs such as hypertension, diabetes mellitus and screening for CKDs and different types of cancers.

In the past decades, health systems in Africa have focused on tackling infectious diseases such as malaria, pneumonia, diarrhea, HIV/AIDS and tuberculosis. In most SSA countries successful vertical programs for treatment and care of HIV/AIDS and tuberculosis which require long-term treatment and follow-up just like other NCDs have been established. The emerging data suggests that these existing health systems and structures could incorporate management and care of chronic NCDs to achieve high impact with little investment - especially for aHT and DM [264,265].

A scarcity of clinical research for the estimation of disease burden and management of NCDs in SSA remains. Robust high-quality evidence directed at informing national stakeholders is required to induce change. The dual existence of communicable and NCDs complicates comparisons with findings in developed countries, and hinders identification of the key drivers of NCDs across Africa. Dissecting the issues around NCDs will not only help to control the burden of NCDs but also will help to train more next generation Africans scientists in the future.

Figure 6: Top 10 causes of mortality in Tanzania (2017) and percent change (2007 – 2017).

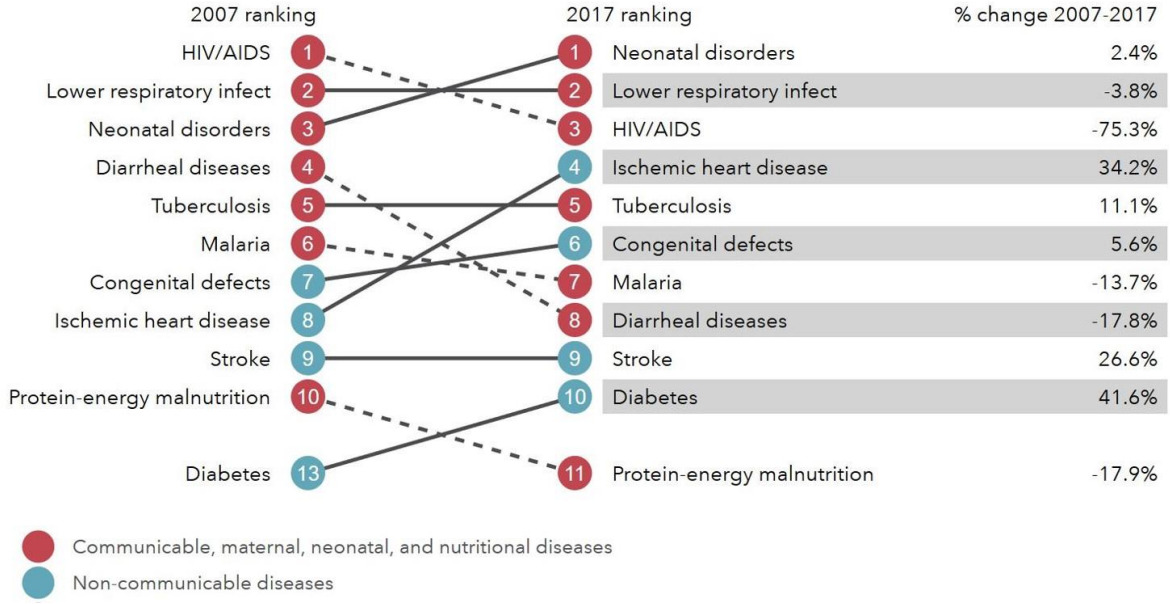

Table 1: Most common cardiac diseases in a large Tanzanian study

	Adults (n = 815)	Children (n = 59)
Hypertensive HD, n (%)	337 (41%)	3 (5%)
- Hypertensive dilated cardiopathy with eccentric hypertrophy, n (%)	76 (9%)	1 (2%)
- Hypertensive HD with concentric hypertrophy, n (%)	160 (20%)	2 (3%)
Valvular HD, n (%)	146 (18%)	12 (20%)
- Rheumatic HD, n (%)	68 (8%)	5 (8%)
- Endocarditis, n (%)	9 (1%)	2 (3%)
- Valvular HD with hypertension, n (%)	43 (5%)	0 (0%)
Coronary HD, n (%)	145 (18%)	0 (0%)
- Coronary HD without hypertension, n (%)	29 (4%)	0 (0%)
- Coronary HD with hypertension, n (%)	116 (14%)	0 (0%)
Peripartum cardiomyopathy, n (%)	56 (7%)	0 (0%)
- Peripartum cardiomyopathy with hypertension, n (%)	14 (2%)	0 (0%)
Dilated cardiomyopathy, other, n (%)	52 (6%)	9 (15%)
Hypertrophic cardiomyopathy, other, n (%)	8 (1%)	2 (3%)
Endomyocardial fibrosis, n (%)	3 (0.4%)	1 (2%)
TB-pericarditis, n (%)	16 (2%)	5 (8%)
Pericarditis constrictiva, n (%)	8 (1%)	0 (0%)
Right heart failure due to pulmonal hypertension/normal LAP, n (%)	37 (5%)	7 (12%)
Arrhythmogenic right ventricular cardiomyopathy, n (%)	2 (0.2%)	1 (2%)
VSD*, n (%)	2 (0.2%)	6 (10%)
ASD, n (%)	3 (0.4%)	6 (10%)
TOF, n (%)	0 (0%)	6 (10%)
Complete AV defect, n (%)	0 (0%)	1 (2%)
PDA, n (%)	0 (0%)	6 (10%)

HD, heart disease; TB, tuberculosis; LAP, left atrial pressure; VSD, ventricular septal defect; ASD, atrial septal defect; TOF, Tetralogy of Fallot; AV, atrioventricular; PDA, patent ductus arteriosus. * VSD in absence of TOF. Children with congenital heart disease: n = 20 (34%). Two children with TOF had concomitant ASD and one child with TOF had concomitant PDA. One child had VSD and ASD, one child had VSD, ASD and PDA.

Table 2: Factors associated with albuminuria, impaired kidney function and chronic kidney disease in general population in Tanzania

Associated factors	Factors associated with albuminuria				Factors associated with impaired kidney function				Factors associated with chronic kidney disease			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	OR (CI)	p-value	OR (CI)	p-value	OR (CI)	p-value	OR (CI)	p-value	OR (CI)	p-value	OR (CI)	p-value
Age (years)	1.03 (1.02–1.04)	<0.001	1.00 (0.99–1.02)	0.68	1.06 (1.04–1.09)	<0.001	1.05 (1.01–1.09)	0.007	1.04 (1.02–1.05)	<0.001	1.01 (0.99–1.03)	0.18
Sex (female vs. male)	0.90 (0.59–1.38)	0.62	0.64 (0.35–1.19)	0.16	0.82 (0.36–1.96)	0.64	0.22 (0.06–0.75)	0.01	0.86 (0.58–1.31)	0.48	0.63 (0.35–1.15)	0.13
BMI (kg/m^2)[a]	0.98 (0.95–1.02)	0.33	0.93 (0.88–0.97)	0.002	1.03 (0.97–1.10)	0.28	0.98 (0.89–1.06)	0.60	0.98 (0.95–1.02)	0.32	0.92 (0.88–0.96)	<0.001
BP syst (mmHg)[b]	1.02 (1.01–1.03)	<0.001	1.01 (1.00–1.03)	0.02	1.02 (1.01–1.03)	0.002	1.00 (0.97–1.02)	0.95	1.02 (1.01–1.03)	<0.001	1.02 (1.00–1.03)	0.01
BP diast (mmHg)[c]	1.03 (1.02–1.05)	<0.001	1.02 (0.99–1.04)	0.16	1.04 (1.02–1.06)	<0.001	1.03 (0.98–1.08)	0.21	1.03 (1.02–1.05)	<0.001	1.01 (0.99–1.03)	0.25
History of hypertension	2.13 (1.33–3.34)	<0.001	1.29 (0.68–2.40)	0.42	4.06 (1.77–9.11)	<0.001	2.74 (0.78–9.33)	0.11	2.45 (1.57–3.78)	<0.001	1.50 (0.82–2.72)	0.18
Diabetes mellitus	3.06 (1.64–5.48)	<0.001	2.81 (1.26–6.00)	0.009	1.87 (0.43–5.60)	0.32	0.32 (0.02–2.01)	0.32	3.22 (1.77–5.58)	<0.001	2.20 (0.98–4.71)	0.05
Haemoglobin (g/dl)	0.88 (0.80–0.98)	0.02	0.82 (0.72–0.94)	0.005	0.78 (0.64–0.95)	0.01	0.62 (0.46–0.82)	<0.001	0.88 (0.80–0.98)	0.02	0.82 (0.72–0.94)	0.004
HIV positive vs. negative[d]	1.24 (0.53–2.59)	0.59	0.77 (0.28–1.87)	0.58	0.65 (0.04–3.28)	0.68	0.25 (0.01–2.09)	0.29	1.08 (0.46–2.25)	0.85	0.65 (0.23–1.57)	0.37
HIV negative vs. unknown	1.06 (0.65–1.68)	0.81	0.62 (0.31–1.17)	0.16	1.24 (0.47–2.92)	0.64	0.24 (0.03–1.05)	0.10	0.90 (0.55–1.43)	0.88	0.52 (0.26–0.99)	0.06
History of UTI[e]	0.79 (0.04–4.29)	0.83	2.29 (0.12–13.79)	0.45	4.00 (0.21–22.66)	0.20	16.9 (0.63–200.7)	0.04	0.70 (0.04–3.85)	0.75	2.14 (0.11–12.9)	0.49
History of smoking	1.01(0.46–2.00)	0.97	1.19 (0.44–2.89)	0.71	0.47 (0.03–2.26)	0.46	0.67 (0.03–4.64)	0.72	0.95 (0.43–1.87)	0.84	0.98 (0.36–2.36)	0.96
History of tuberculosis	3.28 (1.56–6.52)	0.001	3.80 (1.65–8.36)	0.001	4.31 (1.21–12.06)	0.01	5.53 (1.32–19.5)	0.01	3.29 (1.60–6.46)	<0.001	3.75 (1.66–8.18)	0.001
History of schistosomiasis	1.62 (0.80–3.04)	0.15	2.28 (1.01–4.79)	0.04	1.73(0.40–5.17)	0.38	4.34 (0.81–18.07)	0.06	1.66 (0.84–3.07)	0.12	2.49 (1.13–5.18)	0.02

Factors associated with albuminuria: ACR ≥30mg/g, (≥3 mg/mmol); impaired kidney function: eGFR <60ml/min/1.73m^2; chronic kidney disease: eGFR <60ml/min/1.73m^2 and/orACR ≥30 mg/g (≥3mg/mmol);

[a]BMI: Body mass index (kg/m^2);

[b]BP syst: Blood pressure systolic;

[c]BP diast: blood pressure diastolic,

[d]HIV positive: 43 patients were diagnosed within the study, 21 patients had a history of HIV and 15 of them were on antiretroviral therapy.

[e]History of urinary tract infection (UTI): >2 episodes of UTI/year.

ACR: albumin-creatinine-ration; eGFR: estimated glomerular filtration rate. All variables shown in the table were included in the multivariate logistic regression analysis.

Recent study reveals association between kidney diseases and infectious diseases

Manuscript 2. Prevalence, incidence and predictors of renal impairment in persons with HIV receiving protease-inhibitors in rural Tanzania

Herry Mapesi[1,2,3,4*], James Okuma[2], Fabian Franzeck[5], Herieth Ismael Wilson[1,4], Elizabeth Senkoro[1,4], Theonestina Byakuzana[1], Robert Ndege[1,4], Fiona Vanobberghen[2,3], Tracy Renée Glass[2,3], Manuel Battegay[3,5], Maja Weisser[1,2,3,5] and Daniel Henry Paris[2,3] on behalf of the KIULARCO Study Group

[1]Ifakara Health Institute, Ifakara branch, Ifakara, United Republic of Tanzania

[2]Swiss Tropical and Public Health Institute, Basel, Switzerland

[3]University of Basel, Basel, Switzerland

[4]St. Francis Referral Hospital, Ifakara, United Republic of Tanzania

[5]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Basel, Switzerland

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Abstract

Objective: Ritonavir-boosted protease inhibitors (bPI) in people living with HIV (PLWH) have been associated with renal impairment. Limited data are available from rural sub-Saharan Africa.

Methods: Using data from the Kilombero and Ulanga Antiretroviral Cohort Study (KIULARCO) in rural Tanzania from 2005-01/2020, we assessed the prevalence of renal impairment (estimated glomerular filtration rate <60 mL/min/1.73m^2) at the time of switch from first-line antiretroviral treatment (ART) to bPI-regimen and the incidence of renal impairment on bPI. We assessed risk factors for renal impairment using logistic and Cox regression models.

Results: Renal impairment was present in 52/687 PLWH (7.6%) at the switch to bPI. Among 556 participants with normal kidney function at switch, 41 (7.4%) developed renal impairment after a median time of 3.5 (IQR 1.6-5.1) years (incidence 22/1,000 person-years (95%CI 16.1-29.8)). Factors associated with renal impairment at switch were older age (adjusted odds ratio (aOR) 1.55 per 10 years; 95%CI 1.15-2.11), body mass index (BMI) <18.5 kg/m^2 (aOR 2.80 versus ≥18kg/m^2; 95%CI 1.28-6.14) and arterial hypertension (aOR 2.33; 95%CI 1.03-5.28). The risk of renal impairment was lower with increased duration of ART use (aOR 0.78 per one-year increase; 95%CI 0.67-0.91). The renal impairment incidence under bPI was associated with older age (adjusted hazard ratio 2.01 per 10 years; 95%CI 1.46-2.78).

Conclusions: In PLWH in rural sub-Saharan Africa, prevalence and incidence of renal impairment among those who were switched from first-line to bPI-regimens were high. We found associations between renal impairment and older age, arterial hypertension, low BMI and time on ART.

Keywords: HIV, renal impairment, sub-Saharan Africa, antiretroviral treatment, ritonavir boosted-protease inhibitors

Introduction

Rollout and improvement in HIV care and treatment have led to a shift in the main causes of morbidity and mortality in people living with HIV (PLWH) away from opportunistic infections to chronic non-communicable diseases such as liver, cardiovascular and renal diseases [266]. With a global prevalence of 11-13% [267], chronic kidney disease (CKD) is regarded as an independent risk factor for cardiovascular diseases (CVD) and a leading cause of mortality and morbidity in PLWH [268,269].

The pooled prevalence of CKD among PLWH in sub-Saharan Africa (sSA) is estimated to be 14.6% [270]. Apart from traditional risk factors for CKD such as arterial hypertension and diabetes mellitus, PLWH in sSA are facing the additional burden of other infectious diseases associated with CKD and renal impairment such as tuberculosis and schistosomiasis [271]. In Tanzania, the prevalence of CKD in the general population is estimated to be around 7-15% and in PLWH up to 28% [102,271–273].

Among PLWH, long-term toxicity of antiretroviral treatment (ART) remains a key concern. World Health Organization (WHO) treatment guidelines recommend the use of tenofovir disoproxil fumarate (TDF) as first-line nucleotide reverse transcriptase inhibitor (NRTI) in combination with either emtricitabine (FTC) or lamivudine (3TC) and a non-nucleotide reverse transcriptase inhibitor (NNRTI) or an integrase inhibitor [274]. For second-line treatment, the same guidelines recommend the use of TDF in combination with ritonavir-boosted protease inhibitors (bPI) - either atazanavir (ATV/r) or lopinavir (LPV/r). The Tanzania treatment guidelines follow the WHO treatment guidelines [275]. Longer cumulative exposure to the use of TDF [101,276] and bPIs [134,139] has been associated with CKD or kidney dysfunction. Furthermore, the risk of kidney dysfunction increases when patients receive TDF in combination with a bPI [134,147,148]. The mechanism of CKD is not well understood, although previous studies suggested it might be due to crystalluria, proximal tubular dysfunction, urolithiasis, and interstitial nephritis [140,141].

Using data from a cohort of HIV-positive patients in rural Tanzania - the Kilombero and Ulanga Antiretroviral Cohort (KIULARCO) - we investigated the prevalence and associated factors of renal impairment in PLWH at the time of switch from NNRTI to bPI, and renal impairment incidence and associated factors among those who had normal kidney function at the time of switch from NNRTI to bPI.

Methods

Study design and settings

The KIULARCO is a prospective cohort with more than 11,000 PLWH ever enrolled and 4,500 on active follow-up as of January 2020. Since 2005, all individuals who attend the Chronic Diseases Clinic of Ifakara (CDCI) at the St. Francis Referral Hospital in Ifakara, Tanzania are asked for consent to participate in the cohort. Data on demographics, clinical presentation, ART, HIV-1 RNA viral load, CD4 T-cell count and other laboratory investigations are recorded electronically at enrolment and during follow-up visits. Details of the cohort have been published elsewhere [277,278].

In this nested study, participants from KIULARCO who were switched from first-line ART regimens to bPI-based regimens were eligible, if they met the following criteria: age ≥15 years, availability of eGFR measurement within 6 months before or after the time of the ART switch and at least one eGFR measurement during follow-up visits. We excluded participants who either started treatment with regimens containing a bPI or entered the cohort while receiving bPI. All participants were offered treatment and care according to the Tanzania standard treatment guidelines [275].

Procedures

We included participants who attended KIULARCO from 2005 to January 2020. During the time of the study, participants started ART with at least 2 NRTIs and 1 NNRTI. The use of Integrase strand transfer inhibitor (dolutegravir) as first-line ART was implemented only in March 2019 [275]. By the time of this analysis, no participant had been switched from dolutegravir to bPI, therefore participants on dolutegravir were not included in this analysis. During follow-up, once a clinician suspected clinical or immunological failure, participants were switched to second-line that usually contained 2 NRTIs and a bPI [275]. Routine HIV-1 RNA viral load monitoring was not available until 2018, thus, treatment failures mostly were not confirmed virologically.

Laboratory and clinical investigations

Routine laboratory investigations (serum creatinine, CD4 cell count, aspartate aminotransferase, alanine aminotransferase and complete blood cell count) were performed routinely once a year. Additional measurements can be performed upon clinical indication. During the time of the study, routine HIV-1 RNA viral load monitoring was not available, however, it was performed upon physician request if immunological or treatment failure was suspected or if participants were enrolled in a specific nested study within a cohort. For all laboratory and clinical measurements, we considered the closest measurement prior to the switching date from NNRTI to bPI within the time window of six months before or after the switch. We measured serum creatinine using Cobas c 111 Analyzer (Roche Diagnostics, Rotkreuz, Switzerland) and we used the Chronic Kidney

Diseases Epidemiology (CKD-EPI) formula to calculate the estimated glomerular filtration rate (eGFR) [279]. We measured the CD4 cell count using flow cytometry (BD FACS Calibur, Franklin Lakes, NJ) and categorized into CD4 cell counts <200 cell/mm3 or ≥200 cells/mm^3 [280].

We defined tuberculosis (TB) if the participant had a recorded positive GeneXpert (Cepheid, Sunnyvale, CA) result in the sputum or another body fluid sample. The GeneXpert was established in KIULARCO from 2013 onwards. Additionally, participants were categorized to have TB if they had a chest x-ray suggesting TB with at least 1 TB symptom and receiving TB treatment at the time of switch.

Blood pressure and body weight were measured at every clinical visit. We defined arterial hypertension as having either a systolic BP of ≥140mmHg and/or a diastolic BP ≥90mmHg on 2 consecutive clinical visits [150], being currently on antihypertensive treatment or a previous history of arterial hypertension diagnosis. Body mass index (BMI) was calculated using weight (kilograms/height^2 (m^2)) and was categorized as either underweight (BMI <18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2) or overweight (≥25 kg/m^2). The current ART regimen before the switch (pre-bPI) was defined as the closest ART regimen the patient was receiving before the switch. The bPI (post-bPI) was defined as the first second line ART the patient received after switch.

Statistical analysis

We extracted demographic, clinical, laboratory and treatment information from the KIULARCO electronic database. We summarized categorical variables using frequencies and percentages and continuous variables using median and interquartile range (IQR). We used logistic regression models to assess the predictors of renal impairment at the time of switch from NNRTI to bPIs. Results are presented with odds ratios (OR) and 95% confidence intervals (CI).

Cox regression models were fitted to assess the association between covariates at the time of the switch to bPIs and development of renal impairment. Study participants who had renal impairment at the time of switch to bPI were excluded from this analysis. Results are presented with hazard ratios (HR) and 95% CI.

Renal impairment was defined as having moderate or severe eGFR decrease (<60 mL/min/1.73m^2) at the time of the switch from first-line ART to bPI by using single eGFR measurement (Kidney Diseases Improving Global Outcomes KDIGO Stage G3-G5) [281]. Additionally, for participants who had normal kidney function at the time of the switch we defined the incidence of renal impairment if their eGFR dropped to <60 mL/min/1.73m^2 using single eGFR measurement [281]. The differentiation of renal impairment into CKD and acute kidney disease (AKI) was not possible due to lack of systematic repeat creatinine measurements in routine care

[282]. In most of the studies from sSA estimation of renal impairment is based on one measurement only due to lack of repeat measurements of serum creatinine [271,283–285]. We conducted a sensitivity analysis to assess CKD for participants who had two measurements of eGFR <60 mL/min/1.73m^2 three months as recommended by KDIGO [281].

A priori, we identified the following variables for multivariable analysis: age, BMI, HIV World Health Organization (WHO) stage, CD4 cell counts, hypertension, ART regimen, calendar year of switching, and TB. All analyses were performed using Stata, version 15.1 (Stat Corp, College Station, Texas, USA).

Ethics statement

All patients' data were anonymized before we conducted analysis. At enrolment in KIULARCO, a written informed consent is sought from all study participants; those who refused consent were excluded. Ethical approval was obtained from the Ifakara Health Institute review board (IHI/IRB/No16-2006), the National Health Research Committee of the National Institute of Medical Research of Tanzania (NIMR/HQ/R.8a/Vol.IX/620) with yearly renewal, as well as from the Ethikkomission Nordwest und Zentralschweiz (EKNZ; Switzerland).

Results

A total of 11,128 participants were enrolled into KIULARCO from 2005 up until January 17, 2020. Of these, 9,935 were never prescribed a bPI-regimen and 163 participants were excluded because they started treatment with a bPI-regimen at the time of enrolment or entered the cohort already receiving a bPI-regimen. A further 147 participants were aged <15 years, and 196 did not have creatinine measurements at the time of switch. For this analysis, 687 participants were included at the time of switch to a bPI-regimen, of whom 556 had a normal baseline creatinine and at least one follow-up creatinine measurement (Figure 7).

Demographic and clinical characteristics of participants at the time of switch from first-line ART to bPI-regimen are summarized in Table 3. The majority of participants (63.5%) were female, with a median age of 41 years (IQR 33-48). An advanced WHO stage III or IV was present in 60.7% of participants. The median BMI was 21.68 kg/m^2 (IQR 19.1-24.5) with 53% of participants having a normal BMI (≥18.5-24.9 kg/m^2). The median CD4 cell count was 218 cells/mm^3 (IQR 95-383), with 52.1% of participants having a CD4 cell count of <200 cells/mm^3. There were 61 participants (8.9%) who were diagnosed with tuberculosis and 116 (16.9%) were diagnosed with arterial hypertension either 6 months before or after switch.

The median time on first-line ART before the switch to bPI-based regimen was 3.6 years (1.5-6.0); the most common first-line treatment used at the time of switch was TDF in combination with lamivudine (3TC) and efavirenz (EFV) (44.0%), followed by zidovudine (AZT), 3TC and nevirapine (21.1%), AZT, 3TC and EFV (13.5%) and TDF, emtricitabine (FTC) and EFV (13.1%). Majority of participants 363 (52.8%) were switched to bPI before the year 2015.

Renal impairment at the time of switch

The median eGFR at the time of switch was 126.2 ml/1.73m^2 (IQR 102.9-40.8). A total of 52 participants (7.6%) had renal impairment at the time of switch. In these participants, renal impairment resolved (eGFR ≥60 mL/min/1.73m^2) in 29 (55.8%) by the time of study closure, therefore, most likely AKI.

Results from univariable and multivariable logistic regression models assessing the association of renal impairment and independent predictors at the time of switch are presented in Table 4. After adjustment for potential confounding factors, we found evidence of associations between renal impairment and increasing age (adjusted odd ratio (aOR) 1.55 per 10 years; 95% CI 1.15-2.11; *P* 0.004), BMI <18.5 kg/m^2 (aOR 2.80 versus ≥18.5 kg/m^2; 95% CI 1.28-6.14; *P* 0.010) and arterial hypertension (aOR 2.33; 95% CI 1.03-5.28; *P* 0.043). The risk of renal impairment was reduced with increased exposure to first-line ART (per one-year increase) (aOR 0.78; 95% CI 0.67-0.91; *P* 0.002). We did not find an association between renal impairment and CD4 cell count, WHO stage, TB diagnosis, and calendar year of switch.

Renal impairment during follow-up

The median time under observation for the 556 participants who had normal renal function at the time of switch and at least one follow-up creatinine measurement was 3.49 years (IQR 1.63 – 5.01) (Table S1). The majority of participants (161 participants, 29%) received an ATV/r-based regimen (TDF, FTC, ATV/r, 29%) followed by TDF, FTC and LPV/r (113 participants, 20.3%).

A total of 41 (7.4%) participants developed renal impairment during follow-up at the median time of 3.5 years (IQR 1.6-5.1). Among these participants, renal impairment resolved (eGFR ≥60 mL/min/1.73m^2) in 35 (85.4%) by the time of study closure. The total time at risk was 1,864.10 person-years and the incidence of renal impairment was 22 per 1,000 person-years (16.1-29.8). Results from univariable and multivariable Cox regression models assessing the association of development of a new renal impairment under bPI treatment and independent predictors at the time of switch are presented in Table 5. We found strong associations between development of renal impairment and older age (adjusted hazard ratio (aHR) 2.22 per 10 years; 95% CI 1.56-3.15; *P* <0.001). We found some association between development of renal impairment and being

switched to a TDF-based regimen (aHR 2.12 versus non-TDF-based regimen; 95% CI 0.93-4.80; *P* 0.072). We did not find evidence of an association between development of renal impairment and BMI (aHR 0.96 for <18 versus ≥18 kg/m^2; 95% CI 0.37-2.43; *P* 0.924), CD4 cell count (aHR 0.87 ≥200 versus <200 cells/mm^3; 95% CI 0.41-1.84; *P* 0.715), and WHO stage (aHR 1.83 for WHO stages I/II versus III/IV; 95% CI 0.83-4.01; *P* 0.133). Furthermore, we did not find association between renal impairment and arterial hypertension (aHR 1.19; 95% CI 0.55-2.61.59; *P* 0.657), TB diagnosis (aHR 2.04; 95% CI 0.75-5.55; *P* 0.161), total time on ART before the switch (per one year) (aHR 0.97; 95% CI 0.73-1.27; *P* 0.807) and calendar year of switch (aHR 0.83; <2015 versus ≥2015; 95% CI 0.34-2.00; *P* 0.674). The final multivariable model met the proportional hazard assumptions (Schoenfeld's global *P* 0.5281).

Confirmed CKD with 2 eGFR measurements 90 days apart

Out of 52 patients with renal impairment at the time of switch, 5 (9.6%) had a CKD confirmed by a second eGFR measurement <60 ml/min/1.73m^2 at least three months apart. By the time of study closure, 26 participants (50%) were still on active follow-up, 15 participants (28.9%) were lost to follow-up, nine participants (17.3%) died and two participants (3.9%) transferred out to other clinic. Among the five participants with confirmed CKD at the time of switch, by the time of study closure, 2 participants were on active follow-up, 2 participants were lost to follow-up and 1 participant died.

Out of 41 patients with development of renal impairment after switch, 9 (22%) had a CKD confirmed by a second eGFR measurement <60 ml/min/1.73m^2 at least three months apart. The median time to development of a confirmed CKD was 1.9 years (IQR 1.5-2.4). At the time of switch, 4 participants were prescribed abacavir (ABC), didanosine (ddl) and LPV/r, 4 participants were prescribed TDF, FTC, and LPV/r and 1 participant was prescribed TDF, FTC, and ATV/r combination. By the time of study closure, seven participants (17.1%) had at least one improved eGFR measurement ≥60 ml/min/1.73m^2, thus most likely an AKI, one participant died and one participant still had eGFR <60 ml/min/1.73m^2.

Discussion

In this prospective cohort study in rural sSA, we found an incidence of renal impairment of 22 per 1,000 person-years (16.1-29.8) among participants under second-line treatment during a follow-up of 1,864.10 person-years. We found strong association between developing renal impairment and older age. The association between renal impairment and switch to TDF-based regimen was not statistically significant. At the time of switch – thus failure on first-line treatment – the prevalence of renal impairment was 7.6% and subsequently resolved in about half of these

participants. Risk factors for renal impairment at the time of switch were older age, low BMI, arterial hypertension and total time on ART before the switch to second-line.

The comparison of renal impairment in different settings is challenging due to different laboratory methods for creatinine measurements, different definitions of renal impairment and different formula for calculation of eGFR [93]. A study reporting data from a community survey done in rural Kenya and Uganda reported a prevalence of CKD (defined as eGFR <60 mL/min/1.73m^2 and/or proteinuria at a single measurement) in the general population of 6.8% with HIV infection being a risk factor (adjusted prevalence ratio 1.58 (1.11-2.24)) [286]. In a cross-sectional population study conducted in four African countries (South Africa, Burkina Faso, Kenya and Ghana) using the same definition [284] CKD was slightly higher (10.7%). A study from Tanzania [271] reported a CKD prevalence of 13.6% in elderly people (40-60 years) presenting to an outpatient clinic. In a previous study from our center - using the same definition as in this study - the prevalence of renal impairment among 1093 newly diagnosed PLWH was lower with 6.6% in patients under first-line treatment [102]. The increase to 7.6% from our current study could reflect increasing age of patients, selection of failing patients with higher risk of other comorbidities or possibly be drug-related. However, the previous two studies [271,284], defined CKD using a single measurement of eGFR <60 mL/min/1.73m^2 and/or proteinuria hence might lead to slight overestimation of CKD compared to our study [102].

Among PLWH treated with bPI-regimens from developed countries the risk of renal impairment and CKD is increased [134,139]. In a study from the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) CKD developed in 5.9% of patients on Atazanavir or Darunavir treatment (incidence rate, 10.0/1000 person-years (95% CI, 9.5-10.4/1000 person-years)) during a median follow-up of 6.8 years (5.4-7.1) [139]. This incidence is slightly lower compared to the results from our study, however, the authors defined CKD as having an eGFR <60 mL/min/1.73m^2 on two measurements three months apart. In sSA, there are limited studies to evaluate the long term effects of bPIs on the kidney - mostly due to the lack of pharmacovigilance systems in the region [274,275,287]. This is of public health importance since the burden of CKD is on the rise in the region and it is associated with a high mortality and morbidity among PLWH [268,269].

Age is a well-documented risk factor for renal impairment. In this study, the odds of having renal impairment at the time of switch to second-line increased by 55% for every 10 years increase in age. Studies from comparable settings have shown a similar association [102,271,288]. In our study, participants with a low BMI at the time of switch had almost 3 times higher odds of having renal impairment, which is likely explained by the fact that participants had advanced disease at the time of switch due to immunological or clinical treatment failure. Additionally, previous

studies showed an increased risk of renal impairment and CKD among people with a low BMI [289]. This is a public health concern since low BMI is associated with high mortality among CKD patients [290]. Moreover, participants who were diagnosed with arterial hypertension had more than twice the odds of having CKD at the time of switch as previously reported [102,285]. This is worrisome since patients with renal impairment have increased risk of developing cardiovascular diseases [291,292]. Interestingly, each year of increase in ART use before the switch, reduced the risk of renal impairment by 22% at the time of switch. This could be due to the fact that more than half of our patients present at the clinic with advanced HIV disease and patients under longer-term treatment are usually more stable [102,277,278,293].

The association between developing renal impairment and older age was confirmed also in patients developing renal impairment while being on a bPI as previously reported [102,271]. At the same time, we observed an association between renal impairment and being switched to a bPI-regimen with a TDF-backbone versus a non-TDF backbone, although this was not statistically significant. The association of TDF and renal impairment is well known [276,294,295]. Nevertheless, this is an important finding since most treatment guidelines in sSA recommend the use of TDF- based regimens as both first-line and second-line treatments [274,275]. The time point of switch to bPI-regimens reflected mostly immunological or clinical failure under first-line therapy and less virological failure (which usually precedes immunological failure), as routine HIV-1 RNA viral load testing was implemented only in 2018. The reason for raised creatinine levels therefore might have been concomitant diseases or an HIV-associated nephropathy. However, analyzing biobanked samples in retrospect in a previous study from the same cohort, we documented virological failure in less than half of patients (79/185 (42%)) being switched to second-line treatment based on immunological or clinical failure [296]. This could be due to the fact that fact before rollout of universal monitoring of HIV-1 RNA viral load, immunological or clinical failure was defined using CD4 cell count and WHO stage hence led to misclassification of patients with treatment failure [297].

This study highlights that renal impairment is of clinical relevance at the time of switch from first-line treatment, as well as after switch to bPI-regimens - thus signaling a clear need for i) improved awareness of kidney diseases in this setting; ii) more regular creatinine measurements; iii) improved history taking of concomitant drugs, and iv) developing improved pharmacovigilance activities.

In this study, we faced several limitations. Firstly, our definition of renal impairment is based on a single-point measurement of serum creatinine. Thus, we could not differentiate well between acute and chronic kidney failure for all patients due to lack of follow-up measurements. Despite

recommendations by treatment guidelines, routine serum creatinine measurements are still not done in most of sSA due to logistic challenges, costs and shortages of reagents and machine-breakdowns. Also, patients face challenges to come to frequent visits due to high transport costs and daily responsibilities. Secondly, 22% of participants at the time of switch and almost 12% during follow-up had no serum creatinine measurements, which could represent a selection bias. As per guidelines patients who regularly visit the clinic would eventually receive a creatinine measurement with documentation. However, those not returning to the clinic could die from kidney failure. Thirdly, we did not systematically collect information on the use of traditional medicines, which is a potential differential reason for renal impairment. In a previous study, 70% of patients with CKD were reported to use traditional medicine in Tanzania [114]. Fourthly, we did not collect urine samples, therefore, information on proteinuria could not be evaluated in our study hence might lead to underestimation of the prevalence of renal impairment among our patients. Finally, since we conducted an observational study, there may be unmeasured confounders that we are unable to account for hence may have affected our results.

Conclusion

In sSA, PLWH who develop treatment or clinical failure have limited ART options for the second-line treatment. Our study shows a high prevalence of renal impairment at the time of switch from first-line ART to bPI and a high incidence of renal impairment after switch to bPI-regimens. Additionally, our findings support strong associations between renal impairment and older age, BMI, arterial hypertension and time on ART before the switch. Given the need for lifelong ART, these data support the implementation of universal routine monitoring of renal function, the need of follow-up measurements improved pharmacovigilance monitoring.

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The Kilombero and Ulanga Antiretroviral Cohort study group (KIULARCO): Aschola Asantiel[1], Farida Bani[1], Manuel Battegay[3,5], Anna Eichenberger[1,2], Adolphina Chale[1,4], Gideon Francis[4], Hansjakob Furrer, Anna Gamell[2,3], Tracy R Glass[2,3], Speciosa Hwaya[4], Aneth V. Kalinjuma[1], Bryson Kasuga[4], Andrew Katende[1,4], Namvua Kimera[1], Yassin Kisunga[1], Thomas Klimkait[3], Emilio Letang[2], Ezekiel Luoga[1,4], Herry Mapesi[1,2,3,4], Mengi Mkulila[4], Julius Mkumbo[1], Margareth Mkusa[4], Dorcas K Mnzava[1,], Getrud Joseph Mollel[1,4], Lilian Moshi[1,4], Germana Mossad[4], Dolores Mpundunga[4], Athumani Mtandanguo[1,4], Selerine Myeya[1,4], Sanula Nahota[1], Robert C. Ndege[1,4], Agatha Ngulukila[1], Alex John Ntamatungiro[1], Amina Nyuri[1], Daniel Henry Paris[2,3], Leila

Samson[1,4], Juerg Utzinger[2,3], Fiona Vanobberghen[2,3], John Wigay[1,4], Herieth Ismael Wilson[1,4], Elizabeth Senkoro[1,4] and Maja Weisser[1,2,3,5].

Affiliations:

[1]Ifakara Health Institute, Ifakara branch, Ifakara, United Republic of Tanzania
[2]Swiss Tropical and Public Health Institute, Basel, Switzerland
[3]University of Basel, Basel, Switzerland
[4]St. Francis Referral Hospital, Ifakara, United Republic of Tanzania
[5]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Basel, Switzerland

Lead author of KIULARCO Study Group: Prof. Maja Weisser (m.weisser@unibas.ch).

Authors' contribution

HM, DHP, MB and MW have contributed in conception and design of the study. HM perform statistical analysis. HM , MW and DHP wrote the first draft of the manuscript. DHP, MB and MW supervised the work. JO, FF, HIW, TB, ES, RN, FV,TRG and DHP were involved in revising the manuscript for important intellectual content. All authors read, revised, and approved the final manuscript submitted.

Competing interests

All authors declare that they have no competing interests.

Figure 7. Participants' flow chart

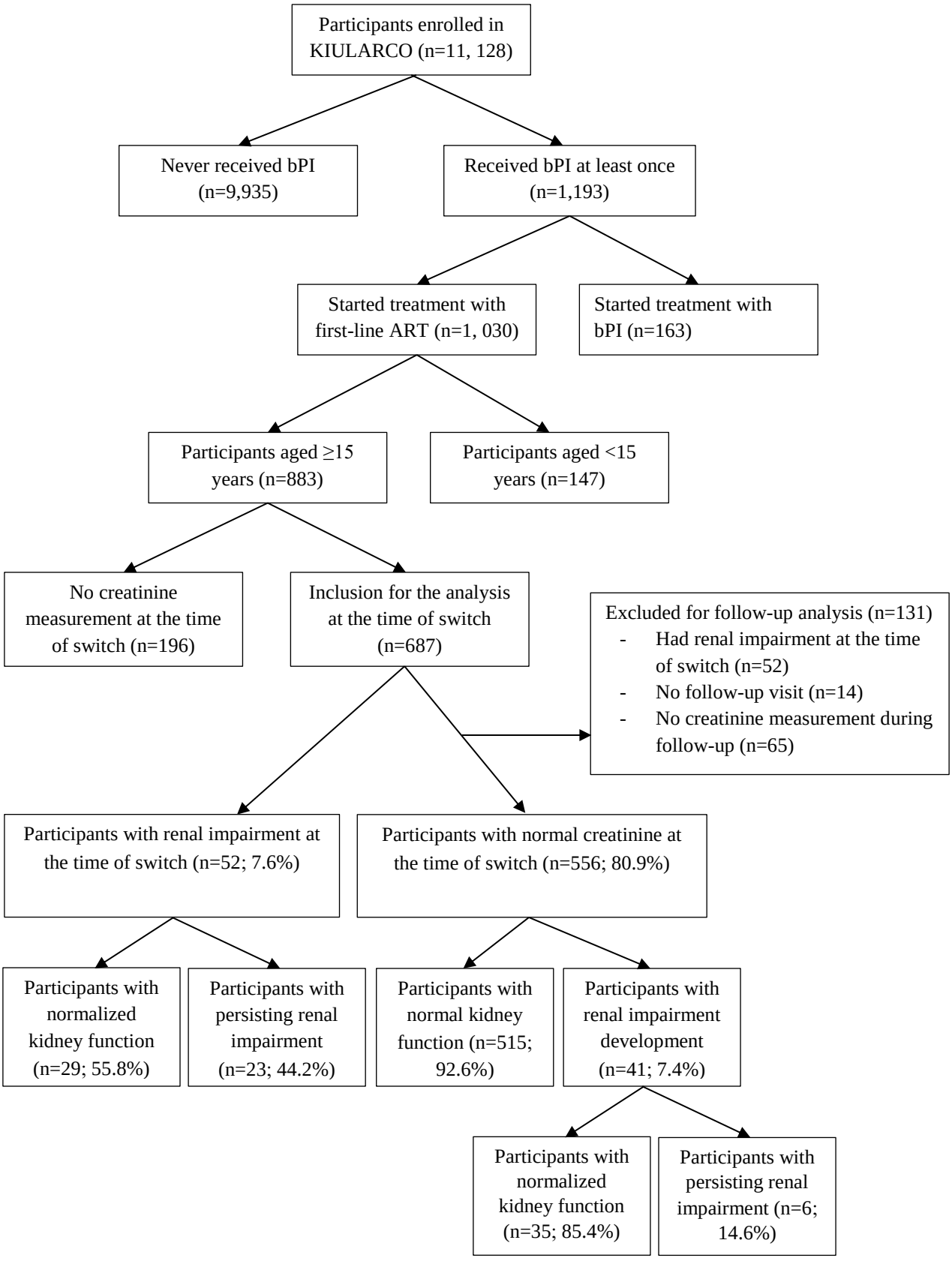

Table 3. Characteristics of the 687 patients at the time of switch to second-line treatment

	Total n=687	Normal kidney function at baseline (eGFR ≥60 ml/min/1.73m²) n=635	Renal impairment at baseline (eGFR <60 ml/min/1.73m²) n=52
Sex			
Male	251 (36.5)	234 (36.9)	17 (32.7)
Female	436 (63.5)	401 (63.2)	35 (67.3)
Age, years, Median (IQR)	40.9 (33.17 - 48.48)	40.8 (32.5 – 48.3)	43.7 (36.2 – 57.2)
WHO Stage			
I	119 (17.3)	116 (18.3)	3 (5.8)
II	145 (21.1)	136 (21.4)	9 (17.3)
III	234 (34.1)	219 (34.5)	15 (28.9)
IV	183 (26.6)	161 (25.4)	22 (42.3)
Missing	6 (0.9)	3 (0.5)	3 (5.8)
BMI (Kg/M²)			
<18.5	115 (16.7)	97 (15.3)	18 (34.6)
≥18.5 – 24.9	364 (53.0)	341 (53.7)	23 (44.2)
≥25	140 (20.4)	133 (20.9)	7 (13.5)
Missing	68 (10.0)	64 (10.1)	4 (7.7)
CD4 cell count (cells/mm3)			
<200	358 (52.1)	260 (40.9)	30 (57.7)
≥200	290 (42.2)	342 (53.9)	16 (30.8)
Missing	39 (5.7)	33 (5.2)	6 (11.5)
Tuberculosis			
Yes	61 (8.9)	52 (8.2)	9 (17.3)
No	623 (90.7)	581 (91.5)	42 (80.8)
Missing	3 (0.4)	2 (0.3)	1 (1.9)
Arterial hypertension			
Yes	116 (16.9)	101 (15.9)	15 (28.9)
No	560 (81.5)	527 (83.0)	33 (63.5)
Missing	11 1.6)	7 (1.1)	4 (7.7)
ART before switch			
AZT+3TC+NVP	145 (21.1)	139 (21.9)	6 (11.5)
AZT+3TC+EFV	93 (13.5)	90 (14.2)	3 (5.8)
TDF+FTC+EFV	90 (13.1)	81 (12.8)	9 (17.3)
TDF+FTC+NVP	26 (3.8)	23 (3.6)	3 (5.8)
TDF+3TC+EFV	302 (44.0)	284 (44.7)	18 (34.6)
ABC+3TC+EFV	24 (3.5)	13 (2.0)	11 (21.2)
Other first-line ART	7 (1.0)	5 (0.8)	2 (3.8)
Viral load (copies/ml)*			
<1000	252 (36.7)	238 (37.5)	14 (26.9)
≥1000	141 (20.5)	131 (20.6)	10 (19.2)
Missing	294 (42.8)	266 (41.9)	28 (53.9)
Time on ART before switch (years)			
Median (IQR)	3.6 (1.5-6.0)	3.7 (1.6-6.1)	1.48 (0.6 – 4.2)
Calendar year of switch			
<2015	363 (52.8)	338 (53.2)	25 (48.1)

≥2015	324	(47.2)	297	(46.8)	27	(51.9)

Abbreviations: eGFR, estimated glomerular filtration rate; BMI, body mass index; WHO, World Health Organization; IQR, inter quartile range; ART, antiretroviral treatment; AZT, zidovudine; 3TC, lamivudine; NVP, nevirapine; EFV, efavirenz; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; ABC, abacavir.

**requested only in patients with suspected treatment failure and those who were involved in s specific study*

Table 4. Univariate and multivariate logistic regression model for predictors of renal impairment at switch to second line ART (n = 687)

Variable	Univariate model Unadjusted OR (95% CI)	P value	Multivariate model Adjusted OR (95% CI)	P value
Age (per 10 years)	1.43 (1.15-1.79)	0.002	1.55 (1.15-2.11)	0.004
BMI (Kg/M^2)				
≥18.5	1			
<18.5	2.84 (1.53-5.28)	0.001	2.80 (1.28-6.14)	0.010
CD4 count (cells/mm^3)				
≥200	1		1	
<200	2.47 (1.32-4.62)	0.005	1.29 (0.63-2.66)	0.492
WHO stage				
I or II	1		1	
II or IV	2.04 (1.05-4.00)	0.036	1.29 (0.59-2.84)	0.520
Arterial hypertension				
No	1		1	
Yes	2.37 (1.24-4.53)	0.009	2.33 (1.03-5.28)	0.043
Tuberculosis diagnosis				
No	1		1	
Yes	2.39 (1.10-5.19)	0.027	2.11 (0.86-5.20)	0.103
Total time on ART before the switch (per one year)	0.81 (0.72-0.92)	0.001	0.78 (0.67-0.91)	0.002
Calendar year of switch				
<2015	1		1	
≥2015	1.22 (0.70-2.16)	0.475	1.17 (0.59-2.31)	0.650

Abbreviations: BMI, body mass index; ART, antiretroviral treatment; OR, odds ratio; CI, confidence interval; WHO, World Health Organization

Table 5. Univariate and multivariate Cox proportional hazards for predictors of renal impairment (with baseline covariates) (n = 556)

Variable	Univariate model Unadjusted HR (95% CI)	P value	Multivariate model Adjusted HR (95% CI)	P value
Age (per 10 years)	1.80 (1.41-2.31)	<0.001	2.22 (1.56-3.15)	<0.001
BMI (Kg/M^2)				
≥18.5	1		1	
<18.5	1.12 (0.49-2.52)	0.791	0.96 (0.37-2.43)	0.924
CD4 count (cells/mm^3)				
≥200	1		1	
<200	1.01 (0.54-1.90)	0.967	0.87 (0.41-0.84)	0.715
WHO stage				
I or II	1		1	
III or IV	1.74 (0.89-3.41)	0.107	1.83 (0.83-4.01)	0.133
Arterial hypertension				
No	1		1	
Yes	1.94 (0.97-3.90)	0.060	1.19 (0.55-2.61)	0.657
Tuberculosis diagnosis				
No	1		1	
Yes	3.08 (1.37-6.95)	0.007	2.04 (0.75-5.55)	0.161
Total time on ART before the switch (per one year)	0.98 (0.78-1.22)	0.842	0.97 (0.73-1.27)	0.807
Calendar year of switch				
<2015	1		1	
≥2015	0.78 (0.41-1.49)	0.450	0.83 (0.34-2.00)	0.674
First second-line ART				
Non-TDF– based	1		1	
TDF-based	1.87 (0.99-3.55)	0.055	2.12 (0.93-4.80)	0.072

Abbreviations: BMI, body mass index; ART, antiretroviral treatment; HR, hazard ratio; CI, confidence interval; WHO, World Health Organization; TDF, tenofovir disoproxil fumarate

Manuscript 3. Body Weight Evolution among HIV-infected Patients Starting Antiretroviral Therapy with Dolutegravir or Efavirenz Based Regimens in Rural Tanzania

Herry Mapesi[1,2,3], Fiona Vanobberghen[2,3], James Okuma[2,3], Anna Eichenberger[2], Herieth Ismael Wilson[1,4], Tracy Renée Glass[2,3], Daniel Henry Paris[2,3] and Manuel Battegay[3,5], Maja Weisser[1,2,3,5*] and Fabian Franzeck[5*], on behalf of the KIULARCO Study Group

[1]Ifakara Health Institute, Ifakara branch, Ifakara, United Republic of Tanzania

[2]Swiss Tropical and Public Health Institute, Basel, Switzerland

[3]University of Basel, Basel, Switzerland

[4]St. Francis Referral Hospital, Ifakara, United Republic of Tanzania

[5]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Basel, Switzerland

*Equal contribution

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Abstract

Background: Studies from Europe and North America have demonstrated excess weight gain to be associated with dolutegravir-based antiretroviral treatment (ART). Data reporting on weight changes after large-scale rollout of dolutegravir as first-line treatment in sub-Sahara Africa are lacking.

Methods: We included ART-naïve, non-pregnant adults (≥18 years) enrolled in the Kilombero and Ulanga Antiretroviral Cohort (KIULARCO) in Ifakara, Tanzania initiating efavirenz-based (from December 2016) or dolutegravir-based ART (from March 2019). We used linear mixed-effect modelling to assess weight changes overtime. Logistic regression models were used to assess risk factors associated with weight gain ≥10% after 12 months of treatment.

Results: Among 1,025 participants, 709 (69.2%) started treatment with efavirenz and 316 participants (30.8%) dolutegravir-based regimens. In an adjusted analysis, participants in the dolutegravir group gained 0.48 kg/month (95% CI, 0.39 to 0.58) and participants receiving efavirenz gained 0.28 kg/month (95% CI, 0.22-0.34) within the first year, with a between-group difference of 0.20 kg/month (95% CI, 0.09-0.32, $P<0.001$). In participants who started ART with a normal BMI, those in dolutegravir gained 0.46 kg/month (95% CI, 0.34-0.57) compared to 0.24 kg/month (95% CI, 0.17-0.31) in the efavirenz group, with a between-group difference of 0.22 kg/month (95% CI, 0.08-0.35, $P<0.001$). Factors associated with ≥10% increase of body weight at 12 months were use of dolutegravir, being female, WHO stage III/IV, and low CD4+ cell count at baseline.

Conclusion: Initiating a dolutegravir-based ART regimen was associated with more weight gain compared to efavirenz-based regimens during the first 12 months of treatment, confirming observations from industrialized settings. Weight gain of ≥10% was associated with use of dolutegravir, level of immunosuppression, BMI at ART initiation and being female.

Background

According to the World Health Organization (WHO) estimates, there are around 1.9 billion adults, who are overweight globally and among them over 650 million are obese [173]. Excessive weight gain and obesity have been associated with increased risk of development of cardiovascular diseases (CVDs), chronic kidney diseases, cancer, metabolic and musculoskeletal disorders [41,298].

Over the years, the prevalence of obesity has been increasing among people living with HIV (PLHIV) [299,300]. This is of additional concern, since PLHIV have an increased longer-term risk of developing CVDs and metabolic disorders such as diabetes mellitus compared to HIV-negative population [41,51,301,302]. An initial increase in body weight among PLHIV after initiation of antiretroviral treatment (ART) corresponding to a 'return-to-health effect' has been well described [46,53]. With the current increase in HIV awareness and 'test and treat' strategy, many patients are likely to start antiretroviral treatment (ART) with either a normal weight or overweight [62]. However, excessive weight gain and obesity have been associated with poor outcomes among PLHIV - particularly in those who start ART while already overweight or obese [41,45,303].

Dolutegravir-based regimens are being rolled out as first-line therapy in most of low-income and middle-income countries due to its high efficacy, favorable safety profile and lower price compared to previously used ART regimens [32,304]. In Tanzania, just like most countries, dolutegravir-based regimens are recommended as first-line ART [27,30–33]. In the 2019 update of the HIV treatment guidelines [305], the WHO cautioned about the potential implications of possible excessive weight gain associated with dolutegravir. The recommendation was based on increasing evidence from randomized clinical trials and observational studies indicating higher weight gain with the use of dolutegravir-based compared to other ART regimens [46,53,54,57,137]. While certain demographics such as black ethnicity and female gender were underrepresented in the majority of the studies, they seem to be disproportionately affected by excessive weight gain [306,307].

The NAMSAL clinical trial, reported a median weight gain of 5 kg among participants randomized in dolutegravir group compared to 3 kg among participants in low dose efavirenz (400mg) group, both combined with tenofovir disoproxil fumarate (TDF) and lamivudine with an increased risk of incident obesity in the dolutegravir group [306]. The ADVANCE clinical trial, weight increase was 6.4 kg among females in the tenofovir alafenamide fumarate (TAF)/emtricitabine/dolutegravir group, 3.2 kg in the TDF/emtricitabine/dolutegravir group,

and 1.7 kg in the standard-care group (TDF/emtricitabine/efavirenz) 48 weeks after treatment initiation [137]. Additional results from same trial have indicted a strong association between weight gain and strong metabolizers of the *CYP2B6* metabolizer genotype, among participants in efavirenz group [308].

Apart from the two clinical trials, there is lack of longitudinal data has reported weight change among PLHIV starting ART using dolutegravir-based in sub-Saharan Africa. Using data from the Kilombero and Ulanga Antiretroviral Cohort (KIULARCO) we evaluated weight change among newly diagnosed PLHIV starting treatment with either dolutegravir-based or efavirenz-based regimen in rural Tanzania. Additionally, we assessed risk factors associated with increased body weight ≥10% after 12 months of treatment.

Methods

Study design and population

The KIULARCO is an ongoing cohort of PLHIV in rural Tanzania established in 2005. All PLHIV who attend at the Chronic Diseases Clinic of Ifakara (CDCI) at the St. Francis Referral Hospital are offered to participate in the cohort. More than 11, 500 participants have been enrolled in the cohort with more than 4,500 on active follow-up. Sociodemographic, clinical and laboratory values are recorded at the time of starting ART and during follow-up visits into an electronic medical records system. Details of the cohort have been published elsewhere [277,278].

For the present study, we included ART-naïve, non-pregnant adults (≥18 years) enrolled in the KIULARCO and initiating and maintaining efavirenz-based (from December 2016 until December 2020) or dolutegravir-based ART (from March 2019 until December 2020). The reason for start of inclusion from December 2016 was the adoption of the 'test and treat' strategy in Tanzania following the updated WHO treatment guidelines [305,309]. We included patients with a weight measurement within +/- 28 days of starting ART with availability of at least one weight measurement during follow-up visits. We excluded women with a recorded pregnancy within 18 months (date of visit documenting the pregnancy) of starting ART (to account for the delayed recording of pregnancies / reduce the risk of including women who might have been unknowingly pregnant during the first year).

Outcomes and definitions

The primary aim of this study was to compare weight changes among ART-naïve patients starting treatment with either dolutegravir-based or efavirenz-based regimens. Secondary outcomes were to assess predictors associated with weight gain ≥10% after 12 months of treatment.

While there is no established cut-off of what constitutes disproportionate weight gain, previous studies mostly used ≥10% of pre-ART baseline weight, which we think is clinically meaningful [57]. Additionally, we assessed the proportion of participants who changed their body mass index (BMI) categories after 12 months of treatment compared to the baseline BMI. We categorized BMI into the following categories; underweight or wasting (<18.5 kg/m^2), normal weight (≥18.5-24.9 kg/m^2), overweight/obesity (≥25 kg/m^2) [183].

For all demographics and laboratory measurements, we considered the closest one to the date of ART initiation. Weight at ART initiation was defined as a weight measured on the date of ART initiation +/- 28 days. During follow-up, weight was measured during every visit. Distance to the clinic was defined as an approximate distance (in kilometres [km]) from the participant's residence to the St. Francis Referral Hospital and was categorized as either 1<25, ≥25<50, or ≥50 km. WHO Stage, CD4+ cell count which were categorized according to WHO criteria for advanced HIV disease (WHO stage I/II vs III/IV and CD4+ cell count <200 vs ≥200 cells/mm^3 [280].

Statistical analysis

We summarized continuous variables using median and interquartile range (IQR) and categorical variables using frequencies and percentages. We used a linear mixed-effects model with random intercepts for each participant and random slopes for time on to estimate the mean weight changes over time. Additionally, an interaction term between the two groups (either dolutegravir or efavirenz group) and time was placed in order to assess the weight changes over time between the two groups. We plotted trajectories of weight changes over time in order to assess the relationship between weight change and time (Supplementary figure 9), which was judged to be linear. Therefore, no transformation of time was applied. To account for different weight gain among participants with different BMI categories, we stratified the analysis in three different BMI categories (underweight, normal weight and overweight/obesity). The final multivariable model was adjusted for predefined baseline characteristics that are associated with weight gain; weight at start of ART, age at start of ART, sex, distance to the clinic, WHO stage, CD4+ cell count and tuberculosis diagnosis at the time starting ART.

For participants who had weight measurement after 12 months of treatment, we used logistic regression model to assess risk factors associated with weight gain ≥10%. The baseline weight was defined as the patients' weight measurement during ART initiation. Weight after 12 months of treatment was defined as the closest weight measurement at after 12 (9-15 months) of treatment. The final model was adjusted for weight at start of ART, age at start of ART, sex,

distance to the clinic, WHO stage, CD4+ cell count and tuberculosis diagnosis at the time of starting ART.

Finally, we assessed the BMI categories changes at between the time of ART initiation and after 12 months of treatment. The baseline BMI measurement was defined as the patients' BMI measurement during ART initiation. BMI after 12 months of treatment was defined as the closest BMI after 12 months (9-15) of treatment. All statistical analyses were done using Stata version 15.1 (StataCorp LP, College Station, Texas, USA).

Ethics statement

All patients' data were anonymized before we conducted analysis. At enrolment in KIULARCO, a written informed consent is sought from all study participants; those who refused consent were excluded. Ethical approval was obtained from the Ifakara Health Institute review board (IHI/IRB/No16-2006), the National Health Research Committee of the National Institute of Medical Research of Tanzania (NIMR/HQ/R.8a/Vol.IX/620) with yearly renewal, as well as from the Ethikkomission Nordwest und Zentralschweiz (EKNZ; Switzerland).

Results

Baseline characteristics

A total of 2,677 participants were in enrolled in KIULARCO between December 2016 and December 2020. We included 1,025 participants in the analysis whereof 709 (69.2%) in the efavirenz group and 316 (30.8%) in the dolutegravir group (Figure 8). Baseline characteristics are shown in Table 6. The median age at start of ART was 39.2 years (Interquartile range [IQR] 31.6-39.2), 622 (60.7%) were female and 588 (57.4%) were living close to the clinic (1-25 km). The majority of participants (61.9%) had normal BMI, 14.2% were underweight, and 23.9% were overweight/obese. Around 35.2% of participants had a CD4+ cell count between 200-499 cells/mm^3. Almost two-thirds of participants had WHO stage I or II and 4.4% were diagnosed with tuberculosis at the time of starting ART.

Participants in the dolutegravir group had a higher median baseline weight (57.2 versus 54.7 kg) and were slightly older (40.3 versus 38.9 years) compared to the efavirenz group. Compared to the participants in the efavirenz group, those who started ART with dolutegravir were more likely to live close to the clinic (64.6 versus 54.2%) and were more likely to present with a WHO stage I or II (71.8 versus 61.3%). More participants on efavirenz presented with a normal BMI compared to those on dolutegravir (64.6 versus 56.0%, respectively) and were less likely to be overweight/obese (21.9% vs 28.5%, respectively). The majority of participants in both efavirenz

and the dolutegravir groups started a treatment combination with lamivudine and tenofovir disoproxil fumarate (TDF) (82.4% and 96.2%, respectively).

Changes in weight

In the adjusted analysis, participants who started ART in the dolutegravir group gained 0.48 kg/month (95% CI, 0.39 to 0.58, *P* <0.001) and participants in efavirenz group gained 0.28 kg/month (95% CI, 0.22 to 0.34, *P* <0.001), with a between-group difference of 0.20 kg/month (95% CI, 0.09 to 0.32, *P* <0.001) (Table 8). In order to understand weight changes after starting ART among different BMI categories, we stratified the analysis according underweight, normal weight and overweight/obese (Figure 10). In the adjusted analyses, participants in the dolutegravir group who were underweight at the time of starting ART gained 0.80 kg/month (95% CI, 0.51 to 1.09, *P* <0.001) compared 0.67 kg/month (95% CI, 0.47 to 0.88, *P* <0.001) in the efavirenz group with a between-group difference of 0.13 kg/month (95% CI, -0.23 to 0.48, *P* =0.477). For participants who started treatment with a normal BMI, those in dolutegravir gained 0.46 kg/month (95% CI, 0.34 to 0.57, *P* <0.001) compared to those in efavirenz who gained 0.24 kg/month (95% CI, 0.17 to 0.31, *P* <0.001) with a between group difference of 0.22 kg/month (95% CI, 0.08 to 0.35, *P* =0.001). For participants who were overweight/obese, those in dolutegravir gained 0.34 kg/month (95% CI, 0.14 to 0.54, *P* =0.001) compared to 0.19 kg/month (95% CI, 0.06 to 0.32, *P* =0.003) in efavirenz with a between-group difference of 0.15 kg/month (95% CI, -0.09 to 0.38, *P* =0.225).

Risk Factors for ≥10% Weight Increase in Participants Initiating ART

Table 3 shows risk factors associated with weight gain of ≥10% from starting of ART to 12 months of treatment (9-15 months). Among the 508 participants who had a weight measurement after 12 months of treatment 168 (33%) gained ≥10% (Supplementary table 7).

In a multivariable model, participants who started treatment in dolutegravir had almost twice the odds of gaining ≥10% of body weight compared to the efavirenz group (odds ratio [OR], 1.91 [95% CI, 1.13-3.23]; *P* <0.015). Compared to male participants, females had almost three times the odds of gaining ≥10% (OR, 2.86 [95% CI, 1.72-4.75]; *P* <0.001). Furthermore, we found a strong association between gaining weight and presenting with a WHO stage III/IV versus I/II (OR, 2.67 [95% CI, 1.63-4.38]; *P* <0.001) a low CD4+ cell count <200 cells/mm^3 vs 200-499 cells/mm^3 (OR, 2.47 [95% CI, 1.51-4.05]; *P* =0.002). Contrary, participants who were overweight/obese were less likely to gain weight (OR, 0.53 [95% CI, 0.29-0.98]; *P* =0.042). We did not find an association between weight gain and age, distance to the clinic, presenting with low BMI (<18.5 kg/m^2), high CD4+ cell count and TB diagnosis.

Change in BMI categories over time

To understand the changes in BMI category after one year of treatment between the participants in the two groups, we compared the BMI categories at baseline and the BMI measured closest to 12 months of treatment (Table 10). The majority of participants who were underweight at the time of starting ART, changed to a normal BMI (dolutegravir group versus efavirenz group (66.7% vs 77.6%)). The proportion of participants who were underweight at the start of ART and remained in the same categories after 12 months of treatment were 27.8% in the dolutegravir group vs 18.2% in the efavirenz group. Participants who started underweight and changed to overweight/obesity were 5.6% in the dolutegravir group vs 2.2% in the efavirenz group.

The majority of participants, who had a normal BMI at the time of ART start, remained within the same BMI category (dolutegravir group versus efavirenz group (72.6% vs 78%)). The proportion of participants, who had a normal BMI at the start of ART and became overweight/obese after 12 months of ART was 24.7% vs 18.8% in the dolutegravir vs efavirenz group, respectively. Few participants with a normal BMI at treatment start changed to underweight (dolutegravir group 2.7% versus efavirenz group 3.2%).

The majority of participants, who were overweight/obese at the time of ART start, remained in the same category within the first 12 months of ART (dolutegravir group 86.2% versus efavirenz group 79.8%). The proportion of participants who were overweight/obese and changed to normal weight were 13.8% in the dolutegravir group versus 19.2% in the efavirenz group. Only one participant in the efavirenz group who was overweight at the time of starting ART changed her BMI category to underweight.

Discussion

In this observational longitudinal cohort study from rural Tanzania, we demonstrated an overall weight gain among ART-naïve PLHIV starting ART over the first 12 months. Weight gain was more pronounced among participants who started in dolutegravir-based regimens compared to participants who started in efavirenz-based regimen, which was particularly evident among participants with a normal BMI at ART start. Factors associated with a weight gain ≥10% after 12 months of ART were starting in a dolutegravir-based regimen, being female, having WHO stage III/IV, and CD4+ cell count <200 cells/mm^3. The majority of participants who were underweight at baseline had a normal BMI during at 12 month on ART, while participants who had either a normal BMI or an overweight/obese BMI at ART start remained in the same BMI category at 12 months.

The increased weight gain of participants in dolutegravir-based regimens compared to an efavirenz-based regimen has been reported from studies performed in the United States and in South Africa [57,137]. An excessive weight gain (≥10%) documented in a 33% of participants in our study is worrisome, since obesity [310] contributes to an increased risk of cardiovascular diseases and metabolic disorders [41,298]. Participants who were underweight at the time of starting ART had more weight gain compared to other BMI categories, although the difference between the two groups was not significant. This most likely is explained by a return-to-health effect, which has been reported previously [46,53]. In our study, participants starting in a dolutegravir-based regimen had a higher median baseline weight than participants who started treatment in efavirenz-based regimen. This likely is due to more recent enrolment of patients starting on dolutegravir with improved screening programs for HIV/AIDS in the communities and therefore earlier presentation to the clinics and a lower proportion of advanced HIV disease compared to previous years [5]. Moreover, a recent study by Griesel *et al*, has reported a strong association between weight gain and strong metabolizers of the *CYP2B6* metabolizer genotype, among participants in efavirenz-based regimen [308]. Hence, the pronounced weight gain in dolutegravir group could be rather due to 'return to health' effect and not a side effect of the individual drug.

Besides dolutegravir, being female was associated with a weight gain of ≥10% after 12 months on ART. This has been reported in other studies [46,59,311,312]. In sub-Saharan Africa, around 60% of PLHIV patients are females, highlighting the importance of counselling and education on preventive measures such as a physical activity in this patient population [313]. Advanced HIV disease at the time of ART initiation (WHO stage III/IV, and CD4+ cell count <200 cells/mm^3), as a factor associated with weight gain is consistent with results from other studies [46,53] and likely corresponds to a return to health phenomenon as previously reported. The risk of gaining weight of ≥10% was reduced among participants who were overweight/obese at the time of start ART. This is reassuring since excessive weight gain for participants with normal or overweight is associated with an increased risk of non-communicable diseases [41,45,298,303]. Most of the participants who started treatment with a low BMI had normal weight at the time of study closure. This goes in line with return to health effect as previously described [46,53].

Our study has several limitations. The observational study design might lead to some residual bias despite controlling for several potential confounders. Our assessment did not include participants who were switched from efavirenz-based regimen to dolutegravir-based regimes. Previous studies have indicated excessive weight gain among stable and virologically suppressed patients who are switched from efavirenz to intergrase inhibitors [55,59]. In our study we can conclude only on weight gain in patients started newly on ART, which partly is beneficial in those

underweight corresponding to the return to health effect. Additionally, our study did not assess ART switches of the concomitant treatment with nucleoside/nucleotide reverse transcriptase inhibitors, which could also affect weight changes. However, more than 85% of participants were receiving tenofovir and lamivudine or abacavir and lamivudine - the most used backbone in sub-Saharan Africa [62,309]. Therefore, most of the switches were between these two drugs, which we do not expect to cause difference in weight gain. Also, in the cohort no patient was receiving TAF, which has been sown to affect weight gain [138]. Information on body fat composition (peripheral, central fat depots and lean mass) were not routinely collected in KIULARCO. Central obesity has been associated with increased risk of non-communicable diseases and CVDs, however, several studies have indicated that weight gained due to ART rather leads to general weight gain and not central obesity [314,315]. Additionally, information on concomitant weight-modifying medications, lipid and glucose levels as well as physical activities was not routinely collected in KIULARCO.

Our study has several strengths. It is among the first longitudinal studies to evaluate weight change among ART naïve patients starting newly available integrase inhibitors in rural Africa in the first year after ART start. Moreover, we expect data collected within KIULARCO as a rural cohort of PLHIV to be generalizable to similar settings in rural sub-Saharan Africa.

In conclusion, our results indicate that patients who start treatment in a dolutegravir-based regimen gain more weight compared to those starting in an efavirenz-based regimen, confirming observations from industrialized settings. Additionally, we showed association between excessive weight gain and advanced HIV disease at ART start, being female and normal BMI at start of ART. As a return-to-health effect in participants starting on ART is beneficial, further studies should evaluate weight gain among virologically suppressed participant who are switched from efavirenz-based to dolutegravir-based regimen in order to demonstrate weight changes among stable patients. Further investigations are needed to assess the long-term effects of weight gain among newly diagnosed patients such as metabolic changes (dyslipidemia and hyperglycemia). Our findings highlight the importance of a well-functioning pharmacovigilance system to monitor adverse events of new medications in the sub-Saharan Africa region.

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The Kilombero and Ulanga Antiretroviral Cohort study group (KIULARCO): Aschola Asantiel[1], Farida Bani[1], Manuel Battegay[3,5], Anna Eichenberger[1,2], Adolphina Chale[1,4], Gideon

Francis[4], Hansjakob Furrer, Anna Gamell[2,3], Tracy R Glass[2,3], Speciosa Hwaya[4], Aneth V. Kalinjuma[1], Bryson Kasuga[4], Andrew Katende[1,4], Namvua Kimera[1], Yassin Kisunga[1], Thomas Klimkait[3], Emilio Letang[2], Ezekiel Luoga[1,4], Herry Mapesi[1,2,3,4], Mengi Mkulila[4], Julius Mkumbo[1], Margareth Mkusa[4], Dorcas K Mnzava[1,], Getrud Joseph Mollel[1,4], Lilian Moshi[1,4], Germana Mossad[4], Dolores Mpundunga[4], Athumani Mtandanguo[1,4], Selerine Myeya[1,4], Sanula Nahota[1], Robert C. Ndege[1,4], Agatha Ngulukila[1], Alex John Ntamatungiro[1], Amina Nyuri[1], Daniel Henry Paris[2,3], Leila Samson[1,4], Juerg Utzinger[2,3], Fiona Vanobberghen[2,3], John Wigay[1,4], Herieth Ismael Wilson[1,4], Elizabeth Senkoro[1,4] and Maja Weisser[1,2,3,5].

Affiliations:

[1]Ifakara Health Institute, Ifakara branch, Ifakara, United Republic of Tanzania

[2]Swiss Tropical and Public Health Institute, Basel, Switzerland

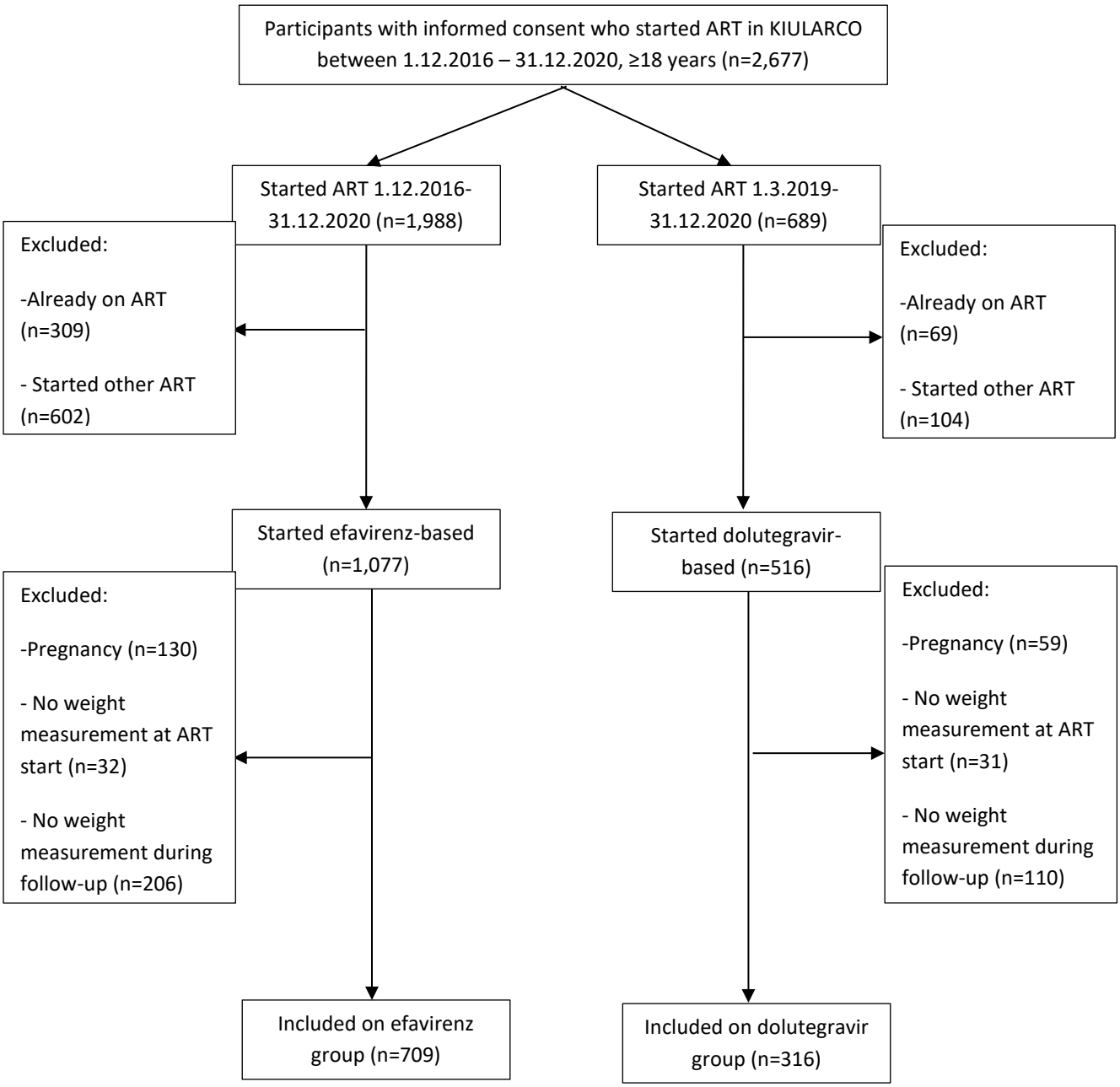
[3]University of Basel, Basel, Switzerland

[4]St. Francis Referral Hospital, Ifakara, United Republic of Tanzania

[5]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Basel, Switzerland

Lead author of KIULARCO Study Group: Prof. Maja Weisser (m.weisser@unibas.ch).

Figure 8. Participants' flow chart



Supplementary figure 9. Relationship between weight change and time

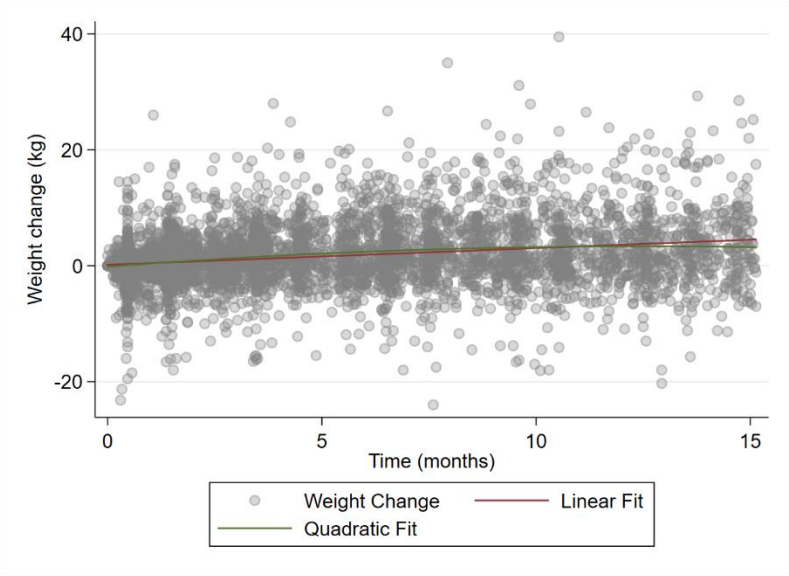
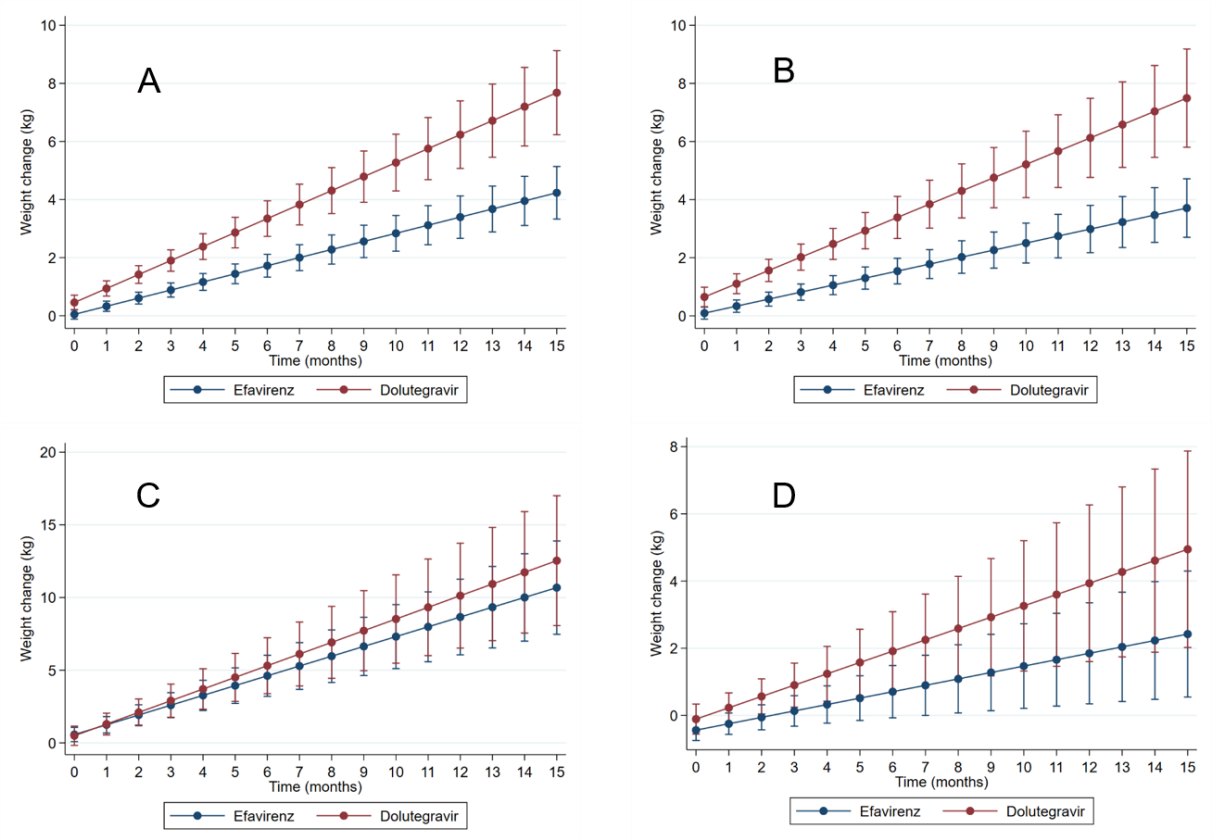


Figure 9. Adjusted mean weight change over time stratified by BMI categories



Mean change in weight after starting treatment with either dolutegravir or efavirenz-based regimens. The final multivariable model was adjusted for weight at ART start, sex, CD4 cell count, WHO stage, age at ART start, and tuberculosis diagnosis. A, All participants. B, Participants with normal BMI (18.5-24.9 kg/m^2). C, Participants who were underweight (<18.5 Kg/m^2). D, Participants who were overweight/obese (≥25 Kg/m^2). Abbreviation: ART: antiretroviral treatment BMI: Body Mass Index

Table 6: Characteristics of patients at ART initiation

	Total (n=1,025)	Started EFV-based regimen (n= 709)	Started DTG-based regimen (n=316)
Weight (Kg), median (IQR)	55.5 (48.5-63)	54.7 (48.2-62.5)	57.15 (49.1-64.4)
Age, years, median (IQR)	39.2 (31.6-39.2)	38.9 (31.6-47.4)	40.3 (31.6-48.3)
Sex			
Male, n (%)	403 (39.3)	277 (39.1)	126 (39.8)
Female, n (%)	622 (60.7)	432 (60.9)	190 (60.1)
Distance to the clinic (km) , median (IQR)			
1 < 25	588 (57.4)	384 (54.2)	204 (64.6)
≥ 25 < 50	237 (23.1)	168 (23.7)	69 (21.8)
≥ 50	163 (15.9)	131 (18.5)	32 (10.1)
WHO stage, n (%)			
I	478 (46.3)	325 (45.8)	153 (48.4)
II	184 (18.0)	110 (15.5)	74 (23.4)
III	245 (23.9)	188 (26.5)	57 (18.0)
IV	84 (8.2)	58 (8.2)	26 (8.2)
BMI (Kg/M²) , n (%)			
Underweight (BMI<18.5)	145 (14.2)	96 (13.5)	49 (15.5)
Normal (BMI ≥18.5 – 24.9)	635 (61.9)	458 (64.6)	177 (56.1)
Overweight and Obese (BMI≥25)	245 (23.9)	155 (21.9)	90 (28.5)
CD4 cell count (cells/mm3), n (%)			
<200	344 (33.6)	250 (35.3)	94 (29.8)
200-499	361 (35.2)	234 (33.0)	127 (40.2)
≥500	198 (19.3)	135 (19.0)	63 (19.9)
First ART regimen, n (%)			
TDF+3TC+EFV	584 (57.0)	584 (82.4)	0(0)
TDF+FTC+EFV	98 (9.6)	98 (13.8)	0(0)
ABC+3TC+EFV	24 (2.3)	24 (3.4)	0(0)
AZT+3TC+EFV	3 (0.3)	3 (0.4)	0(0)
TDF+3TC+DTG	304 (29.7)	0(0)	304 (96.2)
ABC+3TC+DTG	12 (1.2)	0(0)	12 (3.8)
Tuberculosis, n (%)			
Yes	45 (4.4)	29 (4.1)	16 (5.1)
No	966 (94.2)	667 (94.1)	299 (94.6)
Calendar year of ART initiation, n (%)			
2016	26 (2.5)	26 (3.7)	0(0)
2017	311 (30.3)	311 (43.9)	0(0)
2018	310 (30.2)	310 (43.7)	0(0)
2019	225 (21.9)	57 (8.0)	168 (53.2)
2020	153 (14.9)	5 (0.7)	148 (46.8)

Abbreviations: BMI, body mass index; WHO, World Health Organization; IQR, inter quartile range; ART, antiretroviral treatment; 3TC, lamivudine; EFV, efavirenz; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; ABC, abacavir; DTG, dolutegravir.

Table 7s: Characteristics at ART initiation of patients with weight measurement after one year of treatment

	Total (n=508)	Started EFV-based regimen (n=388)	Started DTG-based regimen (n=120)
Weight (Kg), Median (IQR)	55.1 (43.6-63.0)	55 (48.8-62.7)	56.8 (49.8-63.7)
Age, years, Median (IQR)	39.4 (32.2-47.5)	38.7 (31.8-46.4)	41.3 (34.3-48.5)
Sex			
Male	197 (38.8)	143 (36.9)	54 (45.0)
Female	311 (61.2)	245 (63.1)	66 (55.0)
Distance to the clinic (km)			
1 < 25	285 (56.1)	204 (52.6)	81 (67.5)
≥ 25 < 50	119 (23.4)	95 (24.5)	24 (20.0)
≥ 50	85 (16.7)	74 (19.2)	11 (9.2)
WHO stage			
I	253 (49.8)	200 (51.6)	53 (44.2)
II	87 (17.1)	52 (13.4)	35 (29.2)
III	114 (22.4)	89 (22.9)	25 (20.8)
IV	42 (8.3)	35 (9.0)	7 (5.8)
BMI (Kg/M²)			
Underweight (BMI<18.5)	62 (12.2)	44 (11.3)	18 (15.0)
Normal (BMI ≥18.5 – 24.9)	323 (63.6)	250 (64.4)	73 (60.8)
Overweight and Obese (BMI≥25)	123 (24.2)	94 (24.2)	29 (24.2)
CD4 cell count (cells/mm3)			
<200	157 (30.9)	122 (31.4)	35 (29.2)
200-499	186 (36.6)	134 (34.5)	52 (43.3)
≥500	98 (19.3)	77 (19.9)	21 (17.5)
First ART regimen			
TDF+3TC+EFV	328 (64.6)	328 (84.5)	0(0)
TDF+FTC+EFV	51 (10.0)	51 (13.1)	0(0)
ABC+3TC+EFV	8 (1.6)	8 (2.1)	0(0)
AZT+3TC+EFV	1 (0.2)	1 (0.3)	0(0)
TDF+3TC+DTG	118 (23.2)		118 (98.3)
ABC+3TC+DTG	2 (0.4)		2 (1.7)
Tuberculosis			
Yes	22 (4.3)	17 (4.4)	5 (4.2)
No	484 (95.4)	369 (95.1)	115 (95.8)
Calendar year of ART initiation			
2016	19 (3.7)	19 (4.9)	0(0)
2017	226 (44.5)	226 (58.3)	0(0)
2018	133 (26.2)	133 (34.3)	0(0)
2019	116 (22.8)	10 (2.6)	106 (88.3)
2020	14 (2.8)	0(0)	14 (11.7)

Abbreviations: BMI, body mass index; WHO, World Health Organization; IQR, inter quartile range; ART, antiretroviral treatment; 3TC, lamivudine; EFV, efavirenz; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; ABC, abacavir; DTG, dolutegravir.

Table 8. Adjusted weight changes in weight from ART initiation visit to one year of treatment

	Dolutegravir group (kg/month) (95% CI)	Efavirenz group (kg/month) (95% CI)	Difference (kg/month) (95% CI)
All patients	0.48 (0.39 to 0.58)*	0.28 (0.22 to 0.34)*	0.20 (0.09 to 0.32)*
BMI < 18.5 (kg/m^2)	0.80 (0.51 to 1.09)*	0.67 (0.47 to 0.88)*	0.13 (-0.23 to 0.48)
BMI 18.5-24.9 (kg/m^2)	0.46 (0.34 to 0.57)*	0.24 (0.17 to 0.31)*	0.22 (0.08 to 0.35)*
BMI >25 (kg/m^2)	0.34 (0.14 to 0.54)*	0.19 (0.06 to 0.32)*	0.15 (-0.09 to 0.38)

*P value <0.05
The model was adjusted for sex, CD4+ T cell count, WHO Stage, Age at start of ART, and weight at start of ART, TB diagnosis.
Abbreviations: BMI, body mass index

Table 9. Univariate and multivariate logistic regression model with the outcome of ≥10% bodyweight increase after 12 months of treatment

Variable	Univariate model Unadjusted OR (95% CI)	P value	Multivariate model Adjusted OR (95% CI)	P value
First ART regimen				
EFV-based regimen	1		1	
DTG-based regimen	1.49 (0.97-2.27)	0.066	1.91 (1.13-3.23)	0.015
Age (per 10 years)	1.15 (0.97-1.37)	0.105	1.20 (0.97-1.49)	0.093
Sex				
Male	1		1	
Female	2.03 (1.36-3.03)	<0.001	2.86 (1.72-4.75)	<0.001
Distance to the clinic (km)				
1 < 25	1		1	
≥ 25 < 50	1.36 (0.87-2.13)	0.177	1.49 (0.87-2.57)	0.146
≥ 50	1.04 (0.62-1.76)	0.877	1.19 (0.63-2.22)	0.594
WHO stage				
I or II	1		1	
III or IV	4.02 (2.68-6.02)	<0.001	2.67 (1.63-4.38)	<0.001
BMI (kg/m^2)				
<18.5	2.76 (1.58-4.80)	<0.001	1.25 (0.62-2.54)	0.534
18.5-24.9	1		1	
≥25	0.48 (0.29-0.80)	0.04	0.53 (0.29-0.98)	0.042
CD4+ count (cells/mm^3)				
<200	2.68 (1.71-4.19)	<0.001	2.47 (1.51-4.05)	0.002
200-499	1		1	
≥500	0.50 (0.27-0.94)	0.031	0.55 (0.28-1.08)	0.083
Tuberculosis				
Yes	3.75 (1.54-9.13)	0.004	1.68 (0.55-5.10)	0.363
No	1		1	

Abbreviations: BMI, body mass index; OR, odds ratio; CI, confidence interval; WHO, World Health Organization; EFV, efavirenz; DTG, dolutegravir.

Table 10: BMI categories changes overtime

Baseline			After one year		
	Dolutegravir	**Efavirenz**		**Dolutegravir**	**Efavirenz**
BMI	**N (%)**	**N (%)**	**BMI**	**N (%)**	**N (%)**
<18.5	18 (29)	44 (71)	<18.5	5 (27.8)	8 (18.2)
			18.5-24.9	12 (66.7)	35 (79.6)
			≥25	1 (5.6)	1 (2.2)
18.5-24.9	73 (22.6)	250 (77.4)	<18.5	2 (2.7)	8 (3.2)
			18.5-24.9	53 (72.6)	195 (78.0)
			≥25	18 (24.7)	47 (18.8)
≥25	29 (23.6)	94 (76.4)	<18.5	0 (0)	1 (1.1)
			18.5-24.9	4 (13.8)	18 (19.2)
			≥25	25 (86.2)	75 (79.8)

Abbreviations: BMI, body mass index

Manuscript 4. Rollout of dolutegravir-based antiretroviral therapy in sub-Saharan Africa and its public health implications

Authors

Herieth Ismael Wilson[1] and Herry Mapesi[1, 2, 3]

[1]Ifakara Health Institute, Ifakara branch, Ifakara, United Republic of Tanzania

[2]Swiss Tropical and Public Health Institute, Basel, Switzerland

[3]University of Basel, Basel, Switzerland

Key words: HIV/AIDS, Dolutegravir, Pharmacovigilance.

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To the editors of the Pan African Medical Journal

Globally, approximately 33 million people are living with Human Immunodeficiency Virus (HIV) and more than 60% of them live in sub-Saharan Africa. Widespread availability of antiretroviral treatment (ART) has reduced morbidity and mortality among people living with HIV (PLHIV). The increase in life expectancy in PLHIV has been associated with an increased burden of non-communicable diseases (NCDs), mainly being metabolic disorders [316]. PLHIV have an increased risk of developing NCDs since traditional risk factors for NCDs such as obesity, genetic predisposition and sedentary life intersect with HIV-specific risk factors such as long-term exposure to ART and chronic inflammation [317].

Integrase-strand-transfer inhibitors (INSTI)-based regimens have recently been rolled out as the new first-line treatment in most low and middle-income countries due to their excellent safety profile, lower price, and sustained treatment success compared to the currently used ART regimens [33]. In sub-Saharan Africa, most of the current guidelines recommends the use of dolutegravir-based regimens as the first line ART among PLHIV [33]. However, there is a lack of studies to evaluate long-term side effects of dolutegravir-based regimens among PLHIV living in low and middle-income countries.

Dolutegravir-based regimens and excess weight gain

Recent studies have demonstrated excessive weight gain among PLHIV switched from other ART regimens such Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)-based regimens to dolutegravir-based regimens [59]. The same effect has been observed among ART-naïve patients starting treatment with dolutegravir-based regimen compared to patients starting treatment with NNRTI-based regimens [57]. Although short-term weight gain is a positive prognostic factor for PLHIV, who are underweight due to advanced HIV disease, the development into obesity increases the risk of developing cardiovascular diseases [318]. As a consequence, the current World Health Organization guidelines cautioned clinicians about the potential implications of possible weight gain associated with dolutegravir-based regimens [319].

Dolutegravir-based regimens and neural tube defects

In 2018, there was a safety signal alert from Botswana Tsepamo birth-outcome surveillance study, which results indicated an increased absolute risk of neural-tube defects in infants born to women who used dolutegravir-based regimen at conception compared to those who used other non-dolutegravir-based regimen [320]. The public release of this report by drug monitoring

authorities led to uncertainty about the use of dolutegravir-based regimen among women of reproductive potential. In *The New England Journal of Medicine*, Rebecca Zash and colleagues reported the follow-up results from the same surveillance demonstrating a potential association between dolutegravir exposure at conception and the development of neural-tube defects among women of childbearing potential [321].

Discussion

What lessons do we take from the previous studies evaluating potential side effects of using dolutegravir-based regimens in PLHIV? First, it is currently unknown whether the increased risk of developing excess weight gain among ART-naïve patients starting a dolutegravir-based regimen will be observed also sub-Saharan African settings, specifically in rural environments, where the living conditions and comorbidities might be quite different. The risk factors for developing excessive weight gain include black ethnicity, being a woman, low CD4 count and high HIV viral load [57,59]. This is of particular concern since in sub-Saharan Africa, majority of PLHIV are women, and still patients present to the health care facilities with advanced HIV disease with low CD4 count, and high HIV viral load. Second, PLHIV with viral suppression from older ART regimen such as NNRTI have an increased risk of developing excess weight gain once switched to dolutegravir-based regimen [59]. Third, there is a potential risk of developing neural-tube defects among women who were using dolutegravir-based regimen during conception.

Despite the urgent need to introduce new ART in sub-Saharan Africa, establishment of proper pharmacovigilance systems is essential for monitoring the safety of these new medications. In order to detect rare events such as short-term weight gain and development of neural-tube defects, a large number of exposures is needed, which is possible only if after introduction of new drugs in the community and systematic reporting is done. Implementing improved pharmacovigilance systems will not only help to monitor the safety of new antiretroviral drugs, but also to monitor medications from other chronic diseases requiring lifelong treatment such as hypertension, diabetes mellitus, cancers and epilepsy, all of which are on the rise in low-income and middle-income countries. Furthermore, it will provide data on pharmacokinetics and safety in pregnancy since this information is usually available on average six years after registration of the new drug [322].

Conclusion

It is vital that low-income and middle-income countries improve their pharmacovigilance systems to produce robust and high-quality evidence to monitor the safety of new drugs. Additionally, there is an urgent need for longitudinal post-licensing studies to evaluate potential mechanisms

of newly detected adverse events such as the dolutegravir signal for a possible neural-tube defect, which might be easier to capture in settings with a high number of HIV-positive women in childbearing age.

Competing interests

The authors declare no competing interest.

Authors' contributions

HIW and HM conceptualized the work, gathered the evidence and wrote the paper. Both authors read and approved the final paper.

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Manuscript 5. Age-Related Comorbidities and Mortality in People Living with HIV in Rural Tanzania: Data from a Prospective Cohort Study

Sascha Albrecht[1,2,3]*, Fabian Christoph Franzeck[4]*, Herry Mapesi[1,2,3,5], Christoph Hatz[2,3], Aneth Vedastus Kalinjuma[1], Tracy Renee Glass[2,3], Dorcas Mnzava[1], Emili Letang[1,2,3,6], Daniel Henry Paris[2,3], Manuel Battegay[4], Maja Weisser[1,2,3,4,§] On Behalf Of The KIULARCO Study Group

1 Ifakara Health Institute, Ifakara, United Republic of Tanzania
2 Swiss Tropical and Public Health Institute, University of Basel, Basel, Switzerland
3 University of Basel, Basel, Switzerland
4 Division of Infectious Diseases & Hospital Epidemiology, University Hospital Basel, University of Basel, Basel, Switzerland
5 Saint Francis Referral Hospital, Ifakara, United Republic of Tanzania
6 ISGlobal, Barcelona Ctr. Int. Health Res. (CRESIB), Hospital Clínic - Universitat de Barcelona, Barcelona, Spain
* These authors have contributed equally to the work.

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Abstract

Objective: Causes of morbidity and mortality of people living with HIV (PLHIV) are changing with access to antiretroviral therapy and increased life expectancy. Age-related data on comorbidities and their impact on mortality in sub-Saharan Africa is scarce.

Design: This prospective analysis evaluated comorbidities, assessed by means of ICD-10 codes and clinical variables, derived from data collected from the Kilombero & Ulanga antiretroviral cohort of PLHIV in rural Tanzania.

Methods: We calculated prevalences and incidences of comorbidities in patients enrolled from 2013 – 2017 and evaluated their association with a combined endpoint of death and loss to follow-up (LTFU) in various age groups (15-29, 30-49 and ≥ 50 years) using Cox regression analysis.

Results: Of 1622 patients (65% females, median age 38 years (IQR 31-46)), 11% were ≥ 50 years. During a median follow-up of 22.1 months (IQR 10.6-37.3), 48 (2.9%) patients died and 306 (18.9%) were LTFU. Anaemia was the most prevalent comorbidity(66.3%) irrespective of age and was associated with increased mortality/LTFU (HR 2.02 (95%CI 1.57-2.60); p<0.001). In patients aged ≥ 50 years, arterial hypertension was highly prevalent (43.8%), but not associated with mortality/LTFU (HR 1.04 (95%CI 0.56-1.93), p=0.9). Undernutrition ranged from 25.5% in the youngest to 29.1% in the oldest age group and contributed to mortality/LTFU (HR 2.24 (95%CI 1.65-3.04); p<0.001). Prevalence of tuberculosis was 21.4% (HR of 2.54 (95%CI 1.72-3.75)), p<0.001 for mortality/LTFU.

Conclusions: We show that anaemia, arterial hypertension and undernutrition are the most relevant comorbidities with different age-associated frequencies and impact on death/LTFU in this population.

Keywords: HIV, age, comorbidities, antiretroviral treatment, sub-Saharan Africa, rural

Introduction

Improved access to antiretroviral therapy (ART) has led to a drastic reduction in mortality of people living with HIV (PLHIV). Life expectancy of PLHIV in high-income countries is currently comparable to that of HIV-negative individuals [323–326] and impressive gains in life expectancy have also been made in resource-limited settings [327–329]. The UNAIDS Gap report 2014 estimated, that in sub-Saharan Africa (SSA) more than 2 million PLHIV are aged 50 years and older and are therefore prone to developing chronic diseases. [330].

In SSA AIDS-defining conditions remain an important cause of comorbidity and death [331], but the recent increase in age span of PLHIV has been associated with a relevant risk of developing a chronic non-communicable disease such as arterial hypertension or diabetes [332]. This necessitates the integration of different health care services into the existing HIV focused care [333]. A recent meta-analysis on selected non-communicable diseases in PLHIV in low and middle-income countries has shown pooled estimates for prevalence of arterial hypertension, dyslipidemia and depression of around 20-30% each [332]. Risks for arterial hypertension, myocardial infarction, end-stage-renal disease, non-AIDS-defining malignancies and frailty in PLHIV are shown to be higher compared with HIV-negative individuals [334–338], particularly in PLHIV in SSA [339]. The increased mortality of PLHIV on ART who are older than 50 years could not be shown to be attributed to differences in WHO stage or CD4 cell counts [340]. This suggests, that comorbidities play an important role in those over 50 years of age. However, within this patient population in SSA little is known about the distribution of comorbidities and their relationship to age.

To date, comprehensive data on the frequency of comorbidities in patients on ART and their impact on outcomes in SSA are limited, particularly in elderly PLHIV and in rural settings. Our prospective study nested within a large cohort of PLHIV aimed to assess the prevalence and incidence of comorbidities, as well as their association with mortality among different age groups of HIV-infected patients on ART in a rural Tanzanian setting.

Methods

Study Design and Setting

The Kilombero and Ulanga Antiretroviral Cohort (KIULARCO) is an ongoing prospective cohort of PLHIV receiving HIV care and treatment at the Chronic Diseases Clinic (CDCI) of the St. Francis Referral Hospital in Ifakara, Tanzania [341,342]. In brief, patients are monitored and treated according to the National AIDS Control Program guidelines including 3-monthly visits

- twice a year with a nurse and twice with a physician for a full clinical workup. Additional unscheduled visits and hospitalizations are registered. All patient data is entered into an electronic health record system (OpenMRS, http://openmrs.org). Comorbidities are systematically assessed according to the International Classification of Diseases and Related Health problems 10th revision (ICD-10). Routine laboratory monitoring including CD4 cell count, full blood count, serum creatinine and liver function tests are performed twice a year. During the study period, HIV-1 RNA viral load and genotypic drug resistance testing was done only upon clinical or immunological suspicion of treatment failure. Screening for opportunistic diseases and co-infections were performed at baseline and upon clinical suspicion (chest X-ray, Venereal Disease Research Laboratory test (VDRL), HBsAg, cervical cancer screening using visual inspection with acetic acid, as well as serum cryptococcal antigen testing in patients with CD4 cell count below 150 cells/mm^3). No further microbiological or histopathological testing was available.

Participants and Data

From the KIULARCO cohort, we included all adult patients (≥ 15 years) with a documented HIV infection enrolled between January 1, 2013 and December 31, 2017, who had no prior intake of ART and started ART within 3 months after enrolment. Patients <15 years of age and patients with prior ART or no ART within 3 months from enrolment were excluded to ensure comparability of patients. A minimal follow-up time of two months was requested to allow for sufficient time to diagnose comorbidities of chronic nature. All data used for the analysis was extracted from the electronic database.

Definitions

Comorbidities were grouped as: haematological, metabolic, cardiovascular, opportunistic infections (exclusive tuberculosis), cancer, pulmonary, tuberculosis, gastro-intestinal, renal/urogenital and malarial. A specific diagnosis was defined either by an ICD-10 code documented by a clinician or alternatively by measurements of vital signs and laboratory parameters if applicable for a condition. ICD-10 codes depended on the clinicians' assessment without mandatory documentation of underlying signs and symptoms or diagnostic testing. Case definitions of comorbidities are shown in Supplementary Table 1. Clinical HIV WHO stage was defined according to international guidelines [343].

Prevalence was defined as a period prevalence over the individual follow-up, i.e. the proportion of subjects manifesting a condition at any time point during the whole period of observation starting from inclusion into the cohort. Incident disease was defined as first diagnosis of a new condition in subjects under follow-up not manifesting the disease during the preceding

observation period. To ensure a disease was truly incident, we defined a disease-specific period of observation after enrolment (e.g. 60 days for hypertension, 15 days for malaria), during which the diagnosis of a condition was judged as prevalent at enrolment (instead of incident under observation). Patients were considered being lost to follow-up (LTFU) if they did not present to the clinic within 60 days after their last scheduled appointment. A composite outcome of death and LTFU was chosen due to a high rate of LTFU and an assumed high mortality in those patients [344,345].

Statistical analysis

Continuous variables were summarized using median and interquartile range and categorical variables with counts and frequencies. P-values for comparisons were derived from the Mann-Whitney-U test for continuous variables and the chi-square test for categorical variables. Results were stratified into three pre-defined age groups (15-29, 30-49 and ≥ 50 years). The group aged ≥ 50 years corresponded to the oldest 10% of the population according to the Tanzanian 2012 census [346].

Kaplan–Meier estimates were used to plot cumulative survival probabilities. Univariate and multivariate Cox proportional hazards models with time-updated exposure variables were adjusted according to the initiation of ART. This was done to explore associations between comorbidities with a composite outcome of death and LTFU. Sex, categorized CD4 cell count at baseline and WHO stage were included a priori in the multivariate models. Schoenfeld residuals were used to test the proportional hazard assumption. Results are presented with hazard ratios and 95% confidence intervals. All statistical analyses were performed using Stata Version 11.2 (StataCorp, USA).

Ethical Considerations

All participants involved in this study gave written informed consent for the collection, storage and use of clinical data and sample specimens for research purposes within KIULARCO. The study protocol of KIULARCO was approved by the Ifakara Health Institute Institutional Review Board, the National Institute of Medical Research in Tanzania, the Tanzanian Commission of Science and Technology as well as the Ethics committee of Northwest and Central Switzerland.

Results

Study Population

Of the 3,501 patients enrolled into KIULARCO from January 2013 to December 2017, 1,879 (53.7%) were excluded: 325 (17.2%) due to age <15 years, 530 (28.2%) had prior ART use, 623 (33.1%) had insufficient follow-up and 401 (21.3%) started ART > 3 months after enrolment. The 1,622 (46.3%) patients were included in the final analysis (Supplementary Figure 13) contributing to 3,296 patient-years with a median follow-up of 22.1 months (IQR 10.6-37.3).

At enrolment, median age was 38 years (IQR 31-46) and 65.2% were female (Table 11). Almost half of the patients (42.1%) were classified as WHO stage 3 or 4. The median CD4 cell count at inclusion was 196 cells/mm^3 (IQR 83 - 335). After enrolment, patients started ART after a median interval of 8 days (IQR 3-19). The most frequent initial therapeutic regimens consisted of tenofovir disoproxil fumarate (TDF)/lamivudine/efavirenz in 70.6%, TDF/emtricitabine/efavirenz in 19.2% and zidovudine/lamivudine/efavirenz in 5.4%.

Baseline characteristics differed by age strata: younger patients (15-29 years) were more often female, more often living with a partner, had higher educational levels, and were less likely to drink alcohol or smoke cigarettes (Table 1). Younger patients also had higher CD4 cell counts and presented less frequently with a clinical WHO stage 4 condition. Patients reported only few comorbidities in their personal history, i.e. before enrolment (Supplementary Table 2). Among these, herpes zoster was reported most frequently (104 patients, 6.4%), followed by pulmonary tuberculosis (58 patients, 3.6%), arterial hypertension (38 patients, 2.3%), urogenital diseases (17 patients, 1.0%), malaria (10 patients, 0.6%) and mucocutaneous mycosis (9 patients, 0.6%). Other comorbidities were reported by less than 0.5% of patients.

The 623 patients excluded for this analysis due to < 2 months follow-up, were more frequently enrolled during later years, male, unmarried, in a higher HIV/AIDS WHO stage and had a lower level of education compared to the 1,622 patients fulfilling inclusion criteria. They reported more frequently smoking and alcohol consumption (data not shown). Also, patients, who were LTFU/died differed from patients remaining in care/relocated: patients in active care were more frequently enrolled in recent years, were more often females, reported less smoking and had a lower WHO stage at enrolment (Supplementary Table 16).

Prevalence

In all age groups the most prevalent conditions were anaemia (66.3%), undernutrition (27.2%), arterial hypertension (27.0%), mucocutaneous mycosis (25.1%) and tuberculosis (21.4%; Table 2). The oldest age group (≥ 50 years) had the highest rates of comorbidities in general. The most prevalent diseases in this group were anaemia in 203 patients (66.3%),

arterial hypertension in 134 patients (43.8%), undernutrition in 89 patients (29.1%), thrombocytopenia in 80 patients (26.1%) and tuberculosis in 65 patients (21.2%). Diseases most prevalent in middle-aged patients (30-49 years) were also anaemia in 678 patients (68.7%), undernutrition in 268 patients (27.2%), mucocutaneous mycosis in 266 patients (27%), arterial hypertension in 262 patients (26.5%) and tuberculosis in 223 patients (22.6%). Younger patients (< 30 years) had fewer comorbidities compared to older patients, but still high prevalence rates for anaemia (59%), undernutrition (25%) and mucocutaneous mycosis (24%).

Incidence

The comorbidities (Figure 11 and Supplementary Table 17) with the highest incidence were respiratory tract infections (overall 194 new events; 71.3/1000 patient years (py)) – notably highest in the oldest age group with 80.4/1000py. In patients ≥ 50 years of age, arterial hypertension was the most common incident comorbidity (96.8/1000py) followed by thrombocytopenia (84.9/1000py), respiratory tract infection (80.4/1000py), undernutrition (69.9/1000py), anaemia (67.8/1000py), acute kidney injury (39.3/1000py) and tuberculosis (37.3/1000py). Patients aged 30-49 years suffered mainly from respiratory tract infections (72.6/1000py) followed by thrombocytopenia (66.1/1000py), arterial hypertension (65.7/1000py), anaemia (62.7/1000py) and mucocutaneus mycosis (62.4/1000py). In the youngest age group, the highest incidence rates were observed with anaemia (79.5/1000py), thrombocytopenia (60.9/1000py) and mucocutaneus mycosis (59.1/1000py).

To understand the temporal distribution of incident comorbidities, we depicted the individual time intervals between enrolment and occurrence of an incident condition in a temporal plot (Supplementary Figure 14). Most comorbidities were diagnosed in the first year after inclusion. Of note, the early incidence of certain conditions might be explained by immune reconstitution syndromes.

Outcomes

During the study period, 48 patients died (2.9%) and 306 patients (18.9%) were lost to follow-up. The combined endpoint was more commonly reached in younger patients (Figure 12). The most common causes of death were tuberculosis (18 patients, 37.5%), cryptococcal meningitis (7 patients, 14.5%), anaemia (4 patients, 8.3%), renal failure, bacterial pneumonia and non-HIV-associated cancer (each 3 patients, 6.2%). The remaining 10 patients (20.8%) died from *pneumocystis jirovecii* pneumonia, Kaposi sarcoma, heart failure, hypertensive crisis, malaria,

electrolyte disorder, multiple infections and meningitis. In one case cause of death was unknown.

In the time-updated Cox proportional hazard models fitted to analyze factors associated with the composite outcome of death and lost to follow-up we found no significant interactions between the different comorbidities (data not shown). Overall, the adjusted hazard ratios (aHR, Table 13) were significantly increased for tuberculosis (aHR 2.54 [95% CI 1.72-3.75]; p<0.001), opportunistic infections (2.41 [1.56-3.74]; p<0.001) undernutrition (aHR 2.24 [1.65-3.04]; p<0.001) and anaemia (aHR 2.02 [1.57-2.60]; p<0.001). Stratified according age, in the oldest age group tuberculosis (aHR 6.41 [3.10-13.25]), p<0.001), undernutrition (aHR 2.37 [1.19-4.73]), p=0.015) and anaemia (aHR 1.92 [1.04-3.54]; p=0.036) were associated with death/LTFU. In the youngest group, only tuberculosis (aHR 3.31 [1.28-8.60]), p<0.001) and anaemia (aHR 2.14 [1.22-3.73]; p=0.008) was associated with death/LTFU. Opportunistic infections had the strongest association with death/LTFU (aHR 2.72 [1.57-4.72] in the middle-aged group. In this age group, additionally undernutrition (HR 2.61 [1.76-3.89], p<0.001), cancer (2.02 [1.18-3.46]), p=0.01) and anaemia (2.00 [1.43-2.79]), p<0.001) disease associations were seen.

Protective hazard ratios were found for female sex (0.60 [0.47-0.77]; p=0.001) with the lowest hazard in the youngest age group (0.52 [0.27-0.99], p=0.048). As a sensitivity analysis, we performed Cox models in the overall population for the outcome of mortality only using the same predictors: Overall hazards ratios remained high for tuberculosis (4.40 [2.10-9.21], p<0.001), anaemia (3.77 [1.47-9.64], p=0.005), undernutrition (6.09 [3.04-12.21], p<0.001) and opportunistic infections other than tuberculosis (5.16 [2.39-11.15], p<0.001). In contrast to the model with the combined endpoint, arterial hypertension (2.87 [1.29-6.94], p=0.019) was a significant predictor.

Discussion

In this prospective cohort study investigating the prevalence and incidence of comorbidities in 1622 PLHIV, we found that anaemia was by far the most prevalent comorbidity in all age groups and was associated with mortality. Arterial hypertension had the highest prevalence and incidence in elderly patients, however it´s impact on mortality is not yet determinable. Undernutrition was present in a fourth of all patients and tuberculosis was prevalent mostly in those > 50 years or older. The most common incident diseases were arterial hypertension in elderly, anaemia in younger patients and respiratory tract infections, thrombocytopenia and mucocutaneous mycoses in all age groups.

The high prevalence (66.3%) and incidence (66.6/1000py) of anaemia and its association with the combined endpoint throughout all age groups confirm numbers of the report on global anaemia burden. The report also documents anaemia as the most common hematological complication in PLHIV [347]. Data from Tanzania show rates of 71% in PLHIV [348]. In our cohort we do not have information on the etiology of anaemia. In similar settings, the most common risk factors were zidovudine-based ART (OR=3.3), advanced WHO stage (OR=5.3), low baseline CD4 count (OR=2.27) [348] and low body mass index <18.5 kg/m^2 [349]. Anaemia mostly improves after initiation of ART [350]. However, a study from Tanzania showed persisten anaemia beyond 12 months [351] in a third of patients, which may be due to reasons such as parasitic diseases including malaria, peripartum bleeding in women, tuberculosis and undernutrition. The association of anaemia with mortality and HIV disease progression has been previously shown [347,352,353], and was similarly true for all age groups in our study, despite the fact, that only 21% of incident anaemias were severe (Hemoglobin < 8 g/dl). Furthermore, the association was independent of co-factors such as diagnosed tuberculosis, HIV/AIDS WHO stage and malaria.

Arterial hypertension contributed to morbidity mostly in those > 50 years or older. In SSA, arterial hypertension is the most important risk factor for cardiovascular disease [354]. In our study, arterial hypertension was present in 27% of all patients, increasing to 44% in patients aged > 50 years and was also the most incident comorbidity in this age group (96.8/1000py). The high prevalence of arterial hypertension in our cohort has been shown previously [355] and corresponds to a high prevalence of arterial hypertension in the general Tanzanian population (28%) [356]. Data from developed countries (Netherland, Italy, USA) confirm arterial hypertension as a major comorbidity in PLHIV, albeit not as frequently as in SSA [357–359]. Likely due to a relatively low observation time in our study, arterial hypertension in our cohort was not associated with an increased mortality/loss to follow-up.

Undernutrition was observed commonly with a period prevalence of 27% and an incidence of 69.9/1000py in patients > 50 years. Furthermore, undernutrition was associated with mortality and loss to follow-up. The majority of patients on ART show weight gain [360], which is associated with improved survival [361,362]. The fact that in our study half of cases with undernutrition were diagnosed in the first two months after start of ART might suggest the unmasking of opportunistic infections, e.g. tuberculosis [363]. Obesity on the other hand was not a frequent comorbidity in our setting (9.4% prevalence) compared to other studies from SSA, possibly due to differences in rural and urban life styles [364].

Tuberculosis - reported separately from opportunistic infections – remains a major comorbidity, especially in the oldest patient group (prevalence of 21%, incidence 37.3/1000py). This is not surprising, as Tanzania is among the 30 high-burden countries with a tuberculosis incidence of 287 cases/100'000 population in 2016, with 34% being HIV-positive [365]. In our study, Tuberculosis was associated with a 6 times higher risk of death in patients aged 50 years and older, which is in line with a study from South Africa showing Tuberculosis to be a major factor for HIV-infected inpatients [366] and the leading cause of death among PLHIV [330].

The low prevalence of opportunistic infections other than tuberculosis under ART in our study confirms the success of antiretroviral treatment programs [330] and corresponds with a previous study of KIULARCO showing that 91% of patients attending the clinic were virologically suppressed [367]. In the current study, we focused on age-related distribution of comorbidities in PLHIV under chronic care. Therefore, patients with advanced HIV disease were underrepresented, reflected by a low overall mortality rate of 2.9% compared to the overall cohort mortality, which was previously 9% [342].

Thrombocytopenia was highly prevalent and incident in our study, especially in the oldest group with 26% (overall 21%) and 85/1000py (overall 69/1000py) respectively. In other studies, thrombocytopenia in HIV-positive patients in Africa has been lower with 5% to 17.4% in ART-naive and treated PLHIV respectively [368–370]. While HIV is a major cause for thrombocytopenia, under ART the prevalence has been documented to be lower. Therefore, other factors like tuberculosis, undernutrition, malaria and hypersplenism might be important. In another cohort of patients on ART in a rural hospital in Tanzania thrombocytopenia was shown to be an independent predictor of mortality with an aHR of 2.3 (95% CI 1.33-3.99) [371].

Acute infections such as respiratory tract infections and mucocutaneous mycoses were most prevalent and incident in middle-aged PLHIV in our cohort. Respiratory tract infections are frequent all over the world, however mucocutaneous mycoses might reflect an uncomplicated skin disease of subtropical climates and not an opportunistic infection. This is in line with the fact, that skin diseases ranks at number 1 of health-related disabilities in the general population in Tanzania which was published in the Report of the Institute of Health Metrics and Evaluation 2016 (http://www.healthdata.org/tanzania). However, rarely mucocutaneous mycosis can present in the context of an immune-reconstitution syndrome after the initiation of ART [372].

The low number of reported malaria episodes might be due to the fact, that patients rather consult a local dispensary than the HIV clinic in cases of fever which may have led to underreporting of malaria in our cohort.

Overall, confirmed mortality in our study was low with a rate of 2.9%. However, we observed a lost to follow-up of 18.9%. We expect a relevant percentage of those lost to follow-up to have died as determined by patient tracking services done for our cohort [23] and a meta-regression-analysis including data from SSA [46]. Comorbidities most frequently associated with death and lost to follow-up were anaemia, tuberculosis and undernutrition.

Whereas most studies on comorbidities concentrate on single diseases, we were interested to obtain a comprehensive overview of the distribution and age-related effects of comorbidities. A major strength of this study is the prospective and systematic bi-annual data recording by means of ICD-10 codes in a rural SSA setting. To our knowledge, no comprehensive longitudinal data on comorbidities in PLHIV in SSA with respect to different age stratification have been published thus far.

Limitations of our study are the restricted availability of diagnostic tests (e.g. there was no histology or microbiological testing beyond GeneXpert MTB/RIF for tuberculosis and cryptococcal antigen) for etiological confirmation of conditions. By using ICD-10 codes in 6-monthtly intervals for diagnosis of comorbidities we attempted to harmonize data acquisitions. However, there might have been variability between clinicians as no standardization of signs and symptoms and diagnostic procedures was mandatory for ICD-10 coding. Secondly, observation time of patients was varied and limited due to high rates of loss to follow-up (18.9%) and transfer-out (8.0%), which likely leads to bias in reporting of comorbidities. Furthermore, due to small numbers of confirmed deaths and a high number of LTFU we were unable to reliably analyze these two endpoints separately. As in other HIV-cohorts we did not have data from an HIV-negative control group, therefore possible associations of comorbidities with HIV infection cannot be made.

Conclusions

Comorbidities were frequent in this rural HIV-population despite the relatively young average age. Patients aged 50 years and more were more likely to encounter comorbidities, in particular anaemia, arterial hypertension, undernutrition and tuberculosis. In younger patients, anaemia and undernutrition were highly prevalent and independently predicted death/LTFU. Integrated and tailored screening and treatment programs to identify and address comorbidities in different age groups are urgently needed with increased life-expectancy in PLHIV.

Competing interests

The authors have no competing interests to declare

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Authors' contributions

SA and MW conceived of the study. All authors participated in the design of the study. SA, HM, EL and MW were involved in data collection. FF carried out the analysis of cohort data with support from TG. SA, FF and MW drafted the manuscript. All authors approved the final manuscript.

Figure 11. Incidence density rates of comorbidities of 1622 patients

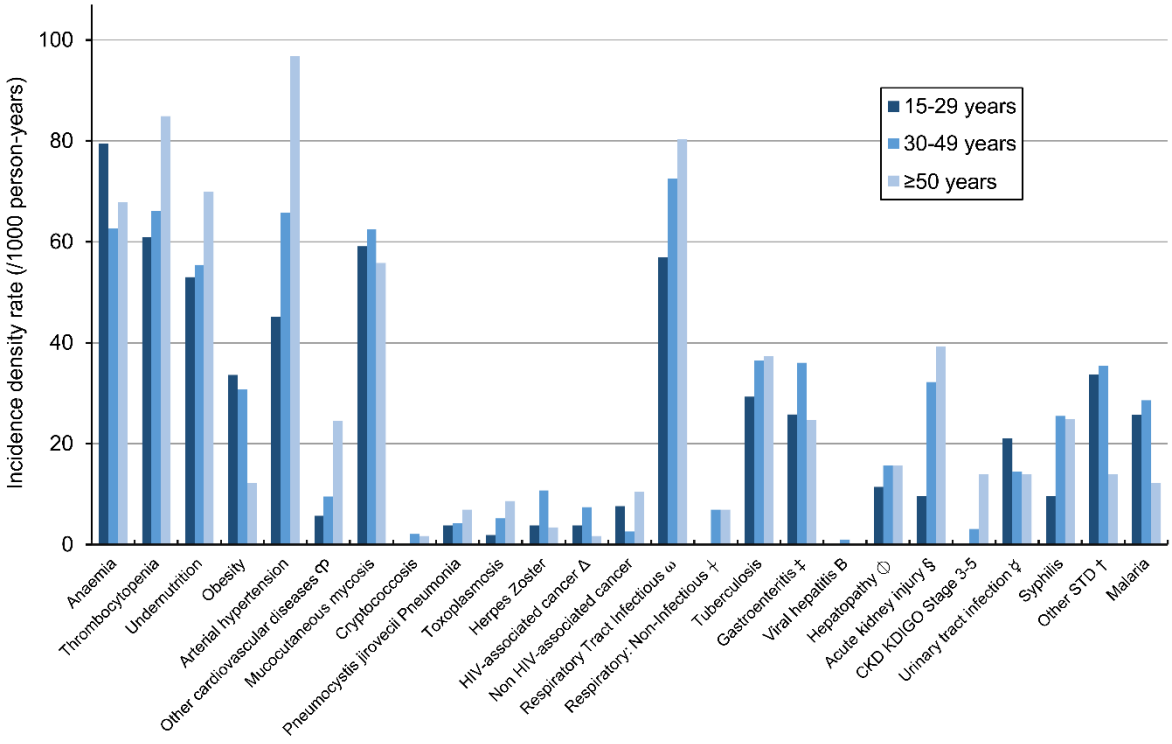
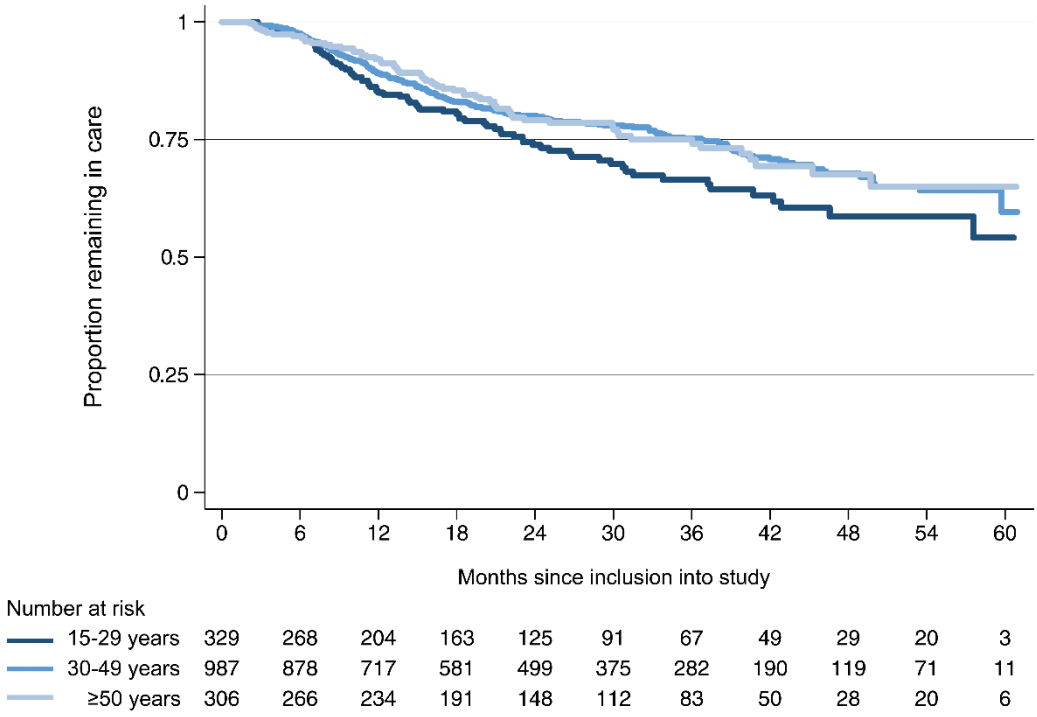
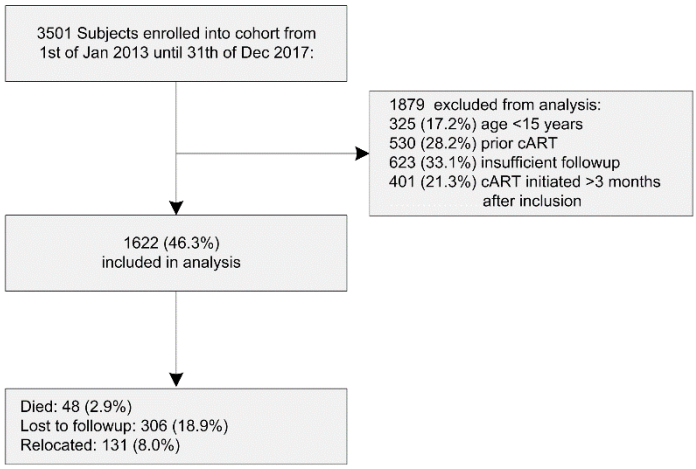


Figure 12. Survival curve.



Supplementary figure 13. Flowchart of enrolment and outcome.



Supplementary Figure 14. Temporal distribution of incident conditions during individual follow-ups.

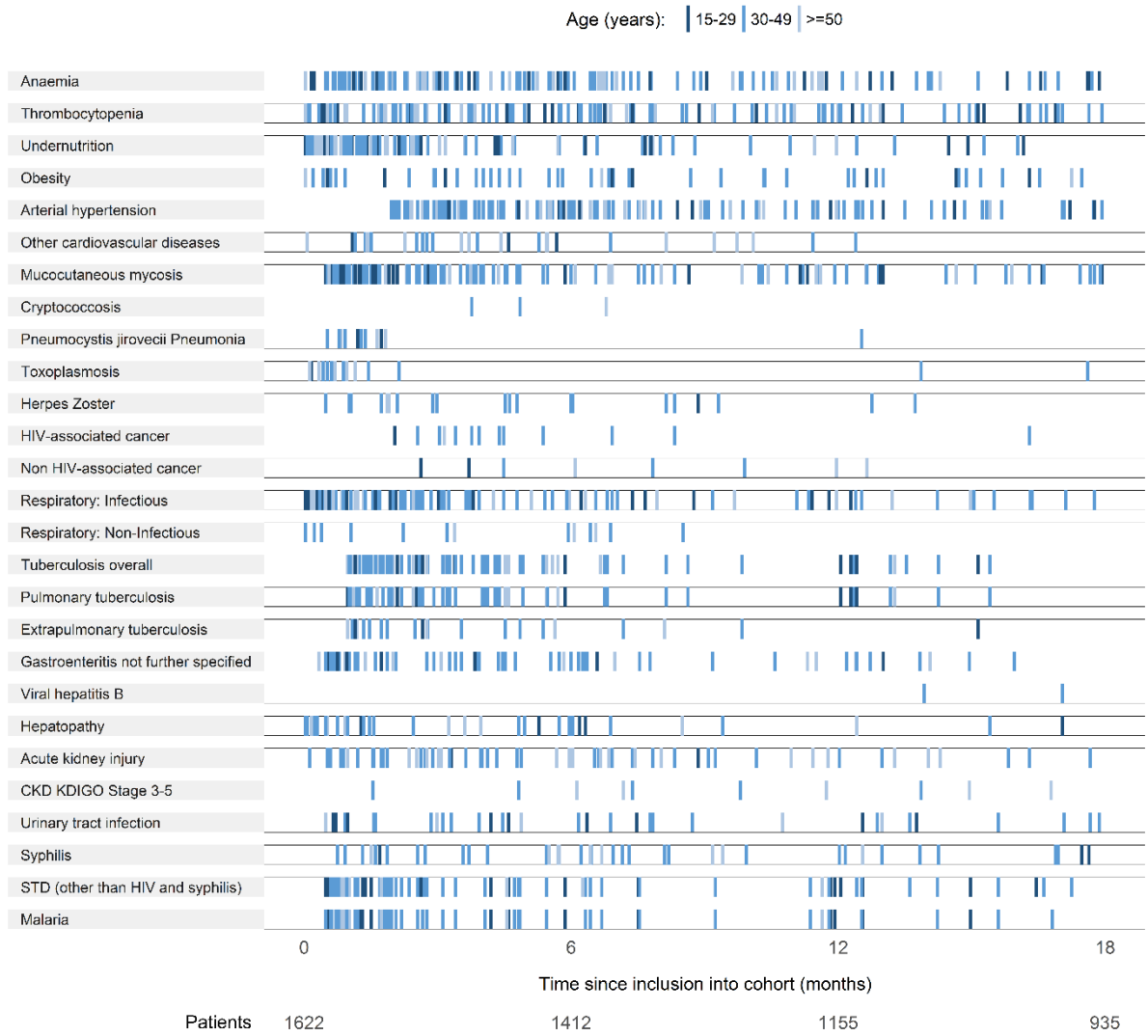


Table 11. Baseline Characteristics of the Participants

	15-29 years	**30-49 years**	**≥ 50 years**	**Overall**	**p**
n	*329*	*987*	*306*	*1622*	
Age years median (IQR)				38 (31, 46)	
Year registered					0.029
2013	41 (12.5)	154 (15.6)	34 (11.1)	229 (14.1)	
2014	61 (18.5)	224 (22.7)	68 (22.2)	353 (21.8)	
2015	74 (22.5)	257 (26.0)	83 (27.1)	414 (25.5)	
2016	78 (23.7)	189 (19.1)	71 (23.2)	338 (20.8)	
2017	75 (22.8)	163 (16.5)	50 (16.3)	288 (17.8)	
Sex					<0.001
Female	267 (81.2)	638 (64.6)	153 (50.0)	1058 (65.2)	
Male	62 (18.8)	349 (35.4)	153 (50.0)	564 (34.8)	
Marital status					0.051
Married/living with partner	201 (61.1)	600 (60.8)	163 (53.3)	964 (59.4)	
Not living with partner	128 (38.9)	387 (39.2)	143 (46.7)	658 (40.6)	
Education					<0.001
None	24 (7.3)	80 (8.1)	43 (14.1)	147 (9.1)	
Primary school	252 (76.6)	865 (87.6)	243 (79.4)	1360 (83.8)	
Secondary school	51 (15.5)	32 (3.2)	13 (4.2)	96 (5.9)	
Tertiary education	2 (0.6)	10 (1.0)	7 (2.3)	19 (1.2)	
Transmission mode†					<0.001
Heterosexual	256 (77.8)	816 (82.7)	236 (77.1)	1308 (80.6)	
Homosexual	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	
Perinatal	12 (3.6)	1 (0.1)	1 (0.3)	14 (0.9)	
Other/unknown	61 (18.6)	169 (17.1)	69 (22.5)	299 (18.4)	
Current smoking	7 (2.1)	48 (4.9)	21 (6.9)	76 (4.7)	0.014
Alcohol consumption	20 (6.1)	149 (15.1)	48 (15.7)	217 (13.4)	<0.001
WHO Stage					<0.001
1	185 (56.2)	350 (35.5)	101 (33.0)	636 (39.2)	
2	42 (12.8)	146 (14.8)	43 (14.1)	231 (14.2)	
3	58 (17.6)	307 (31.1)	110 (35.9)	475 (29.3)	
4	35 (10.6)	137 (13.9)	35 (11.4)	207 (12.8)	
NA	9 (2.7)	47 (4.8)	17 (5.6)	73 (4.5)	
CD4+ cell count (cells/mm^3)					<0.001
<100	58 (17.6)	280 (28.4)	62 (20.3)	400 (24.7)	
100-199	47 (14.3)	189 (19.1)	64 (20.9)	300 (18.5)	
200-499	121 (36.8)	297 (30.1)	122 (39.9)	540 (33.3)	
≥500	49 (14.9)	70 (7.1)	17 (5.6)	136 (8.4)	
NA	54 (16.4)	151 (15.3)	41 (13.4)	246 (15.2)	
CD4+ count, median (IQR)	266 (119, 414)	167 (69, 303)	207 (105, 328)	196 (83, 335)	<0.001

Data are presented as count (column percentage) and median (interquartile range). Abbreviations: IQR, interquartile range; NA, not available (i.e. no test/values available). † no transmission by blood transfusion or IV drug use reported.

Table 12. Period prevalence of comorbidities by age group

		15-29 years	30-49 years	≥ 50 years	Overall
n		*329*	*987*	*306*	*1622*
Hematological	Anaemia	194 (59.0)	678 (68.7)	203 (66.3)	1075 (66.3)
	Severe anaemia (Hb < 8g/dl)	56 (17.0)	184 (18.6)	48 (15.7)	288 (17.8)
	Thrombocytopenia	51 (15.5)	209 (21.2)	80 (26.1)	340 (21.0)
Metabolic	Undernutrition	84 (25.5)	268 (27.2)	89 (29.1)	441 (27.2)
	Obesity	30 (9.1)	105 (10.6)	18 (5.9)	153 (9.4)
Cardiovascular	Arterial hypertension	42 (12.8)	262 (26.5)	134 (43.8)	438 (27.0)
	Other cardiovascular diseases ♈	4 (1.2)	34 (3.4)	25 (8.2)	63 (3.9)
Opportunistic Infections	Mucocutaneous mycosis	79 (24.0)	266 (27.0)	62 (20.3)	407 (25.1)
	Cryptococcosis	1 (0.3)	29 (2.9)	8 (2.6)	38 (2.3)
	Pneumocystis jirovecii Pneumonia	7 (2.1)	21 (2.1)	7 (2.3)	35 (2.2)
	Toxoplasmosis	1 (0.3)	16 (1.6)	6 (2.0)	23 (1.4)
	Herpes Zoster	10 (3.0)	53 (5.4)	23 (7.5)	86 (5.3)
Cancer	HIV-associated cancer Δ	7 (2.1)	37 (3.7)	8 (2.6)	52 (3.2)
	Non HIV-associated cancer	8 (2.4)	21 (2.1)	7 (2.3)	36 (2.2)
Pulmonary	Respiratory: Infectious ω	32 (9.7)	171 (17.3)	55 (18.0)	258 (15.9)
	Respiratory: Non-Infectious ⍭	1 (0.3)	15 (1.5)	5 (1.6)	21 (1.3)
Tuberculosis	Overall	59 (17.9)	223 (22.6)	65 (21.2)	347 (21.4)
	Pulmonary tuberculosis	50 (15.2)	205 (20.8)	60 (19.6)	315 (19.4)
	Extrapulmonary tuberculosis	12 (3.6)	45 (4.6)	12 (3.9)	69 (4.3)
	Unspecified tuberculosis	27 (8.2)	105 (10.6)	30 (9.8)	162 (10.0)
Gastro-Intestinal	Gastroenteritis ‡	29 (8.8)	141 (14.3)	45 (14.7)	215 (13.3)
	Viral hepatitis B	15 (4.6)	76 (7.7)	22 (7.2)	113 (7.0)
	NA	38 (11.6)	111 (11.2)	27 (8.8)	176 (10.9)
	Hepatopathy ⌽	12 (3.6)	35 (3.5)	12 (3.9)	59 (3.6)
Renal/urogenital	Acute kidney injury §	5 (1.5)	59 (6.0)	22 (7.2)	86 (5.3)
	CKD KDIGO Stage 3-5	2 (0.6)	8 (0.8)	26 (8.5)	36 (2.2)
	NA	20 (6.1)	37 (3.7)	8 (2.6)	65 (4.0)
	Urinary tract infection ☿	17 (5.2)	40 (4.1)	11 (3.6)	68 (4.2)
	Syphilis	18 (5.5)	139 (14.1)	67 (21.9)	224 (13.8)
	Other STD †	49 (14.9)	156 (15.8)	24 (7.8)	229 (14.1)
Malaria	Malaria	36 (10.9)	142 (14.4)	21 (6.9)	199 (12.3)

Data are presented as count (column percentage). Abbreviations: KDIGO, Kidney disease improving global outcome; NA, not available (i.e. no test/values available); STD sexually transmitted disease. ♈including ischaemic and other heart diseases, vascular diseases, stroke; Δ including Kaposi sarcoma, cervical cancer, lymphoma; ω including upper respiratory tract infection, acute bronchitis, viral and bacterial pneumonia, lung abscess; ⍭ including pleural effusion, pneumothorax, chronic bronchitis, emphysema, chronic obstructive pulmonary disease, asthma bronchiale; ‡ including protozoal, bacterial, typhoid, isosporiosis; ⌽ including viral hepatitis, alcoholic liver disease, toxic liver diseases, oesophageal varices, other liver diseases; § Acute kidney injury network (AKIN) Stage 2 and above; ☿including cystitis, pyelonephritis; † including cervicitis, pelvic inflammatory disease, urethritis

Table 13. Cox regression analysis of patients on ART (n = 1622) for the composite outcome of death and lost to follow-up.

	15-29 years				30-49 years				≥ 50 years				Overall			
	Unadjusted		Adjusted		Unadjusted		Adjusted		Unadjusted		Adjusted		Unadjusted		Adjusted	
	HR (95 CI)	*p*	*HR (95 CI)*	*p*	*HR (95 CI)*	*p*	*HR (95 CI)*	*p*	*HR (95 CI)*	*p*	*HR (95 CI)*	*p*	*HR (95 CI)*	*p*	*HR (95 CI)*	*p*
Anaemia	**2.01 (1.26,3.22)**	**0.004**	**2.14 (1.22,3.73)**	**0.008**	**2.19 (1.64,2.93)**	**<0.001**	**2 (1.43,2.79)**	**<0.001**	**2.52 (1.48,4.27)**	**0.001**	**1.92 (1.04,3.54)**	**0.036**	**2.16 (1.73,2.69)**	**<0.001**	**2.02 (1.57,2.60)**	**<0.001**
Undernutrition	1.72 (0.91,3.27)	0.097	1.54 (0.74,3.21)	0.249	**3.15 (2.26,4.40)**	**<0.001**	**2.61 (1.76,3.89)**	**<0.001**	**2.46 (1.37,4.40)**	**0.002**	**2.37 (1.19,4.73)**	**0.015**	**2.64 (2.03,3.43)**	**<0.001**	**2.24 (1.65,3.04)**	**<0.001**
Hypertension	0.85 (0.39,1.85)	0.681	1.16 (0.47,2.84)	0.752	0.87 (0.63,1.21)	0.417	1.23 (0.84,1.81)	0.296	0.79 (0.47,1.33)	0.371	1.04 (0.56,1.93)	0.898	0.82 (0.63,1.05)	0.121	1.16 (0.85,1.57)	0.356
Opportunistic infection	1.94 (0.60,6.20)	0.266	1.78 (0.52,6.12)	0.358	**2.56 (1.53,4.29)**	**<0.001**	**2.72 (1.57,4.72)**	**<0.001**	**2.7 (1.06,6.84)**	**0.037**	2.02 (0.76,5.39)	0.159	**2.39 (1.57,3.63)**	**<0.001**	**2.41 (1.56,3.74)**	**<0.001**
Cancer	1.53 (0.56,4.21)	0.406	1.01 (0.30,3.39)	0.989	**1.7 (1.05,2.75)**	**0.032**	**2.02 (1.18,3.46)**	**0.01**	0.37 (0.05,2.70)	0.33	0.41 (0.06,3.05)	0.385	1.44 (0.94,2.20)	0.091	1.5 (0.94,2.41)	0.09
Pulmonary diseases	*omitted*		*omitted*		0.81 (0.11,5.77)	0.833	1.31 (0.18,9.47)	0.787	*omitted*		*omitted*		0.49 (0.07,3.48)	0.474	0.81 (0.11,5.77)	0.829
Tuberculosis	**5.73 (2.58,12.72)**	**<0.001**	**3.31 (1.28,8.60)**	**0.014**	**2.29 (1.40,3.75)**	**0.001**	**1.43 (0.80,2.57)**	**0.229**	**8.6 (4.59,16.10)**	**<0.001**	**6.41 (3.10,13.25)**	**<0.001**	**3.57 (2.54,5.02)**	**<0.001**	**2.54 (1.72,3.75)**	**<0.001**
Hepatic diseases	**2.13 (1.02,4.43)**	**0.043**	1.92 (0.73,5.04)	0.188	0.81 (0.47,1.40)	0.449	0.62 (0.32,1.19)	0.149	0.91 (0.37,2.28)	0.848	0.71 (0.25,1.99)	0.509	1.01 (0.68,1.49)	0.975	0.86 (0.53,1.37)	0.514
Renal impairment	4.29 (0.59,31.40)	0.152	4.23 (0.50,35.54)	0.184	2.7 (1.11,6.57)	0.028	2.32 (0.85,6.38)	0.102	0.43 (0.11,1.77)	0.242	0.22 (0.03,1.62)	0.137	1.13 (0.56,2.28)	0.73	0.85 (0.37,1.97)	0.705
Female sex	**0.55 (0.33,0.93)**	**0.025**	**0.52 (0.27,0.99)**	**0.048**	**0.64 (0.49,0.84)**	**0.001**	**0.55 (0.40,0.76)**	**<0.001**	0.66 (0.40,1.08)	0.1	0.77 (0.42,1.41)	0.402	**0.68 (0.55,0.84)**	**<0.001**	**0.6 (0.47,0.77)**	**<0.001**
WHO Stage at baseline																
Stage 1/2	1		1		1		1		1		1		1		1	
Stage 3/4	1.49 (0.93,2.40)	0.1	0.91 (0.49,1.68)	0.765	**1.76 (1.32,2.36)**	**<0.001**	**1.5 (1.07,2.12)**	**0.019**	**1.8 (1.04,3.12)**	**0.035**	1.3 (0.73,2.33)	0.376	**1.62 (1.30,2.03)**	**<0.001**	**1.3 (1.01,1.69)**	**0.045**
CD4+ at baseline																
>200 cells/mm^3	1		1		1		1		1		1		1		1	
100-199 cells/mm^3	1.12 (0.57,2.23)	0.739	0.9 (0.44,1.85)	0.774	0.71 (0.46,1.09)	0.119	0.65 (0.41,1.01)	0.053	1.03 (0.50,2.09)	0.942	0.93 (0.44,1.97)	0.853	0.82 (0.60,1.14)	0.241	0.71 (0.51,0.99)	0.043
<100 cells/mm^3	1.62 (0.92,2.87)	0.096	1.26 (0.66,2.39)	0.484	1.15 (0.82,1.60)	0.423	0.82 (0.57,1.16)	0.258	1.69 (0.92,3.09)	0.092	1.04 (0.52,2.05)	0.916	1.28 (0.99,1.66)	0.061	0.9 (0.68,1.20)	0.485
Age at baseline [years]																
15-29	-		-		-		-		-		-		1		1	
30-49	-		-		-		-		-		-		0.75 (0.58,0.97)	0.027	0.61 (0.45,0.84)	0.002
≥ 50	-		-		-		-		-		-		0.74 (0.53,1.02)	0.068	0.53 (0.35,0.79)	0.002

Supplementary Tables

Supplementary Table 14. Diagnosis definitions used in analysis

	Disease	Measured values	ICD-10 Code (* = including all sublevels)
Haematological	Anaemia	Hb: female < 11g/dl, male < 12g/dl	
	Severe anaemia	Hb < 8g/dl	
	Thrombocytopenia	Tc < 150 G/l	
Metabolic	Undernutrition	BMI < 18.5 kg/m2 based on ≥ 2 consecutive measurements	E44-E46
	Obesity	BMI ≥ 30.0 kg/m2 based on ≥ 2 consecutive measurements	E66*
	Diabetes		E10-E14.9
Cardiovascular	Arterial hypertension	> 140/90mmHg upon two consecutive measureme OR under treatment	I10-I15.9
	Other cardiovascular diseases ♈		I00-I09.9, I20-I52.9, I60-I83.9, I86-94.9, I96-I99.9
Opportunistic Infectio	Mucocutaneous mycosis		B20.4, B20.5, B35-B49.9
	Cryptococcosis	Cryptococcus-Antigen	B45*, G02.1
	Pneumocystis jirovecii Pneumonia		B20.6, B59*
	Toxoplasmosis		B58*, G05.2, J17.3
	Herpes Zoster		B02*
Cancer	HIV-associated cancer Δ		B21*, C21, C46*, C53*, C81-C86.9, D06*
	Non HIV-associated cancer		C00-C45, C47, C52.9, C54-D05.9, D0 D48.9
Pulmonary	Respiratory: Infectious ω		J00-J06.9, J13-J16.9, J17.0, J18*, J2 J40-J42.9, J85*
	Respiratory: Non-Infectious ⍭		J43-J46.9, J90-J99.9
Tuberculosis	Pulmonary tuberculosis	Xpert® TB/RIF sputum OR positive screening questions & Anti-tuberculosis treatment	A15-A16.9
	Extrapulmonary tuberculosis	Xpert® TB/RIF other sample than sputum	A17-A19.9, G01*, G07*, G99.8
	Unspecified tuberculosis	Xpert® TB/RIF without further information sample information	
Gastro-Intestinal	Gastroenteritis not further specified ‡		A00, A01, A02-A05.9, A06-A09.9, B78.0, K61, K65
	Viral hepatitis B	HBs-Antigen	
	Hepatopathy ⌽		B15*, B17*, B18*, B19*, K70-K77.9, R16-R18.9
Renal/Urogenital	Acute kidney injury §	eGFR (CKD-EPI) < 60 ml/min/1.73m2 with a subsequent eGFR > 90 ml/min/1.73m2	
	CKD KDIGO Stage 3-5	eGFR (CKD-EPI) < 60ml/min/1.73m2 based on ≥ 2 consecutive measurements	
	Urinary tract infection ☿		N10-N12.9, N30*, N39.0, O23.0, O23
	Syphilis	positive VDRL	A50-A53.9
	Sexually transmitted diseases (other than HIV and syphilis) †		B50-B54.9, N34*, N70*, N71*, N72, N73*, N74*
Malaria	Malaria	blood smears or rapid diagnostic test (RDT)	B50.0 - B54.9

Abbreviations: Hb Hemoglobin; Tc Thrombocytes; BMI Body Mass Index; KDIGO, Kidney disease improving global outcome; CKD-EPI Chronic Kidney Disease Epidemiology Collaboration; VDRL Venereal Disease Research Laboratory

♈including ischaemic and other heart diseases, vascular diseases, stroke; Δ including kaposi sarcoma, cervical cancer, lymphoma; ω including upper respiratory tract infection, acute bronchitis, viral and bacterial pneumonia, lung abscess; ⍭ including pleural effusion, pneumothorax, chronic bronchitis, emphysema, chronic obstructive pulmonary disease, asthma bronchiale; ‡ including protozoal, bacterial, typhoid, isosporiosis; ⌽ including viral hepatitis, alcoholic liver disease, toxic liver diseases, oesophageal varices, other liver diseases; § Acute kidney injury network (AKIN) Stage 2 and above; ☿including cystitis, pyelonephritis; † including cervicitis, pelvic inflammatory disease, urethritis

Supplementary Table 15. Self-reported medical history before enrollment into care

		15-29 years	30-49 years	≥ 50 years	Overall
n		*329*	*987*	*306*	*1622*
Haematological	Anaemia	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Metabolic	Undernutrition	0	0	0	0
	Obesity	0	0	0	0
Cardiovascular	Arterial Hypertension	3 (0.9)	12 (1.2)	23 (7.5)	38 (2.3)
	Other cardiovascular diseases ♈	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)
Opportunistic Infection	Mucocutaneous mycosis	2 (0.6)	7 (0.7)	0 (0.0)	9 (0.6)
	Cryptococcosis	0 (0.0)	2 (0.2)	0 (0.0)	2 (0.1)
	Pneumocystis jirovecii Pneumonia	0	0	0	0
	Toxoplasmosis	0	0	0	0
	Herpes zoster	11 (3.3)	67 (6.8)	26 (8.5)	104 (6.4)
Cancer	HIV-associated cancer Δ	0 (0.0)	2 (0.2)	0 (0.0)	2 (0.1)
	Non HIV-associated cancer	0 (0.0)	0 (0.0)	2 (0.7)	2 (0.1)
Pulmonary	Respiratory: Infectious ω	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
	Respiratory: Non-Infectious ⍭	0 (0.0)	2 (0.2)	1 (0.3)	3 (0.2)
Tuberculosis	Pulmonary tuberculosis	5 (1.5)	40 (4.1)	13 (4.2)	58 (3.6)
Gastro-Intestinal	Gastroenteritis not further specified ‡	0 (0.0)	3 (0.3)	0 (0.0)	3 (0.2)
Renal/Urogenital	Urogenital disease º	3 (0.9)	9 (0.9)	5 (1.6)	17 (1.0)
Malaria	Malaria	1 (0.3)	8 (0.8)	1 (0.3)	10 (0.6)

Data are presented as count (column percentage). Abbreviations: KDIGO, Kidney disease improving global outcome; NA, not available (i.e. no test/values available)

♈including ischaemic and other heart diseases, vascular diseases, stroke; Δ including kaposi sarcoma, cervical cancer, lymphoma; ω including upper respiratory tract infection, acute bronchitis, viral and bacterial pneumonia, lung abscess; ⍭ including pleural effusion, pneumothorax, chronic bronchitis, emphysema, chronic obstructive pulmonary disease, asthma bronchiale; ‡ including protozoal, bacterial, typhoid, isosporiosis; ⏀ including viral hepatitis, alcoholic liver disease, toxic liver diseases, oesophageal varices, other liver diseases; § Acute kidney injury network (AKIN) Stage 2 and above; º including cystitis, pyelonephritis, cervicitis, pelvic inflammatory disease, urethritis

Supplementary Table 16. Comparison of Baseline Characteristics in patients under active care/relocated and those lost to Follow-up/died

	active follow-up	**LTFU/died**	**p**
n	1268	354	
Age years median (IQR)	38 (31, 46)	38 (31, 47)	0.72
Year registered			<0.001
2013	173 (13.6)	56 (15.8)	
2014	261 (20.6)	92 (26.0)	
2015	310 (24.4)	104 (29.4)	
2016	253 (20.0)	85 (24.0)	
2017	271 (21.4)	17 (4.8)	
Sex			0.002
Female	852 (67.2)	206 (58.2)	
Male	416 (32.8)	148 (41.8)	
Marital status			0.66
Married/living with partner	750 (59.1)	214 (60.5)	
Not living with partner	518 (40.9)	140 (39.5)	
Education			0.12
None	125 (9.9)	22 (6.2)	
Primary school	1053 (83.0)	307 (86.7)	
Secondary school	77 (6.1)	19 (5.4)	
Tertiary education	13 (1.0)	6 (1.7)	
Transmission mode Ψ			0.73
Heterosexual	1037 (81.8)	271 (76.6)	
Homosexual	1 (0.1)	0 (0.0)	
Perinatal	11 (0.9)	3 (0.8)	
Other/unknown	219 (17.2)	80 (22.6)	
Current smoking	48 (3.8)	28 (7.9)	<0.001
Alcohol consumption	182 (14.4)	35 (9.9)	0.10
WHO stage			<0.001
1	539 (42.5)	97 (27.4)	
2	186 (14.7)	45 (12.7)	
3	370 (29.2)	105 (29.7)	
4	137 (10.8)	70 (19.8)	
NA	36 (2.8)	37 (10.5)	
CD4+ cell count (/mm^3)			0.009
<100	296 (23.3)	104 (29.4)	
100-199	248 (19.6)	52 (14.7)	
200-499	433 (34.1)	107 (30.2)	
≥500	115 (9.1)	21 (5.9)	
NA	176 (13.9)	70 (19.8)	
CD4+ count, median (IQR)	201 (91, 340)	169 (55, 309)	0.002

Data are presented as count (column percentage) and median (interquartile range). Abbreviations: IQR, interquartile range; NA, not available (i.e. no test/values available). Ψ no transmission by blood transfusion or IV drug use reported.

Supplementary Table 17. Incidence of comorbidities by age group

	15-29 years			30-49 years			≥ 50 years			Overall		
	py	# events	rate / 1000py [95% CI]	py	# events	rate /1000py [95% CI]	py	# events	rate / 1000py [95% CI]	py	# events	rate / 1000py [95% CI]
Anaemia	478	38	79.5 [57.9, 109.3]	1756	110	62.7 [52.0, 75.5]	531	36	67.8 [48.9, 94.1]	2764	184	66.6 [57.6, 76.9]
Severe anaemia	522	8	15.3 [7.7, 30.6]	1888	31	16.4 [11.5, 23.4]	585	3	5.1 [1.7, 15.9]	2995	42	14.0 [10.4, 19.0]
Thrombocytopenia	493	30	60.9 [42.6, 87.1]	1770	117	66.1 [55.2, 79.2]	530	45	84.9 [63.4, 113.7]	2793	192	68.8 [59.7, 79.2]
Undernutrition	490	26	53.0 [36.1, 77.9]	1770	98	55.4 [45.4, 67.5]	515	36	69.9 [50.5, 97.0]	2776	160	57.6 [49.4, 67.3]
Obesity	506	17	33.6 [20.9, 54.0]	1826	56	30.7 [23.6, 39.8]	573	7	12.2 [5.8, 25.6]	2905	80	27.5 [22.1, 34.3]
Arterial hypertension	508	23	45.2 [30.1, 68.1]	1751	115	65.7 [54.7, 78.9]	506	49	96.8 [73.1, 128.0]	2766	187	67.6 [58.6, 78.0]
Other cardiovascular diseases ♈	525	3	5.7 [1.8, 17.7]	1890	18	9.5 [6.0, 15.1]	571	14	24.5 [14.5, 41.4]	2986	35	11.7 [8.4, 16.3]
Mucocutaneous mycosis	491	29	59.1 [41.1, 85.0]	1698	106	62.4 [51.6, 75.5]	537	30	55.8 [39.0, 79.9]	2726	165	60.5 [52.0, 70.5]
Cryptococcosis	529	0	0	1917	4	2.1 [0.8, 5.6]	584	1	1.7 [0.2, 12.1]	3030	5	1.7 [0.7, 4.0]
Pneumocystis jirovecii Pneumonia	525	2	3.8 [1.0, 15.2]	1911	8	4.2 [2.1, 8.4]	579	4	6.9 [2.6, 18.4]	3015	14	4.6 [2.8, 7.8]
Toxoplasmosis	528	1	1.9 [0.3, 13.5]	1906	10	5.2 [2.8, 9.7]	580	5	8.6 [3.6, 20.7]	3014	16	5.3 [3.3, 8.7]
Herpes Zoster	525	2	3.8 [1.0, 15.2]	1873	20	10.7 [6.9, 16.6]	582	2	3.4 [0.9, 13.7]	2981	24	8.1 [5.4, 12.0]
HIV-associated cancer Δ	527	2	3.8 [0.9, 15.2]	1901	14	7.4 [4.4, 12.4]	586	1	1.7 [0.2, 12.1]	3015	17	5.6 [3.5, 9.1]
Non HIV-associated cancer	524	4	7.6 [2.9, 20.4]	1911	5	2.6 [1.1, 6.3]	576	6	10.4 [4.7, 23.2]	3011	15	5.0 [3.0, 8.3]
Respiratory: Infectious ω	492	28	56.9 [39.3, 82.4]	1708	124	72.6 [60.9, 86.6]	522	42	80.4 [59.4, 108.8]	2722	194	71.3 [61.9, 82.0]
Respiratory: Non-Infectious ⍭	529	0	0	1892	13	6.9 [4.0, 11.8]	579	4	6.9 [2.6, 18.4]	3000	17	5.7 [3.5, 9.1]
Tuberculosis overall	512	15	29.3 [17.7, 48.6]	1813	66	36.4 [28.6, 46.3]	563	21	37.3 [24.3, 57.2]	2888	102	35.3 [29.1, 42.9]
- Pulmonary tuberculosis	517	9	17.4 [9.1, 33.4]	1850	45	24.3 [18.2, 32.6]	575	13	22.6 [13.1, 38.9]	2942	67	22.8 [17.9, 28.9]
- Extrapulmonary tuberculosis	526	4	7.6 [2.9, 20.3]	1889	17	9.0 [5.6, 14.5]	580	8	13.8 [6.9, 27.6]	2995	29	9.7 [6.7, 13.9]
- Unspecified tuberculosis	526	5	9.5 [4.0, 22.8]	1886	22	11.7 [7.7, 17.7]	575	9	15.6 [8.1, 30.1]	2987	36	12.1 [8.7, 16.7]
Gastroenteritis not further specified ‡	503	13	25.8 [15.0, 44.5]	1832	66	36.0 [28.3, 45.8]	568	14	24.7 [14.6, 41.6]	2903	93	32.0 [26.1, 39.3]
Viral hepatitis B	529	0	0	1919	2	1.0 [0.3, 4.2]	586	0	0	3034	2	0.7 [0.2, 2.6]
Hepatopathy ⌽	528	6	11.4 [5.1, 25.3]	1864	29	15.6 [10.8, 22.4]	572	9	15.7 [8.2, 30.2]	2964	44	14.8 [11.0, 19.9]
Acute kidney injury §	519	5	9.6 [4.0, 23.1]	1833	59	32.2 [24.9, 41.5]	560	22	39.3 [25.9, 59.7]	2912	86	29.5 [23.9, 36.5]
CKD KDIGO Stage 3-5	529	0	0	1911	6	3.1 [1.4, 7.0]	572	8	14.0 [7.0, 28.0]	3012	14	4.6 [2.8, 7.8]
Urinary tract infection ☿	521	11	21.1 [11.7, 38.1]	1875	27	14.4 [9.9, 21.0]	570	8	14.0 [7.0, 28.1]	2966	46	15.5 [11.6, 20.7]
Syphilis	519	5	9.6 [4.0, 23.2]	1844	47	25.5 [19.2, 33.9]	562	14	24.9 [14.8, 42.1]	2924	66	22.6 [17.7, 28.7]
STD (other than HIV and syphilis) †	504	17	33.7 [21.0, 54.3]	1809	64	35.4 [27.7, 45.2]	570	8	14.0 [7.0, 28.1]	2882	89	30.9 [25.1, 38.0]
Malaria	505	13	25.7 [14.9, 44.3]	1821	52	28.6 [21.8, 37.5]	573	7	12.2 [5.8, 25.6]	2900	72	24.8 [19.7, 31.3]

Abbreviations: KDIGO, Kidney disease improving global outcome; NA, not available (i.e. no test/values available), STD Sexually transmitted diseases. ♈ including ischaemic and other heart diseases, vascular diseases, stroke; Δ including kaposi sarcoma, cervical cancer, lymphoma; ω including upper respiratory tract infection, acute bronchitis, viral and bacterial pneumonia, lung abscess; ⍭ including pleural effusion, pneumothorax, chronic bronchitis, emphysema, chronic obstructive pulmonary disease, asthma bronchiale; ‡ including protozoal, bacterial, typhoid, isosporiosis; ⌽ including viral hepatitis, alcoholic liver disease, toxic liver diseases, oesophageal varices, other liver diseases; § Acute kidney injury network (AKIN) Stage 2 and above; ☿ including cystitis, pyelonephritis; † including cervicitis, pelvic inflammatory disease, urethritis

Manuscript 6. The coArtHA trial - Identifying the most effective treatment strategies to control arterial hypertension in sub-Saharan Africa: study protocol for a randomized controlled trial

Herry Mapesi[1,2,3], Ravi Gupta[4], Herieth Ismael Wilson[1], Blaise Lukau[4], Alain Amstutz[2,3,8], Aza Lyimo[5,6], Josephine Muhairwe[4], Elizabeth Senkoro[1], Theonestina Byakuzana[1], Madavida Mphunyane[7], Moniek Bresser[2,3], Tracy Renée Glass[2,3], Mark Lambiris[2,3], Günther Fink[2,3], Winfrid Gingo[5], Manuel Battegay[3,8], Daniel Henry Paris[2,3], Martin Rohacek[1,2,3,5], Fiona Vanobberghen[2,3], Niklaus Daniel Labhardt[2,3,8], Thilo Burkard[9,10*] and Maja Weisser[1,2,3,8#*]

[1]Ifakara Health Institute, Ifakara branch, Ifakara, United Republic of Tanzania

[2]Swiss Tropical and Public Health Institute, Basel, Switzerland

[3]University of Basel, Basel, Switzerland

[4]SolidarMed, Partnerships for Health, Lesotho

[5]St. Francis Referral Hospital, Ifakara, United Republic of Tanzania

[6]Tanzania Training Center for International Health, Ifakara, United Republic of Tanzania

[7]Ministry of Health, Maseru, Lesotho

[8]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Basel, Switzerland

[9]Medical Outpatient and Hypertension Clinic, ESH Hypertension Centre of Excellence, University Hospital Basel, Basel, Switzerland

[10]Department of Cardiology, University Hospital Basel, Basel, Switzerland

*****Equal contribution

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Abstract

Background

Arterial hypertension is the most prevalent risk factor for cardiovascular disease in sub-Saharan Africa. Only a few and mostly small randomized trials have studied antihypertensive treatments in people of African descent living in sub-Saharan Africa.

Methods

In this open-label, three-arm, parallel randomized controlled trial conducted at two rural hospitals in Lesotho and Tanzania, we compare the efficacy and cost-effectiveness of three antihypertensive treatment strategies among participants aged ≥18 years. The study includes patients with untreated uncomplicated arterial hypertension diagnosed by a standardized office blood pressure ≥ 140/90mmHg. The trial encompasses a superiority comparison between a triple low-dose antihypertensive drug combination versus the current standard of care (monotherapy followed by dual treatment), as well as a non-inferiority comparison for a dual drug combination versus standard of care with optional dose titration after 4 and 8 weeks for participants not reaching the target blood pressure. The sample size is 1268 participants with parallel allocation and a randomization ratio of 2:1:2 for the dual, triple and control arms, respectively. The primary endpoint is the proportion of participants reaching a target blood pressure at 12 weeks of ≤130/80 mmHg and ≤140/90 mmHg among those aged <65 years and ≥65 years, respectively. Clinical manifestations of end-organ damage and cost-effectiveness at 6 months are secondary endpoints.

Discussion

This trial will help to identify the most effective and cost-effective treatment strategies for uncomplicated arterial hypertension among people of African descent living in rural sub-Saharan Africa and inform future clinical guidelines on antihypertensive management in the region.

Trial registration: Clinicaltrials.gov, NCT04129840. Registered on 17 October 2019 (https://www.clinicaltrials.gov/).

Keywords: arterial hypertension; blood pressure; antihypertensive therapy; randomized controlled trial; sub-Saharan Africa; HIV; triple therapy; dual therapy; Tanzania and Lesotho.

Number of references: 78

Background

Cardiovascular morbidity and mortality in low-and middle-income countries – particularly sub-Saharan Africa - are rising [373,374]. The most important risk factor for cardiovascular disease in sub-Saharan Africa is arterial hypertension with a prevalence of 30-46% [159–161,163,164,375,376] and an age-standardized mean systolic blood pressure (BP) being 5-20 mmHg higher compared to North America or Europe [373]. Black ethnicity has been associated with elevated BP [377] due to genetic factors, epigenetic adaptation to climate [169,170] and increased susceptibility to salt intake [171,172]. Moreover, complications of arterial hypertension such as stroke, chronic kidney disease and myocardial infarction have shown to be more prevalent in black compared to white populations [208]. Despite the high burden of arterial hypertension in sub-Saharan Africa, less than 40% of hypertensive patients are aware of their diagnosis. Among those who are aware of their diagnosis, less than 30% are receiving antihypertensive medications and less than 20% of those being treated have a controlled BP [164,378].

Most patients need a combination of at least two antihypertensive drugs to achieve BP control [222,379,380]. The latest American and European guidelines recommend starting a combination pharmacologic treatment with at least two classes of antihypertensive medications for patients with a BP ≥140/90mmHg [381]. However, the World Health Organization (WHO) guidelines still recommend a sequential treatment approach starting with a calcium channel blocker (CCB) or a thiazide diuretic (TZD), and combining both drugs only in case of inadequate response [382–384]. From sub-Saharan Africa, there is very little evidence supporting the WHO approach: Only five, mostly small randomized trials comparing the effectiveness of different antihypertensive regimens were conducted in sub-Saharan Africa [385–389]. A recent trial performed in ten centers in six African countries found amlodipine-containing regimens with either hydrochlorothiazide or perindopril to be superior to perindopril plus hydrochlorothiazide in controlling BP at six months [390].

The control Arterial Hypertension in sub-Saharan Africa (coArtHA) trial aims at comparing three treatment strategies to achieve rapid BP control with widely available drugs within 12 weeks in participants of African descent in rural sub-Saharan Africa. In addition, it assesses hypertension-mediated organ damage and compares the cost-effectiveness of the three treatment strategies considered.

Methods

Study setting

The coArtHA trial is conducted at the St. Francis Referral Hospital in Ifakara, Southwestern Tanzania and Mokhotlong District Hospital, Mokhotlong town, Northern Lesotho. In Tanzania, the STEP survey 2013 showed a prevalence of arterial hypertension of 25.9% in individuals aged 24-65 years of age [391]. At the Chronic Diseases Clinic of Ifakara (CDCI) of the St. Francis Referral Hospital participants of the Kilombero and Ulanga Antiretroviral Cohort (KIULARCO) [277,278] were hypertensive at enrolment in 12% [293]. Among HIV-positive patients on stable ART prevalence of arterial hypertension was even higher with 27% overall and 44% among patients aged ≥50 years [392]. The CDCI cares for about 4,500 patients with an HIV infection, while the general outpatient department sees 36, 000 patients a year [393] .

In Lesotho, prevalence of arterial hypertension in the general population is around 31% among persons aged 25 to 64 years [394] and 28% and 22% among HIV-positive females and males, respectively [395]. Mokhotlong Hospital serves the district of Mokhotlong, which is situated in northeast of Lesotho and has about 120, 000 habitants, the majority living in remote villages scattered over a mountainous area of 4, 075 km^2. The hospital has 110 beds and its outpatient clinic serves 4, 500 – 7, 500 adult patients per month.

Study design

The coArtHA trial is an investigator-initiated, open-label, three-arm randomized controlled two-country trial to compare the effectiveness and cost-effectiveness of three antihypertensive treatment strategies in HIV-positive and negative participants with uncomplicated arterial hypertension in rural Tanzania and Lesotho.

The trial is designed for a superiority comparison between the triple drug combination regimen versus control, and a non-inferiority comparison between the dual drug combination regimen versus control. Allocation is 2:1:2 for the dual combination, triple combination and control arms, respectively, with parallel assignment.

Control and intervention arms

Treatment strategies are shown in Figure 15. The control arm follows standard of care, i.e. national guidelines of Lesotho and Tanzania, which recommend a CCB or a TZD as first line, and if insufficient both drugs are combined [377,381,396,397]. For this trial, participants in the control arm start treatment with amlodipine 10mg. Participants randomized to the dual arm receive a combination of half-dose amlodipine (5mg) and losartan (50mg). Participants randomized to the triple arm receive a combination of quarter-dose amlodipine (2.5mg), hydrochlorothiazide (6.25mg) and losartan (12.5mg). The choice of amlodipine, losartan and hydrochlorothiazide is based on their broad availability and low cost. All of the three drugs are

part of the essential drug list by the WHO [398]. Participants in all three arms follow a prespecified dose titration after 4 and 8 weeks if target BP values are not met (Figure 15).

Study procedures

Screening and eligibility criteria

During routine care at the HIV clinic or the outpatient department, a BP measurement is done, which serves as pre-screening for the study. Individuals with a pre-screening BP ≥140/90mmHg are referred to the study nurse. The study nurse informs the individual about the study, obtains written informed consent and checks eligibility criteria (table 1). Screening of participants is a stepwise procedure starting with a questionnaire to ensure absence of acute disease, followed by a standardized office BP measurement (see below). A urine pregnancy test is performed in all women of childbearing age (18-45 years) to exclude pregnancy. From a fingerpick blood sample an HIV test is done if the participant is not known positive or has not been tested during the last 3 months with a documented result. A point of care creatinine is done to exclude severe renal impairment (creatinine clearance <30ml/min) (Figure 16).

Enrolment and Randomization

Immediately after screening, enrolment is done with a detailed history and a clinical exam. All information is entered into an electronic questionnaire (MACRO®, Elsevier). By venipuncture 5ml of blood are withdrawn and sent to the laboratory for full-blood count, serum creatinine and alanine aminotransferase. Urine is analyzed for albumin-creatinine ratio. A 12-lead-Electrocardiogram (ECG), a focused echocardiography using Lumify® device (Philips) and a retinal picture (iExaminer®, Welch-Allyn) are performed (Figure 16). The results of these analyses are stored electronically for later interpretation by a cardiologist and ophthalmologist.

Randomization is stratified by site (Lesotho, Tanzania), HIV status (negative, positive), and age (<65/≥65 years), using permuted blocks with varying block sizes. The randomization list was prepared in advance by an independent statistician and is stored securely on a server with restricted access. The allocation is concealed by using opaque, sealed and labelled envelopes prepared by independent persons based on the randomization list. The envelopes are labelled on the outside with the stratification information and a sequential identification number, and contain the randomized allocation and subject identification number. The first five randomizations in each stratum are checked in real-time, and subsequent regular checks are performed to ensure that the randomization sequence is respected. The nurse opens the envelope according the stratification, and the study physician fills in an electronic drug prescription according to the arm. The nurse dispenses the drugs accordingly, and provides pre-packed and labelled medication for one month

to the patient. Handing out of study drugs goes along with clear instructions on intake, adherence and appointment for the next follow-up visit.

Follow-up clinic visit procedures

Follow-up visits are scheduled at 4, 8, 12 and 24 weeks after enrolment. During these visits, the study nurse evaluates adherence to the study drugs, asks for symptoms relating to side effects and other adverse events, and performs standardized BP measurements. In women of childbearing age, a pregnancy test is repeated at every visit. The study doctor examines the participant and prescribes study drugs according to the treatment arm (Figure 15). Participants who reach the target BP and do not report side effects are prescribed the same medication at weeks 4, 8 and 12. In participants, who do not reach the target BP, the drug prescription is adapted by dosage increase or addition of other drugs as per protocol (Figure 15). Additional visits can be scheduled if clinically indicated. Participants missing their appointment are tracked within a week of the missed scheduled appointment - first by a phone call, and if the participant is not reachable by tracking with the help of community health workers or a person blinded to the allocation going to the participant's house.

On the last follow-up visit at 24 weeks, participants undergo again examinations to quantify surrogate markers of end-organ damage (Figure 15). After successful completion of the study, participants are referred to the local medical team for continued management including further prescription of drugs. Participants do not receive any payment to be part of the study besides compensation for transport expenses caused by additional clinic visits.

Standardized blood pressure measurement

For the determination of BP, we use a standard operating procedure based on the European Society of Cardiology/European Society of Hypertension (ESC/ESH) guidelines 2018 [150], which has been used in several recent clinical trials and epidemiological studies [399–401]. In brief, arm circumference is measured to determine the cuff size according to the recommendations of the BP device manufacturer (Omron M6 Comfort [HEM-7321-E] [402]. BP measures are taken in sitting position after 5 minutes of rest with feet on floor, back supported, no caffeine, exercise or smoking in the 30 minutes before measurement, emptied bladder, no talking during measurement, comfortable clothes, and arms supported (e.g. on table). At the screening visit, the reference arm is determined by measuring BP on both arms. The reference arm (with higher BP) is noted and used for all further BP measurements. The BP is calculated as the mean value of the last two out of three consecutive measurements, spaced 1-2 min apart.

Endpoints

The primary endpoint is the proportion of participants reaching target BP (≤130/80 mmHg in participants aged <65 years and ≤140/90 mmHg in participants aged ≥65 years) at 12 weeks. We

chose this target BP in line with updated European guidelines and the documented beneficial effect on cardiovascular outcomes [150]. The secondary endpoints are defined in table 2.

Sample size calculation

We hypothesize that the proportion of participants reaching the primary endpoint will be higher in the triple combination arm compared to the control arm. Additionally, we hypothesize that the dual combination arm will be non-inferior to the control arm (table 3). We assumed a response rate in the control arm of 40%, an improvement in the triple combination arm of 15 percentage points (two-sided alpha of 0.05) for the superiority comparison between the triple combination and control arms, and a non-inferiority margin of 10% (one-sided alpha of 0.025) for the non-inferiority comparison between the dual combination and control arms. Based on these assumptions, we calculated a sample size of 431 participants in each of the control and dual combination arms, and 216 participants in the triple combination arm (power of 85% for the non-inferiority comparison and 95% for the superiority comparison). The overall sample size is therefore 1078 participants, with the randomization ratio of 2:1:2 for the dual combination, triple combination and control arms, respectively. Assuming 15% of participants will become lost-to-follow-up [390] brings the total required sample size to 1268 individuals.

Data collection and management

Baseline information containing demographics and clinical evaluation are filled into a standardized electronic data management system (MACRO®, Elsevier) using password-protected laptops. Participants are assigned a unique identifier at screening and randomization which is used on all study documentation.

Data are checked by the principal investigator and the data manager to ensure complete and accurate data, with queries raised within the electronic data capture system to clarify inconsistencies and missing data. At each site, a master list linking the participant's unique identifier to the participant's details such as name is kept in a locked cupboard. Data will be stored in Swiss Tropical and Public Health Institute (Swiss TPH) servers which are located in Basel, Switzerland with a defined policy in place for server set-up, maintenance and security. Data are kept in compliance with local legal requirements, for a minimum of ten years after completion of the study.

Analyses

Analyses and reporting will follow CONSORT guidelines [403–405] and intention-to-treat (ITT) principles, that is including participants as randomized. A flowchart will describe the inclusion and follow-up of participants by study arm. Baseline characteristics will be described by study arm with summary statistics such as median and interquartile range or number and percentage; no formal testing between arms will be performed [406]. Outcomes will be described by arm using

summary statistics. The primary outcome, the proportion of participants reaching the target BP within 12 weeks, will be assessed using a logistic regression model, reporting odds ratios and risk differences with standard errors estimated using the delta method [407]. Binary secondary outcomes will be evaluated in the same way. Continuous secondary outcomes will be assessed using linear regression models, reporting mean differences. Time to event outcomes will be assessed using Kaplan-Meier estimation and Cox proportional hazards models. Estimates will be reported with 95% confidence intervals (CI). All models will be adjusted for baseline BP and the stratification factors of site, HIV status and age [408]. Effect modification of the primary outcome by site and HIV status will be assessed by incorporating an interaction between arm and site or HIV status, respectively, acknowledging that power will be low. Appropriate methods such as multiple imputation will be considered to account for participants with missing outcome data. We will compare each of the intervention arms versus control. For the non-inferiority comparison between the dual combination and control arms, a CI approach will be used. A figure illustrating the CIs and the non-inferiority margin will be presented. Primary analyses for the non-inferiority comparison will be performed on both the ITT and per protocol sets [409]. If the dual combination is found to be non-inferior to the control, then we will assess for superiority using the ITT set. The trial statistician will perform the statistical analyses using Stata (version 15, Stata Corporation, Austin, TX, USA). A full statistical analysis plan will be developed.

Nested studies and additional analyses

In a subset of 100 consenting participants (with a separate informed consent) living close to the CDCI in Ifakara, 24-hour ambulatory BP and standardized unattended BP measurement will be offered, to assess the proportion of participants with white coat hypertension [390]. In consenting participants, the 24-hour BP measurement is started immediately after enrolment, before randomization and study drug dispensing. The device is programmed to take measurements every 20 minutes between 6:00 and 22:00 and every 30 minutes between 22:00 and 6:00 [410]. At the end of the 24-hour ambulatory BP measurement, an unattended automated office BP measurement is done using a Dräger Infinity Delta® monitor, which is programmed to take five consecutive measurements after 5 min of rest, spaced 1 min apart with a calculation of the mean out of all measurements [410–413]. After completing both 24-hours and unattended BP measurements, the participant is randomized and receives study drugs as described above. Both, the 24-hour ambulatory BP measurement and the unattended BP measurement are repeated at 12 weeks. Results have no influence on randomization but will help to evaluate unattended office blood pressure as a tool to investigate white coat hypertension in low resource environments, where ambulatory blood pressure measurement is not widely available. Participants are informed of the results at the end of the study.

For the cost-effectiveness analysis we follow the JAMA guidelines and calculate incremental cost-effectiveness of the three regimens from both a health-systems and a societal perspective [414]. Health systems cost will include total medication cost as well as staff time and a fixed cost for each facility visit, which will be compared to the total health benefits achieved by the three arms [415]. Medical cost will be directly collected at the facility level in the two sites; we will obtain WHO reference prices for the respective drugs and treatments for comparison. For the societal perspective, we will include additional private cost of participants, with a particular focus on out-of-pocket expenditure for visits to facilities (transport, overnight stays) as well as costs for additional medication needed and days of work lost due to sickness [414]. To compute incremental cost effectiveness ratios, we will use the control arm as our reference case, and then compute the additional costs and benefits of the two intervention arms relative to this baseline scenario. Health outcomes will directly be observed over a 24 week period; reduced morbidity will be converted to disability-adjusted life years using the 2013 Global Burden of Disease disability weight estimates [416]. A separate analysis plan will be developed.

Monitoring and independent data monitoring committee

Monitoring is done by the Quality Management team of the Ifakara Health Institute (IHI) in Tanzania and by the Clinical Operations Unit, Swiss TPH in Lesotho. The study sites are visited by the trial monitoring team for site initiation, during the trial and at study closure. An independent data monitoring committee (IDMC) has been established to monitor the trial for efficacy and safety in accordance with an IDMC charter consisting of five members, including clinical experts from both countries and a statistician. An interim analysis to monitor the trial for efficacy and safety is planned after 50% of the target sample size has completed their primary outcome assessment at 12 weeks, which is expected to be approximately one year after the start of the trial. Only IDMC will have access to unblinded efficacy and safety data. Whether further analyses are needed, and the timing of such analyses will be determined by the IDMC. Furthermore, the IDMC will recommend that the trial continues, be modified or terminated based on their review.

Safety

All trial drugs have a well-established safety profile. Safety outcomes are assessed by adverse events (AE) and serious adverse events (SAE), which are captured at every visit and are documented at the earliest possible time point. (S)AEs are documented, graded according to the common terminology criteria for adverse events (CTCAE), and reported according to ethics regulations of Tanzania, Lesotho and Switzerland. The study physician is responsible for management and documentation of all (S)AEs. If a participant develops an AE of grade 2 or higher at the last study visit, he/she remains under observation by the study physicians beyond study termination, until the AE is resolved or stabilized.

Discussion

Worldwide, around 41 million people die annually from non-communicable diseases (NCDs). Arterial hypertension is the most prevalent risk factor for cardiovascular diseases and claims approximately 7.5 million lives annually [154]. Africa has the highest burden of arterial hypertension with an estimated prevalence of 40% [375]. This adds to the burden of the health care systems which are already overwhelmed with the management of a high number of infectious diseases in the region, including long-term care for patients with HIV [73,154,200,201]. Despite the high burden in Africa, there are still few clinical trials evaluating the best treatment for arterial hypertension in sub-Saharan Africa [150].

Since more than two third of patients need a combination therapy of antihypertensive medications to reach optimal BP targets [222,379,381] – which will be even more so in the light of new tighter targets – the question is less about the optimal first line drug class but rather the optimal combination and strategy to reach the target in the shortest time frame. A recent randomized controlled trial found that CCB-containing regimens were superior compared to a combination of diuretics and ACE-inhibitors among Africans [390]. Additionally, BP control has not been studied with respect to possible interactions with ART in people living with HIV, likely affecting treatment response [417–420]. This is of particular public health importance since more than 60% of HIV-infected patients worldwide live in sub-Saharan Africa [421].

With the coArtHA trial we aim to address these gaps by investigating three different regimens of widely available antihypertensive drugs listed in the WHO essential drug list in HIV-positive and HIV-negative participants with uncomplicated arterial hypertension in rural Tanzania and Lesotho. Furthermore, the trial evaluates surrogate markers of end-organ damage such as renal impairment, cardiac function and ocular manifestations.

We foresee some limitations, firstly that 24-hour BP measurement is not feasible for all participants posing a risk that we miss white coat hypertension in participants living remotely from the facility [422,423]. We chose a pragmatic approach using a highly standardized, stringent technique of office BP measurement and plan a nested study to compare in a subset of participants the office BP with a 24-hour ambulatory BP measurement. Secondly, since this is an open-label study, both participants and study staff are aware of the treatment allocation. However clinical endpoints such as ECG, echocardiography, retinal picture and 24-hour ambulatory BP measurements will be interpreted by clinicians blinded to the study arm.

In summary, the coArtHA trial will inform on the best treatment strategies for uncomplicated arterial hypertension in people living in sub-Saharan Africa. The trial aims to inform future

guidelines, to assess hypertension-mediated end-organ damage, and determine the cost-effectiveness of different arterial hypertension treatment strategies.

Timeline

The study duration of the study is planned to be 18 months, with a 12 months recruitment period followed by 6 months of follow-up. Recruitment started at Mokhotlong District Hospital on March 06, 2020 and at St. Francis Referral Hospital, Ifakara on March 24, 2020. Due to national lockdown measures during the SARS-Cov-2 pandemic, recruitment was interrupted in Lesotho from March 29, 2020 and in Tanzania from March 30, 2020. Recruitment was resumed in Lesotho on May 20, 2020 and in Tanzania on June 08, 2020. In case of slow recruitment, it might be extended to nearby hospitals. As of 28.07.2020, the number of participants recruited was 142.

Declarations

Ethics approval and consent to participate

This trial has been approved by Ethikkomission der Nordwest und Zentralschweiz, Switzerland (EKNZ, reference number: 2019-00817), by the Institutional review board of Ifakara Health Institute (reference number: IHI/IRB/No: 29 - 2019), the National Institute for Medical Research (reference number: NIMR/HQ/R.8a/Vol. IX/3277), the Tanzania Medicines and Medical Devices Authority (reference number: TMDA A0020/CTR/0002/03) and by the National Health Research and Ethics Committee, Ministry of Health of Lesotho (reference number: 224 - 2019).

The study investigator (or his/her designee) obtains written informed consent from all study participants before any study procedure and after explaining to the participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant is informed that participation in the study is voluntary, that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment. The participant is given a copy of the document, dated and signed by him and the investigator (or his designee); the original is retained as part of the study records. If the participant is illiterate, the study information is being read to him/her in the presence of a valid witness and the signature of a witness and the fingerprint of the participant is obtained. Study participants do not receive any payment to be part of the study besides compensation for transport expenses for additional clinical visits. Non-consenting participants are not included in the study.

Locally, the results of this trial will be shared to the district officials during district management team meetings at the national research symposium of the Ministry of Health in both countries. Additionally, the results will be disseminated through international presentations at conferences and publication in peer-reviewed journals. We do not intend to use a professional medical writer.

Consent for publication

Consent is asked from study participants for publication of gathered study data without providing identifying information of the participant.

Availability of data and materials

A minimal verified and anonymized dataset will be made available to a public data repository.

Competing interests

All authors declare that they have no competing interests.

Funding

This trial is funded by a grant from the Swiss National Science Foundation (32003B_185263) obtained by MW. HM receives his salary through the Swiss Government Excellence Scholarships for Foreign Scholars (ESKAS-Nr: 2018.0004). The funding sources had no role in the design of the study, and will not be involved in data collection, data analysis, interpretation of the results and writing of the manuscript.

Authors' contributions

MW is the responsible investigator of this trial, has conceived and designed the trial, and has received the grant. HM is the overall principal investigator. HM, TB, MR, NDL, DHP and FV have contributed in conception and design of the trial and in protocol writing. RV, JM, AA, TG, AL, ML, GF, WG, MB, DHP involved in critically revising the manuscript for important intellectual content. TG and FV perform statistical analysis. HW, ES, BL, MM, and MBR contribute to data collection and management. All authors read, revised, and approved the final protocol and manuscript submitted.

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Figures

Figure 15. Study Interventions and Drug Dosing According Study Arm

	Arm A Intervention 1	Arm B Intervention 2	Arm C Control (Standard of Care)
Start	Amlodipine 5mg OD + Losartan 50mg OD	Amlodipine 2.5mg OD + Losartan 12.5mg OD + Hydrochlorothiazide 6.25mg OD	Amlodipine 10mg OD
Week 4[$]	Amlodipine 10mg OD + Losartan 50mg OD *	Amlodipine 5mg OD + Losartan 25mg OD + Hydrochlorothiazide 12.5mg OD *	Amlodipine 10mg OD + Hydrochlorothiazide 25mg OD *
Week 8[$]	Amlodipine 10mg OD + Losartan 100mg OD *	Amlodipine 10mg OD + Losartan 50mg OD + Hydrochlorothiazide 25mg OD *	Amlodipine 10mg OD + Hydrochlorothiazide 50mg OD *
Week 12-24[$]	Amlodipine 10mg OD + Losartan 100mg OD *, **	Amlodipine 10mg OD + Losartan 50mg OD + Hydrochlorothiazide 25mg OD *,**	Amlodipine 10mg OD + Hydrochlorothiazide 50mg OD *, **

OD, once daily

[$] Increases in dosages only if target BP is not reached (see above)

* In case of orthostatic hypotension or adverse events, medication will be reduced to the prior step – or to half of the initial dosage.

** if regimen shows insufficient effect, individualized adaptation possible according the treating physician

Figure 16. Study visit schedule

Study Periods	Baseline (screen & enrolment)		Intervention Period			End of Study
Visit	SV01	ER01	FUP01	FUP02	FUP03	EOS01
Timepoint week day window for visit (days)	Day 0*	Day 1*	**Week 4** Day 28 22-42	**Week 8** Day 56 50-70	**Week 12** Day 84 78-98	**Week 24** Day 168 141-196
Patient Information & Informed Consent	x					
Demographics	x					
Medical History	x					
In- /Exclusion Criteria	x					
Physical Examination	x	x	x	x	x	x
Vital Signs		x	x	x	x	x
Blood pressure measurement	x		x	x	x	x
Screening blood tests (fingerpick) - HIV Test (rapid test as per national GL) - Point of care creatinine	x					
Urine pregnancy test in females 18-45y	x		X£	x£	x£	x£
Laboratory testing (venipuncture) - Blood: Full blood picture, creatinine, ALT, - Blood storage for biomarkers - Urine: Alb/Creat ratio, dipstick		x				x
Remote echocardiography		x				x
Remote fundoscopy		x				x
24hour blood pressure measurement		x**			x**	
Randomization		x				
Administer Study Medication		x	x	x	x	
Assess concomitant therapy or interventions		x	x	x	x	
Assessment of adverse Events		x	x	x	x	x

SV, Screening Visit; ER, Enrolment; FUP, Follow-up; EOS, End of study; ALT, alanine aminotransferase; Alb/Crea, Albumin/Creatinine; HIV, Human Immunodeficiency Virus.

*day 0 (screening) and day 1 (enrolment) are the same day for participants not enrolled in the 24-hour ambulatory BP study, £for all women of reproductive age (18 – 45 years), ** in 100 participants from Ifakara (nested study).

Tables

Table 18. Inclusion and exclusion criteria for coArtHA trial

Inclusion criteria	Exclusion criteria
- Adults (≥18 years of age) - African descent and black ethnicity - Confirmed uncomplicated and currently untreated arterial hypertension* diagnosed at one of the two sites.	- Current hospitalization for any reason - Refusal to do an HIV-test or indeterminate HIV test result - History of cardiovascular event in the last month (angina pain, stroke, myocardial infarction or respective diagnosis by a doctor) - Symptomatic arterial hypertension • blood pressure ≥180/110mmHg plus headache or chest pain) or acute cardiovascular event (see above) - Acute disease, e.g. • temperature >37.5°C or other signs of acute concomitant infection • dyspnea/respiratory distress • acute pain - Clinical signs of hypertension-mediated organ damage, e.g. • Heart failure (bilateral pitting edema, bilateral crackles or pleural effusion, distended jugular veins) • Ischemic heart disease (anginal pain on exertion) • signs of current ischemic/hemorrhagic stroke (hemiparesis, loss of consciousness) - Pregnancy (test required for females 18-45 years of age) - Non-consenting or inability to come for follow-up visits - Creatinine clearance ≤30ml/min by the Chronic Kidney Disease Epidemiology Formula (CKD-EPI) estimation and measurement with a point-of care creatinine from capillary blood

Table 19. Secondary endpoints and Nested Studies

Endpoint	**Time point after randomization**	**Remarks**
Proportion of participants reaching a target BP of ≤130/80 mmHg in patients <65 years of age and ≤140/90 mmHg in patients ≥65 years of age	At 4, 8, and 24 weeks	Same definition of target BP* as for the primary endpoint at 12 weeks
Change in BP from enrolment	At 4, 8, 12 and 24 weeks	Reduction in mmHg
Proportion of participants with treatment adaptations made to the primary treatment	By 12 weeks	Dose increase or decrease, and/or drug additions
Proportion of participants with a blood pressure decrease of at least 20/10 mmHg	4, 8, 12, and 24 weeks	
Number of treatment adaptations per participant made to the primary treatment	By 12 weeks	Dose increase or decrease, and/or drug additions
Time until target BP is (first) reached	Over 24 weeks	Censoring at last visit for those not observed to reach the target BP*, and for patients who achieve the target BP* any subsequent rebounds will be described but not included in this analysis

Proportion of participants with changes in surrogate markers for hypertension-mediated organ damage (resolving, newly occurring or worsening)	Over 24 weeks	Surrogate markers of organ damage
		• Kidney impairment: decrease in eGFR (CKD-EPI formula); increase in proteinuria, measured by albumin/creatinine ratio or
		• Hypertensive heart disease:
		  • positive Sokolow-Lyon Index (Sokolow-Lyon voltage (SV1 + RV5/V6 ≥ 3.5 mV and/or RaVL ≥ 1.1mV) on ECG ([424,425]) or
		  • signs of left ventricular hypertrophy [426] or left atrial remodeling/enlargement assessed by focused echocardiography [427,428] or
		• retinopathy: assessed by retinal picture [429].

Proportion of participants with major cardiovascular endpoints	Over 24 weeks	Major clinical endpoints of mortality, major cardiovascular events such as stroke, myocardial infarction, heart failure, end-stage kidney disease
Proportion of participants lost to follow up or stopped treatment	Over 24 weeks	
Proportion of participants with at least one grade 3/4 adverse event	Over 24 weeks	Adverse events will be graded according to the CTCAE v5.0, January 2018
Proportion of participants with at least one severe adverse event	Over 24 weeks	
Proportion of participants who were non-adherent to study drugs	Over 12 weeks	<90% pill count or <90% of self-reported drug intake
Reasons for non-adherence assessed by pill count and self-report	Over 12 weeks	Descriptive analysis

BP, blood pressure; eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; ECG, electrocardiogram; CTCAE Common Terminology Criteria for Adverse Events; HIV Human Immunodeficiency Virus.

*target BP is defined as ≤130/80 mmHg among participants aged <65 years and ≤140/90 mmHg among participants aged ≥65 years

Table 20. Assumptions for sample size calculation.

	Dual combination Guideline + incremental value of ARB in African patients	**Triple combination** quarter dose for 3 widely available drugs used	**Control** WHO standard of care starting with monotherapy
Literature	Reported response in 67% of Africans (response= diastolic blood pressure <90 mmHg or 10% decrease [377,430])	Reported response in 83% of patients* (response= blood pressure <135/85 mmHg [222])	Reported response in 67% of patients in Nigeria (response= blood pressure <149/90 mmHg [431])
Conservative effect estimation for higher target BP£	60%	75%	50%
Conservative effect estimation for lower target BP$	40%	55%	40%
Comparison with cited studies	Assumption of a smaller effect due to lower BP target	Effect might be lower (3 drugs instead of 4; no single pill) Effect might be higher as allowance to increase dosage	Effect might be lower due to lower target

ARB Angiotensin receptor blocker; BP blood pressure; WHO World Health Organization.

£140/90mmHg; $130/80mmHg

Manuscript 7. Challenges for HIV-infected adolescents during transition from paediatric to adult HIV clinics in Africa

Author

Herry Mapesi[1, 2, 3]

[1]Ifakara Health Institute, Ifakara branch, Ifakara,Tanzania

[2]Swiss Tropical and Public Health Institute, Basel, Switzerland

[3]University of Basel, Basel, Switzerland

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Editorial

In 2017, about 250,000 adolescents aged 15-19 years acquired a new HIV infection [432]. Of the approximately 1.8 million adolescents (10-19 years old) living with HIV/AIDS, 1.5 million (85%) are in sub-Saharan Africa [432,433]. High HIV prevalence and incidence in sub-Saharan Africa exposes increasing numbers of adolescents and young adults to HIV through both perinatal infection and risky behaviours [432]. Before the early 2000s, when antiretroviral treatment (ART) came into common use in Africa, only about half of HIV-infected infants reached their second birthday [434]. ART reduced the number of deaths caused by AIDS-related illnesses by about 42% between 2010 and 2017 [435]. Increasing ART coverage in Africa has made it more likely that perinatally and behaviourally HIV-infected children will reach adulthood, but it has not eliminated the burden; instead, the burden has shifted to adolescents. Now, more than ever, public health must focus on transferring adolescents from paediatric to adult-centred care [436], also called health care transition [437]. HIV-infected adolescents are accountable for their disease progression and are left alone with the responsibility for managing their disease and their health [438]. This is an especially vulnerable period because only 50% of HIV-infected adolescents transferred to adult-centred health care settings remain in care a year after transition [439].

Adolescents and young adults living with HIV in Africa face complex behavioural and psychological challenges, while they also must cope with a chronic disease that carries stigma. They are more likely than their HIV-negative counterparts to develop renal, bone, and neurocognitive diseases [438]. Stunting and skin diseases are also in HIV-infected adolescents. Children and adolescents who suffer from HIV-related comorbidities and opportunistic infections are highly stigmatised.

Health care systems in most African countries are not designed to meet the needs of these adolescents [438]. There is a shortage of health care workers with specialized training in adolescent medicine, infrastructure is inadequate and poorly designed, and clinics are overburdened [440]. These insufficiencies pose barriers to an adolescent's transition from paediatric to adult-centred clinics, and contribute to their poor adherence to treatment, virologic failure, clinical failure, and drug resistance with poor long-term outcomes [441]. Transition may be improved by hiring more trained personnel with expertise in adolescent care, and developing a sufficiently detailed evidence-based policy to guide the transition process, tailored to the resources of the health care provider. Adolescents may benefit from improved communication between health care providers from paediatric and adult clinics (e.g., a summary from the paediatric clinic that updated the adult clinic on an adolescent's current physical and mental health condition). Other interventions that have been implemented to smooth the transition in

low and middle-income countries (which may create an opportunity to address any experience of stigmatization) could be tried in sub-Saharan Africa, e.g., multidisciplinary clinic models, peer support groups, transition readiness and financial support programmes. [442], but little literature describes the best ways to implement these changes.

We need to conduct studies that compare and evaluate the effectiveness of different health care provision models appropriate to the African context, including youth friendly and dedicated teen clinics, use of peer educators and special day clinics for adolescents. With the advances in ART coverage, significant health gains have been made in terms of reduced mortality among this population. Therefore, there is an urgent need to ensure that the transition policy from paediatric to adult-centred clinics is part of health care management for HIV-infected adolescents and young adults in Africa. If this process of transition from paediatric to adult HIV clinic is properly documented, and if a platform to evaluate programs is developed, then other countries across sub-Saharan Africa could use this model to implement, monitor, and improve transition between paediatric and adult-centred clinics for HIV-positive adolescents.

Conflict of interest: the author has not conflict of interest

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General Discussion

The findings presented in this thesis demonstrate the importance of NCDs and comorbidities among PLHIV in sub-Saharan Africa. Specifically, the studies focussing on chronic kidney diseases, drug-associated weight gain, HIV-related comorbidities, and arterial hypertension. The first study summarized the current literature on the disease burden and clinical implications of NCDs in sub-Saharan Africa. The results from the second study demonstrated the prevalence and associated risk factors of developing renal impairment among patients who are switched from first- to second-line ART with boosted protease inhibitors. Body weight evolution among newly diagnosed ART naïve patients starting ART with either efavirenz or dolutegravir-based regimens was demonstrated in the third study of this thesis. The fourth manuscript was a letter to the editor discussing the rollout of dolutegravir-based regimens in sub-Saharan Africa and the associated public health implications. The fifth study assessed the prevalence and incidence of the most important comorbidities affecting PLHIV after initiation of ART and their contribution to mortality, according to age groups. The sixth manuscript is a protocol for a clinical trial to identify the most effective treatment strategies to control arterial hypertension in sub-Saharan Africa. The final manuscript of this PhD thesis is an editorial in which I discussed the different challenges faced by HIV-infected adolescents during their transition from paediatric to adult HIV clinics in Africa.

It is crucial to understand the prevalence and incidence of different comorbidities among PLHIV in order to design integrated care models. The double burden of communicable and non-communicable diseases is a major challenge to the healthcare systems in sub-Saharan Africa, which are already overwhelmed with the burden of infectious diseases, and management of maternal and new-born health issues [71]. Specifically, dramatic increases in the prevalences of lifestyle-related diseases such as obesity, hypertension, and diabetes are being observed [72–74]. The findings of this work (study 1, study 2, study 5 and study 7) underline the need for monitoring patients to improve the early detection of different comorbidities that might arise after starting ART and the importance of pharmacovigilance systems (study 3 and 4) to detect adverse events early after starting new drugs for chronic disease management.

Discussion of key findings

The double burden of NCD and infectious diseases

The first study of the thesis summarized the burden and clinical implications of the most prevalent NCDs in the general population in sub-Saharan Africa. The narrative review focused on arterial hypertension, cardiac diseases, diabetes mellitus and chronic kidney diseases and represents a basis upon which the body of subsequent research projects builds. The rapid rise in NCDs incidence adds to the existing burden of infectious diseases resulting in the devastating dual burden of diseases [71].

A recent study from our group conducted in rural Tanzania showed, that among 1,243 patients undergoing echocardiography from 12/2015 to 10/2017, hypertensive heart disease was the most frequent diagnosis with 41%, followed by valvular heart disease (18%), coronary heart diseases (18%) and peripartum cardiomyopathy (7%) [247]. A systematic review from sub-Saharan Africa also found hypertensive heart disease to account for 39% of clinical heart failures followed by cardiomyopathies (21%) and rheumatic heart diseases (14%) [244]. A community-based survey screening fifteen thousand urban adults and thirteen thousand rural adults found arterial hypertension in 14% participants – 60% of those not being aware nor treated [248]. Despite arterial hypertension being the leading cause of heart diseases in the region, there is still low awareness of the disease in the region [166]. At the time of our review, reported figures of the treatment cascade for hypertension to be poor with less than 40% of hypertensive patients being diagnosed, less than 30% of those being diagnosed receiving medical treatment, and less than 20% of those being treated achieving adequate BP control [443]. Other studies from sub-Saharan Africa have reported almost similar findings for the arterial hypertension treatment cascade [248,444,445].

The increasing burden of diabetes mellitus remains a significant public health challenge in sub-Saharan Africa [230]. In 2021, approximately 24 million adults are living with diabetes mellitus in Africa and the number is projected to reach 55 million (129% increase) by 2045 and it caused around 416,000 deaths in the same year [229]. Early diagnosis and management of diabetes mellitus are of paramount importance to diminish the progression of diabetes mellitus complications since most of the end-organ complications of diabetes are more common among Africans compared to patients from Western countries [232,233].

Finally, in our review we discuss the rise burden of CKD in sub-Saharan Africa, which is an independent risk factor for cardiovascular diseases [107]. The burden is even higher among HIV-

infected patients (ranging from 25% to 77%) compared to general population (13%) and has been associated with increased mortality in this population [102,250,271,446–449].

Overall, tackling the burden of NCDs in Africa requires multifactorial approaches with strengthening of existing health care systems to facilitate early diagnosis, treatment and management. The most common risk factors which cut across different NCDs can be grouped as modifiable risk factors (tobacco use, harmful use of alcohol, consumption of unhealthy diet, physical inactivity) and physiological risk factors (overweight and obesity, high blood pressure, hyperglycemia, and hyperlipidemia. Innovative community-based interventions, that provide education to increase the awareness of modifiable risk factors for NCDs, are vital for improving diagnosis and outcomes in the future. In fact, population-wide preventive measures for NCDs such as lowering of blood pressure, reducing sodium intake, and eliminating the intake of artificial trans fatty acids have been successful in reducing the burden of risk factors for NCDs in the communities [450–453]. In Peru, large community-based campaigns promoted the use of salt substitution, which lead to a reduction of blood pressure values in these populations [454,455]. Moreover, new policies such as establishment of publicly maintained open spaces and playgrounds for people to exercise might eventually increase physical activities in the communities hence a powerful preventive measure to reduce NCDs risk factors in the communities [456,457].

The amount of funding most African countries invest into their healthcare is not adequate to address the increasing need of managing chronic diseases. In 2001, the African Union Heads of State, committed to invest at least 15% of the annual budget to the health sector (Abuja declaration) [458]. However, this has not been the case in many countries and most of the countries [458] still depend on donor funding to run their healthcare systems [459]. For example, in Tanzania, during the annual budget for financial year 2019/2020, the total amount allocated was Tsh 2.21 trillion which accounts for 6.7% of the national budget and 1.5% of the Gross Domestic Product (GDP) [459]. On the other hand, some funding which is allocated to the health sector is diverted to other sectors [458,459]. Therefore, in order to have a well-functioning healthcare system to tackle NCDs it is important for the governments to commit to allocated adequate budget to the health sector.

Renal impairment in people receiving protease inhibitors

Study 2 was designed to investigate the prevalence and associated factors of renal impairment in PLHIV at the time of switch from first-line ART to bPI. This was a follow-up study of a first manuscript on renal impairment (defined as eGFR below 90ml/min/1.73m^2) in patients at start

of ART and under first line treatment [102], where we found a prevalence of renal impairment of 15.7% % at baseline and an incidence of 37 cases per 1000-person years during follow-up.

In the current project - at the time of switch to a bPI containing regimen, the prevalence of renal impairment was 7.6%, which subsequently resolved in about half of these patients under the new ART. The prevalence we found was slightly lower than what has been previously reported in the literature from other studies done in the similar settings (10-15%) [102,271–273]. However, this should be interpreted with caution, since different studies use different definitions of renal impairment [93]. During bPI-based treatment, we found an incident renal impairment of 22 cases per 1000-person years.

While prevalence and incidence of renal impairment are not very high, they represent an important clinically relevant health issue with large potential to generate complications and high treatment costs in the intermediate term if poorly managed, thus justifying the need of early and continual laboratory monitoring once patients start ART. The drug options for second line treatment in sub-Saharan Africa is still limited [274,275,460] with bPI being the only available drug class. An association of bPI-regimens with CKD has been reported previously from the developed world [139,461].

In our study we found older age to be associated with development of renal impairment after switch to bPI – a finding that has been reported previously and is HIV-unrelated [102,270,288]. With the higher life expectancy of PLHIV - nowadays almost reaching the same as the general population – the burden of renal impairment is becoming even more important [327–329,462]. Interestingly, we did not find an association between renal impairment and ART switch to a bPI-regimen with a TDF-backbone versus a non-TDF backbone, which stands in contrast to previous reports [276,294,295]. The reason might be that almost all patients received TDF. Nevertheless, this is an important finding since most treatment guidelines in sub-Saharan Africa recommend the use of TDF- based regimens as both first-line and second-line treatments [274,275,460].

Given the need for lifelong ART, the results from study 2 support the implementation of universal routine monitoring of renal function once patients are switched from first-line to bPI-regimens. Previously, we reported high prevalence and incidence of renal impairment among newly diagnosed ART naïve patients from the same cohort [102]. Combining the results from these two studies stress the importance of renal function monitoring in both newly diagnosed patients and patients on ART. Despite most HIV treatment guidelines in sub-Saharan Africa recommend renal function monitoring after starting ART [275,460], routine serum creatinine measurements are

still not done in most of the countries due to logistic challenges, costs and shortages of reagents and machine-breakdowns.

Furthermore, PLHIV would benefit from individualized treatment approaches, so that they can receive their ART depending on their comorbidities. For example, patients who developed CKD would benefit from a switch from TDF-based regimen to other NRTI such as ABC-based regimen [461,463]. However, this is not always possible since most of the regimens that are available in Africa are in fixed dose combinations hence make it almost impossible to have individualized treatment regimen such as those used in developed countries [275,460].

Weight gain after starting antiretroviral treatment

Rollout of integrase inhibitors such as dolutegravir as first-line ART in sub-Saharan Africa has happened only recently. While this drug class is highly efficient in terms of rapid viral load reduction [32,304], one of the worrisome side effects is weight gain [57,137]. Data reporting on weight change after starting treatment in real-world settings are still lacking – especially from sub-Saharan Africa. Study 3 was designed to assess weight change among newly diagnosed ART-naïve PLHIV starting treatment with either a dolutegravir-based or efavirenz-based regimen in rural Tanzania.

Over the first 12 months of treatment, there was an overall weight gain among participants in both dolutegravir and efavirenz groups which was most evident in patients being underweight at presentation and most likely corresponds to a 'return to health' effect, which has been described previously [46,53]. Participants in the dolutegravir group gained more weight compared to participants receiving efavirenz – most pronounced in the group with a normal weight at baseline (difference of 0.22kg/month) - confirming previous studies from clinical trial settings [57,137]. This finding is worrisome since obesity [310] contributes to an increased risk of cardiovascular diseases and metabolic disorders, mostly among patients who start ART with normal BMI or overweight/obese [41,298]. In fact, PLHIV already have an increased risk of developing NCDs compared to general population [462,464], therefore, excessive weight gain is detrimental in this population. Another key finding was a strong association between being female and weight of ≥10% after 12 months on ART as previously reported [46,59,311,312], which raise an alert since the majority (60%) of PLHIV in sub-Saharan Africa are females [5].

The findings from study 3 highlight several important points. Firstly, PLHIV should receive education and counselling about weight changes at the time of starting ART in order to increase awareness of the consequences of weight gain if excessive and the associated risk of developing

NCDs. Secondly, the recommendations on the use of dolutegravir-based regimens should balance its advantages (high efficacy, favourable safety profile and lower price) with its potential harms such as excessive weight gain. Thirdly, there is a need for individualized medicines approach so that patients with particular risk factors such as females or older patients with renal impairment (as in study 2) would receive individualized ART regimens that do not further increase the risk of a specific comorbidity [461,463]. Fourthly, clinical and laboratory monitoring after starting ART are key in order to allow monitoring of patients' long-term outcomes (such as dyslipidemia and diabetes mellitus) especially in this population. And lastly, there is an urgent need for well-functioning pharmacovigilance systems to monitor adverse events of new medications in the sub-Saharan Africa region [465,466].

Prevalence and incidences of comorbidities after ART initiation

In sub-Saharan Africa, there is a clear lack of comprehensive data on the frequency of comorbidities in patients on ART and their impact on their outcomes particularly in elderly population. Study 5 was designed to assess the prevalence and incidence of comorbidities, as well as their association with mortality among different age groups of HIV-infected patients on ART in a rural Tanzania.

In this study, the most prevalent comorbidities were anaemia, arterial hypertension, undernutrition and tuberculosis. The comorbidities most frequently associated with death and lost to follow-up were anaemia, tuberculosis and undernutrition. The association of anaemia with mortality and HIV disease progression has been previously shown [347,352,353], and was similarly true for all age groups in our study. Tuberculosis was associated with a 6 times higher risk of death in patients aged 50 years and older in Tanzania, which is in line with a study from South Africa showing tuberculosis to be a major factor for HIV-infected inpatients [366] and the leading cause of death among PLHIV [330]. Undernutrition was commonly observed in patients >50 years and was associated with mortality and loss to follow-up. Moreover, we found a high prevalence and incidence of arterial hypertension, which has been shown previously [355]. Furthermore, we found high prevalence of thrombocytopenia, which has been previously associated with poorly controlled infection and high mortality [371].

These results highlight the high frequency of systematically assessed comorbidities in this rural HIV-population despite its relatively young median age of 38 years (IQR 31-46). Patients aged >50 years were more likely to encounter comorbidities, in particular, anaemia, arterial hypertension, undernutrition and tuberculosis. In younger patients, anaemia and undernutrition were highly prevalent and independently predicted death or lost to follow-up.

Therefore, in order to improve patient's outcome establishment integrated screening and treatment programs to identify and address comorbidities in different age groups are key. This will be part of my future work, especially relevant as the current epidemiological transition in sub-Saharan Africa is expected to see an increase in incidence of non-communicable diseases, and improved monitoring of patients for different comorbidities is vital for achieving better outcomes.

The most effective treatment strategy to control arterial hypertension in Africa

Arterial hypertension is the most prevalent risk factor for cardiovascular diseases and claims approximately 7.5 million lives annually [154]. Africa has the highest burden of arterial hypertension with an estimated prevalence of 40% [375]. Apart from a recent clinical trial by Ojji *et al* [228], there are still few clinical trials evaluating the best treatment for arterial hypertension in Africa [150]. Most importantly, more than two third of patients need a combination therapy of antihypertensive medications to reach optimal BP targets [222,379,381]. However, the current treatment guidelines from WHO still recommend the use of a single drug regimen for the treatment of arterial hypertension among people with black ethnicity [174,382,383].

The CoArtHA clinical trial (study 6) is an open-label, three-arm, parallel randomized controlled trial conducted at two rural hospitals in Lesotho and Tanzania. It compares three treatment strategies – a triple low-dose combination vs dual combination vs standard of care - to achieve rapid control of aHT with easily available drugs within 12 weeks in participants of African descent in rural sub-Saharan Africa. The results from the trial will inform future clinical guidelines on antihypertensive management in the region. Most importantly, BP control has not been studied with respect to possible interactions with ART in PLHIV, likely affecting treatment response [417–420]. The results of the trial will help to identify this important research question since more than 60% of PLHIV worldwide live in sub-Saharan Africa [421].

Recruitment of the trial started at Mokhotlong District Hospital on March 06, 2020, and at St. Francis Referral Hospital, Ifakara, on March 24, 2020. Due to COVID-19 pandemic associated country lockdown measures, we had to pause all research activities in both countries for a period of about 3 months (March – May 2021). By 08.12.2021, a total of 1,562 participants were screened and 1,115 were enrolled in the trial (581 in Ifakara and 534 in Lesotho) – leaving 153 participants to reach our targeted sample size of 1,268 participants. So far, 362 and 336 participants have finished their follow-up at the Ifakara and Lesotho sites respectively. In July 2021, we conducted an interim analysis after reaching half of our targeted sample size (634 participants) and the recommendation from the Independent Data Monitoring Committee (IDMC) members was to

continue with the trial. We anticipate to reach our targeted sample size by the end of February 2022, finishing follow-up visits in September 2022 and to finalize formal by the end of 2022.

Challenges for HIV-infected adolescents during transition from paediatric to adult HIV clinics in Africa

Approximately 1.5 million adolescents living with HIV worldwide are residing in sub-Saharan Africa, which accounts for 85% globally [432,433]. High HIV prevalence and incidence in sub-Saharan Africa exposes increasing numbers of adolescents and young adults to HIV through both perinatal infection and risky behaviours [432,434]. With the rollout of antiretroviral treatment (ART), adolescents survive to adulthood; hence, health care transition from paediatric to adult-centred clinic is of vital importance [436,437].

Study 7 is an editorial where I discuss about the challenges faced by adolescents living with HIV during their transition from paediatric to adult clinics. The challenges include facing behavioural and psychological changes, while living with a highly stigmatized disease [438]. Apart from that, the health care system in sub-Saharan Africa lacks well-trained human resources on adolescents' health expertise and essential infrastructures, which overburden the few existing clinics adolescents [438,440]. Moreover, there is a paucity of policy and guidelines for health care providers during this crucial transition process [467]. Hence, in order to improve clinical outcomes of adolescents living with HIV in sub-Saharan Africa, several measures need to be taken into consideration such as capacity building to empower healthcare providers on adolescents' health, improving essential infrastructures and develop evidence-based policies that guide health care providers during the transition period.

Future perspective: implications for policy and practise

Integration of NCDs services within HIV clinics

For the past 3 decades, most of the countries in sub-Saharan Africa have improved treatment and care of PLHIV through strengthening vertical programs for chronic care of PLHIV. This included building of infrastructure, capacity building of healthcare workers, improving access to and methodologies in HIV testing, prevention, promoting family planning and counselling of sexual transmission of infections as well as monitoring of treatment outcome and drug dispensing [5]. In contrast, the provision of NCDs health services outside of medical emergencies remains far behind in most of countries in sub-Saharan Africa. Several studies have demonstrated poor retention in

care of patients suffering from NCDs once they are diagnosed, with less than 30% remaining in care at 12 months [164,166,468,469].

The results from my studies (study 2, study 3, and study 5) have revealed a relevant burden of renal impairment, excessive weight gain/overweight, anemia and tuberculosis among PLHIV in sub-Saharan Africa. In order to be able to achieve the Sustainable Development Goals and Universal Health Coverage [65], the integration of healthcare services is one of the key elements. The UNAIDS Global Strategy for 2016-2021 supports integration of HIV and NCDs services in low and middle-income countries with high burden of HIV and NCDs [470]. This is especially relevant since there is a decrease in external funding for HIV/AIDS programs. As a result, integration of services is a cost-effective way to deliver different services to patients [471–473]. Sando *et al,* reported data from Uganda showing that integrating screening and treatment for arterial hypertension, diabetes mellitus and high cholesterol in services for PLHIV would reduce the overall risk of cardiovascular complications and is cost-effective [474]. Integration of HIV-NCDs chronic care will reduce DALYs and improve outcomes of PLHV with undiagnosed NCDs through early diagnosis and management of NCDs [471–473]. Additionally, it will reduce costs and time expenditures for patients suffering from both conditions and the burden to health care systems which is already overburdened with management of infectious diseases.

Establishment of pharmacovigilance systems in the region

Study number 2 and 3 describe potential side effects of long term drugs. The WHO recommends pharmacovigilance defined as 'science and activities related to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems' [475]. Most of the countries in sub-Saharan Africa still lack full functioning pharmacovigilance systems to monitor the safety of new approved drugs and vaccines [465,466]. Therefore, healthcare workers depend on the side effects information from the existing sub-optimal pharmacovigilance systems in the region or global data/experience [476]. This is key not only for drugs and vaccines of short-term issues (i.e. Malaria and Ebola virus), launched mostly in LMICs [477–479], but also for chronic health problems (i.e. drugs rolled out on large scale such as ART), as most PLHIV are living in sub-Saharan Africa than elsewhere.

The results from study 3 demonstrated excessive weight gain among patients starting treatment with dolutegravir-based regimens compared to efavirenz-based regimens which goes usually unnoticed if pharmacovigilance systems are not in place. Compared to developed countries, the healthcare systems in most of the countries in sub-Saharan Africa are fragmented and complex. Apart from the public health sector (which has primary, secondary and tertiary health centres),

most countries depend on additional services from the private sector - some donor funded and many faith-based centres [476]. Overcrowding of these facilities and a low number of healthcare workers makes it mostly impossible for properly filling the required forms once an adverse event has occurred [79,476]. In addition, self-medication is a challenge in the region, particularly in rural settings where many patients cannot afford to the consultation fees and seek medical attention at unregistered or unauthorized pharmacies [480].

In order to establish well-functioning pharmacovigilance systems to monitor adverse events in sub-Saharan Africa, several measures must be undertaken. First, there is an urgent need for political will, support and commitment from the member States to invest in the healthcare systems [458]. Provided sufficient funding, this will enable to establish and to maintain the pharmacovigilance systems in the region. Second, establishment of pharmacovigilance trainings (methodologies, data collection, data analysis and communications ton the health policy makers) among health care workers. Third, the technological development for collecting safety information in the healthcare systems offers an option to automatic reporting system or at least flagging of safety issues. Fourth, due to high level of self-treatment in sub-Saharan Africa, there is a need to inform and engage the public to report medicine-related adverse events to the authorities.

Urgent need of preventive measures to reduce risk factors for NCDs in Africa

Most of the strategies to control NCDs in Africa focus on diagnosis and management and less on prevention. Although, diagnosis and treatment are key to control the endemic (currently hidden epidemic) of NCDs in the region, programs for prevention and cost-effective interventions to identify, prevent and manage risk factors for NCDs are needed. The awareness of modifiable risk factors [1] is still low and needs to be addressed. For example, healthy diet is not yet promoted to a relevant extent. Most of the countries in sub-Saharan Africa lack e.g., regulations for control of foods and sugary soft drinks that increase the risk of NCDs. In Africa, more than 13% of people with either diabetes mellitus or arterial hypertension are active tobacco smokers [260]. In order to tackle the tobacco-related health problems, the WHO Framework Convention on Tobacco Control (FTTC) proposed population-wide interventions such as increasing prices of tobacco products, banning indoor smoking, and provision of smoking cessation programs in the communities. The most cost-effective way of controlling tobacco use is raising taxes for related products; which is poorly implemented [261,262].

Non-communicable diseases and HIV/AIDS in the era of COVID-19 Pandemic

The outbreak of the coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory coronavirus-2 (SARS-CoV-2) is one of the deadliest pandemics of the last century [481]. The WHO declared the COVID-19 pandemic a global emergency on 11th March, 2020 [482] - as of 26th November, 2021, there were 260,515,160 confirmed cases with 1,187,620 deaths worldwide [483]. Africa has been affected as well – albeit initially it was thought to be affected to a lesser extent – which might be due to underreporting, younger average age or cross-immunity from other infections [484]. As of 26th November, 2021 there were 8,616,912 confirmed cases and 222,301deaths in the region [483].

Risk factors for severe COVID-19 courses and associated mortality shown in recent studies are NCDs such as arterial hypertension, diabetes mellitus, cardiovascular diseases, and obesity [485–489]. The sub-Sahara region with its high burden of – often untreated - NCD accounting for more than 71% NCD-related mortality globally [154] might have a more relevant death toll than initially assumed.

The overburdened health care systems in most of African countries with a low number of health care providers are not able to adequately scale-up services for patients with COVID-19 – requiring care under isolation conditions and often intensive care support [490]. In addition, several studies from Africa demonstrated that COVID-19 has caused disruptions in provision healthcare services with a decrease in number of patients who have access to treatment and care [491]. This is of concern, particularly for infectious diseases such as HIV that require long-term treatment and regular drug dispensing for an optimal outcome. The ongoing COVID-19 pandemic might lead to an increased hidden incidence of these infectious diseases, along with increased morbidity and mortality [492,493].

Therefore, the COVID-19 crisis should alert governments and policy makers to strengthen their commitment in terms of providing funding for adequate healthcare system improvements in Africa. In addition, donors such as Global Funds, Bill and Melinda Gates Foundation, USAID, might focus more on strengthening of the healthcare system rather than providing vertical programs to tackle individual diseases in Africa. The need for a health plan enabling sustainable financing becomes also evident.

Concluding remarks

We have shown in our studies an increased prevalence for the most important NCDs, their risk factors and associations with antiretroviral drugs and other diseases. As the population of well-treated PLHIV is aging, there is an increasing need to address NCDs in parallel to HIV.

Urgent measures such as integration of healthcare services, increased funding in NCDs care, and improved capacity building for NCDs management are key to tackle the double burden of diseases in the region. Importantly, drug-related challenges such as renal impairment or weight gain need to be addressed among PLHIV under care. Implementation of universal routine monitoring of renal function but also weight curve and proper counselling should receive a high priority. Besides individual care establishment of pharmacovigilance systems will support generation of robust and high-quality evidence to monitor the safety of new drugs.

Africa has the highest burden of uncontrolled arterial hypertension worldwide, which represents the most prevalent risk factor for cardiovascular diseases. The results from the coArtHA clinical trial will inform on the most effective and cost-effective treatment strategies for uncomplicated arterial hypertension among people of African descent living in rural sub-Saharan Africa.

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493. Nyoni T, Okumu M. COVID-19-Compliant Strategies for Supporting Treatment Adherence Among People Living with HIV in Sub-Saharan Africa. AIDS Behav. 2020;24:2473–6.

Curriculum Vitae

Herry Mapesi, MD, MSc, PhD candidate

Hofackerstrasse 61, 4132 Basel, Switzerland; Tel. +41788279511; hmapesi@gmail.com; Citizenship: Tanzanian; Birthday: 22nd December 1987; www.linkedin.com/in/herry-mapesi-18b013199/

PROFESSIONAL SUMMARY

As a clinical epidemiologist, I have designed and conducted clinical trials as well as epidemiological studies over the last 8 years. I am passionate in helping people living with HIV by studying its association with non-communicable diseases such as hypertension and chronic kidney diseases. I have facilitated international collaborations among diverse teams alongside colleagues from Ifakara Health Institute, Tanzania National Institute of Medical Research, University Hospital Basel, Swiss Tropical and Public Health Institute, Indiana University, and SolidarMed Partnerships for Health in Lesotho.

EDUCATION

PhD Epidemiology August 2018 – Expected: February 2022

University of Basel, Swiss Tropical and Public Health Institute

MSc Epidemiology (Magna cum laude) August 2015 – February 2017

University of Basel, Swiss Tropical and Public Health Institute

Doctor of Medicine September 2007 – August 2012

Hubert Kairuki Memorial University

WORK EXPERIENCE

Novartis - Ifakara Health Institute Symposium 'B2B East Africa' November 2019 – Present

Role: Local Chairperson and a member of the steering and organizing committee.

- Organizing scientific program for a three days scientific symposium with colleagues from Novartis Institute for Tropical Diseases
- Arranging travel and accommodation for 150 delegates who are expected to attend the symposium
- Symposium delayed due to COVID-19 and anticipated to resume in 2022
- Swiss Tropical and Public Health Institute/University of Basel

PhD candidate August 2018 - Present

- Attending courses at Swiss TPH such as Good Clinical Practice (GCP) training, clinical trial design, statistical analysis, and clinical development processes for drug development and clinical trials
- Grants applications - additional funding for my PhD fellowship.
- I was a PhD students' representative hence presenting fellow students in institutional administration meetings

Head of the Chronic Diseases Clinic of Ifakara (CDCI) January 2018 – August 2018

- Project leader for a HIV clinic serving more than 11, 500 HIV-infected patients
- Coordinated all clinic activities together with 52 clinic staff
- Preparation of documentation for ethical approval, extension/amendment annually
- Coordinated research activities and prepared of quarterly scientific reports for the sponsors
- Drafted operation budgets, work plans and quarterly financial reports for the funders and regulatory authorities
- Collaborated with other local implementing partners and district authorities responsible for HIV and TB programs
- Submitting research proposals to the funding agents
- Representing the team to the National AIDS Control Programs meetings and international meetings
- Working in the matrix environment which involves Statisticians, Data Managers, Medical Monitors, Site Investigators, regulatory authorities, and the funders
- Conducted protocol trainings to the clinical trial team in collaboration with other medical experts
- Training teams the standard operating procedures (SOPs) on how to recruit the right patients for different studies
- Collaborating with National AIDS program to establish viral load testing in the Kilombero district

Deputy Head of the Chronic Diseases Clinic of Ifakara (CDCI) October 2013 – December 2017

- Performed responsibilities of the head of the clinic during her absence.
- Presented the clinic in meetings and workshops organized by Ministry of Health
- Attended HIV/AIDS and tuberculosis patients on an out and inpatient basis

OTHER EXPERIENCES AND PROFESSIONAL MEMBERSHIPS

- **2015 – Present:** Member of the National TB and HIV Technical Working Group (Ministry of Health, Community Development, Gender, Elders and Children, Tanzania)
- **2015 - Ad hoc reviewer for journals:** *The Lancet HIV, PlosOne, British Medical Journal Case reports, Clinical, Cosmetic and Investigational Dermatology, Journal of the International Association of Providers of AIDS Care, Journal of Dermatology* and *Pigmentation Research*

- **2012 - Professional membership:** Tanganyika Medical Association, European Aids Clinical Society, and Medical Association of Tanzania

PROFESSIONAL SKILLS

- Statistical software: Stata
- Languages: Swahili (native), English (fluent: oral and written)

APPROVED RESEARCH PROJECTS

- **2020** – Else Kröner Fresenius Foundation, Germany (€ 673, 000)
  Title of the project: Tackling the hidden epidemic of non-communicable diseases in rural Tanzania; developing the Else Kröner Center for Heart and Lung Disease (EKC-HLD)
  Role: Co-Investigator
- **2019** - Swiss Science National Foundation (CHF 640, 273)
  Title of the project: Identifying most effective treatment strategies to control arterial hypertension in sub-Saharan Africa – a randomized control trial (coArtHA trial)
  Role: Principal Investigator
- **2018** – Swiss Embassy Excellence Scholarship (PhD Fellowship) (CHF 84, 600)
  Title of the project: Non-communicable diseases in People Living with HIV in Rural Africa: tackling the double burden
  Role: Main Applicant
- **2013** – Present: Kilombero and Ulanga Antiretroviral Cohort (KIULARCO), (CHF 330, 000 annually)
  Role: Co – Investigator

AWARDS AND HONORS

August 2006 - Southern African Development Communities Essay competition

- **1st Prize among 14 member States**

October 2019 - Malariaworld

- Recognized as one of the exceptional young researchers from Africa

PRESENTATIONS IN INTERNATIONAL CONFERENCES

- The 23rd International AIDS Conference (AIDS2020), virtual conference (6 – 10, July 2020)
- The 17th European AIDS Conference, Basel, Switzerland (6 – 9, November 2019)
- The 16th European Aids Conference, Milan, Italy (25 – 27, October 2017)
- The 9th European Congress on Tropical Medicine and International Health, Basel, Switzerland (7th September 2015)

PUBLICATIONS

1. **Mapesi H,** Okuma J, Franzeck F, Wilson HI, Senkoro E, Byakuzana T, et al. Prevalence, incidence and predictors of renal impairment in persons with HIV receiving protease-inhibitors in rural Tanzania. PLOS ONE. Public Library of Science; 2021;16:e0261367.
2. **Mapesi, H**., Gupta, R., Wilson, H.I., Lukau, B., Amstutz, A, et al. The coArtHA Trial-Identifying the Most Effective Treatment Strategies to Control Arterial Hypertension in Sub-Saharan Africa: Study Protocol for a Randomized Controlled Trial. Trials. 2021 Jan 21;22(1):77
3. **Herry Mapesi** and Daniel Henry Paris. Non-communicable Diseases on the Rise in Sub-Saharan Africa, the Underappreciated threat of a Dual Disease Burden. *Praxis* 2019; *108* (15): 1–9.
4. **Herry Mapesi.** Challenges for HIV-infected adolescents during transition from paediatric to adult HIV clinics in Africa. *IJPH,* 2020; DOI: 10.1007/s00038-020-01336-z
5. **Mapesi H,** Kalinjuma A, Ngerecha A, Franzeck F, Hatz C, Tanner M, Mayr M, Furrer H, Battegay M, Letang E, Weisser M and Glass T. Prevalence and evolution of renal impairment in people living with HIV in rural Tanzania. *Open Forum Infectious Diseases*. doi.org/10.1093/ofid/ofy072.
6. **Wilson HI and Mapesi H**. Rollout of dolutegravir-based antiretroviral therapy in sub-Saharan Africa and its public health implications. Pan Afr Med J. 2020;37:243
7. **Mapesi H,** Ramírez A, Tanner M, Hatz C, Letang E, KIULARCO Study Group. Immune reconstitution inflammatory syndrome associated with dermatophytoses in two HIV-1 positive patients in rural Tanzania: a case report. *BMC Infect Dis*. 2016;16:495
8. **Mapesi H,** Ramirez A, Hatz C and Letang E. Nodular lymphangitis in HIV-infected patients in Tanzania. *East African Medical Journal* Vol. 92 No. 3 March 2015
9. Sanmartí M, Meyer AC, Jaen A, Robertson K, Tan N, **Mapesi H**, et al. HIV-associated neurocognitive impairment in stable people living with HIV on ART in rural Tanzania. HIV Med. 2021 Feb;22(2):102–12.
10. **Mapesi H,** Sikalengo G, Ntamatungiro A, Weisser M and KIULARCO Study Group. Persistent hiccups due to Tuberculous Meningitis in rural Tanzania – the value of Xpert testing in samples other than sputum. *East African Medical Journal* Vol: 94 No. 5 May 2017.
11. Ndege R, Ngome O, Bani F, Temba Y, Wilson H, Vanobberghen F, et al. Ultrasound in managing extrapulmonary tuberculosis: a randomized controlled two-center study. BMC Infectious Diseases 2020;20:349. https://doi.org/10.1186/s12879-020-05073-9.
12. Stete K, Glass TR, van Dam GJ, Ntamatungiro A, Letang E, de Dood CJ, Corstjens PLAM, Ndege R, **Mapesi H**, et al. Effect of schistosomiasis on the outcome of patients infected with HIV-1 starting antiretroviral therapy in rural Tanzania. PLoS Negl Trop Dis. 2018 Oct;12(10):e0006844.
13. Ndege R, Weisser M, Elzi L, Diggelmann F, Bani F, Gingo W, Sikalengo G, **Mapesi H** et al. Sonography to Rule Out Tuberculosis in Sub-Saharan Africa: A Prospective Observational Study. Open Forum Infect Dis. 2019 Apr;6(4):ofz154.
14. Albrecht S, Franzeck FC, **Mapesi H**, Hatz C, et al. Age-related comorbiditoes and mortality in people living with HIV in rural Tanzania: data from a prospective cohort study. AIDS Lond Engl. 2019 Feb 7.

15. Bircher RE, Ntamatungiro AJ, Glass TR, Mnzava D, Nyuri A, **Mapesi H**, et al. High failure rates of protease inhibitor-based antiretroviral treatment in rural Tanzania – A prospective cohort study. PLOS ONE 2020;15:e0227600. https://doi.org/10.1371/journal.pone.0227600.

16. Erb S, Letang E, Glass T, Ntamatungiro A, Mnzava D, **Mapesi H** *et al*. Healthcare provider communication training in rural Tanzania empowers HIV-infected patients under antiretroviral therapy to discuss adherence problems. *HIV Medicine* (2017);DOI: 10.1111/hiv.12499

17. Erb S, Letang E, Glass TR, Natamatungiro A, Mnzava D, **Mapesi H** et al. (2017) A Simple Visual Analog Scale is a Valuable Tool to Assess Self-Reported Adherence in HIV-Infected Patients on Antiretroviral Treatment in a Resource-Limited Setting. J AIDS Clin Res 8: 731

18. Gamell A, Glass TR, Luwanda LB, **Mapesi H**, Samson L, Mtoi T, *et al*. An Integrated and Comprehensive Service Delivery Model to Improve Pediatric and Maternal HIV Care in Rural Africa. J Acquir Immune DeficSyndr 1999. 2016 Sep 1.

19. Vanobberghen F, Gamell A, A. John; D. Faini, L. Bonaventure, **H. Mapesi** *et al*. Challenges in estimating death and retention rates in a longitudinal cohort of HIV infected persons in rural Tanzania. *Tropical Medicine & International Health*. 20():9, Sep 2015.

20. Vanobberghen F, Letang E, Gamell A, Mnzava DK, Faini D, Luwanda LB, **Mapesi H** *et al*. A decade of HIV care in rural Tanzania: Trends in clinical outcomes and impact of clinic optimisation in an open, prospective cohort. PloS One. 2017;12(7):e0180983.

21. Letang E, Kalinjuma AV, Glass TR, Gamell A, **Mapesi H**, Sikalengo GR, et al. Cohort profile: The Kilombero and Ulanga Antiretroviral Cohort (KIULARCO) - A prospective HIV cohort in rural Tanzania. Swiss Med Wkly. 2017 Jul 11;147:w14485.