Title

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Authors

Okello, Samson

Kanyesigye, Michael

Muyindike, Winnie R

et al.

Incidence and Predictors of Hypertension in Adults with HIV Initiating Antiretroviral Therapy in Southwestern Uganda

Samson Okello, MBchB, MMED, **Michael Kanyesigye, BSc**, **Winnie R Muyindike, MBchB, MMED**, **Brian Herb Annex, MD**, **Peter W Hunt, MD**, **Sebastien Haneuse, PhD**, and **Mark Jacob Siedner, MD, MPH**
Mbarara University of Science and Technology Mbarara, UGANDA

INTRODUCTION

The successful scale-up of antiretroviral therapy (ART) in sub-Saharan Africa substantially reduced mortality from AIDS-related between 2001 and 2012.[1] The increase in access to ART has led to reductions in opportunistic-infection related mortality for people living with HIV (PLWH), and increasing life expectancy, which has approached that of HIV-uninfected persons in the region.[2-5] As a result, it is projected that the number of adults living with HIV in sub-Saharan Africa over the age of 60 will increase by 55% between 2010 and 2025. [6] The transformation of the HIV epidemic to a life-long, chronic disease is shifting the priorities of HIV health care delivery from a primary focus on reduction of early mortality to include more holistic approaches that aim to improve long-term health and quality of life.[7, 8]

Data from developed countries indicate increased risk of cardiovascular disease among PLWH compared to those uninfected [9]. The emerging paradigm to explain the increased risk of cardiovascular disease in general focuses on a combination of HIV associated immune dysregulation, gut microbial translocation to the systemic circulation, and chronic systemic inflammation [10]. For hypertension specifically, studies have found both an increased risk of hypertension for those with HIV [11, 12], and an association between hypertension with elements of the metabolic syndrome, including insulin resistance and lipodystrophy [13, 14]. Similar, to other cardiovascular diseases, the risk of hypertension among those with HIV has been associated with duration of HIV infection [15, 16], as well as traditional risk factors [17, 18], suggesting that HIV infection might have independent effects. The data on the associations between ART and hypertension is inconclusive, with some studies noting increased risk with ART exposure [19], while others not [17, 20]. While preliminary data has indicated high rates of cerebrovascular disease in resource rich settings, [21-23] there is limited data on the epidemiology of hypertension and cardiovascular disease among PLWH in Sub-Saharan Africa[24], home to over 30 million persons infected with HIV.

Corresponding Author's Institution: Mbarara University of Science and Technology, okello.samson@must.ac.ug.

There is an important need to improve epidemiologic study of aging PLWH in sub-Saharan Africa to better prepare for and delivery appropriate healthcare for this population.[24, 25] We sought to estimate the incidence of hypertension, a major contributor to major cardiovascular events, among patients taking ART at a publically operated HIV clinic in rural Uganda.

METHODS

Study Population & data collection

We abstracted data from all adult patients who initiated ART at the Mbarara Regional Referral Hospital Immune Suppression Syndrome (ISS) clinic between January 1st, 2010 and December 31st, 2012 and had a minimum of two clinic visits. We obtained data patient data including: age, gender, height, weight, and blood pressure at each visit, ART regimen history, non-ART medications prescription history, and CD4 T-lymphocyte (CD4) count history. Other laboratory tests, including serum creatinine, glucose and lipid measurements, were not consistently available at the clinic. These were only present for less than 1% of the cohort, and therefore were excluded from this analysis.

At each clinic visit, a trained nurse performed and recorded blood pressure measurements of seated patients using a calibrated aneroid sphygmomanometer (Welch Allyn® Tycos 767 Series; Skaneateles Falls, New York, USA), with small (<21 cm) and normal (22–32 cm) cuff sizes. Patients were seated in a chair and rested for approximately 10 minutes before BP was measured. Patients were seated in a chair and rested for approximately 10 minutes before BP was measured. Following initial BP measurement, patients with SBP > 140mmHg and/or DBP > 90mmHg during this screen underwent two repeat BP measurements one minute after. The average of the two later BPs would then be recorded in the patients clinic review form. Weight and height are measured using a stadiometer attached to a weighing scale. Height was measured to the nearest 0.1 cm after removal of shoes. Weight was measured to the nearest kilogram after removal of shoes and heavy clothing. Data are collected on paper forms and subsequently entered into an electronic database, supported by the International Epidemiologic Databases to Evaluate AIDS (IeDEA) Project (NIH grant U01 AI069919).

Statistical methods

The primary outcome was incident hypertension as defined by the occurrence of either: i) at least two consecutive clinical visits with a systolic blood pressure (SBP) recording 140mmHg and/or a diastolic blood pressure (DBP) recording of 90mmHg or, ii) a clinical visit with a systolic blood pressure recording < 140mmHg and/or a diastolic blood pressure recording of < 90mmHg with prescription for an antihypertensive medication on a subsequent clinic visit after enrollment into the clinic. For the latter we included any antihypertensive medication from the following drugs: atenolol, propranolol, furosemide, bendroflumethiazide, nifedipine, and captopril. These were the antihypertensive medications available at the clinic pharmacy during the study period 2010 - 2012.

We censored blood pressure measurements if systolic blood pressure was recorded as > 300 or <50 and/or diastolic blood pressure was recorded as > 200 or < 30mmHg. We defined pre-treatment nadir CD4 cell count as the lowest CD4 cell count on record up to 90 days after ART initiation. Subjects contributed person-time to the analysis until censored for one of the following: i) date of recorded hypertension, (ii) date of death, (iii) date of transfer out of care, (iv) date of loss-to-follow-up (defined as 6 months before data censoring without a clinical visit), or (v) March 31st, 2013, which was the date of data abstraction.

We examined the following known predictors of interest: old age, male gender, nadir pre-treatment CD4 cell count, high body mass index at the time of ART initiation, and ART regimen at the time of initiation. We created two independent variables for ART regimen based on the predominant use of four regimens at the clinic: 1) tenofovir (TDF) versus zidovudine (AZT)-containing regimens and 2) nevirapine (NVP) versus efavirenz (EFV)-containing regimens. Descriptive statistics for categorical variables were computed as counts and percentages, whereas continuous variables were categorized as follows: age as (< 30, 30-39, and 40 years); BMI as (<18.5, 18.5 – 24.9, 25.0 – 29.9, and 30kg/m^2); and, nadir CD4 cell count as (<100, 100-349, 350 cells/mm^3).

To examine variation in incidence of hypertension across risk factors we first calculated age - and gender-specific incidence rates. Specifically, we computed the total person-time and number of hypertension events in each of six gender-by-age groups. We then modeled the counts using a log-linear model with the log person-time included in the model as an offset. To account for potential over dispersion in the outcome counts, estimation was based on quasi-likelihood and standard errors were computed using the robust sandwich estimator. We also modeled the association between the potential risk factors and time-to-hypertension using a Cox proportional hazards model and survival analysis with logrank tests for comparisons of time-to-hypertension between categories of gender, age groups, nadir CD4 cell counts, and ART regimens. All statistical analyses were performed using R v3.1.1.

Ethics Statement

This study was approved by the ethics review committee at Mbarara University of Science & Technology and the ISS clinic data safety and management committee. The IeDEA database project, which supports research use of the ISS clinic database was reviewed and approved by the Mbarara University of Science and Technology, Uganda National Council of Science and Technology and the University of San Francisco, California.

RESULTS

We identified 4,122 subjects who initiated ART between 2010 and 2012. We excluded 733 patients 326 (7.9 %) who had evidence of hypertension prior to ART initiation, 256 (6.2 %) who were transferred into clinic on ART, and 151 (3.7 %) who had only a single clinic visit on ART, leaving 3,389 patients in our analysis (Figure 1). Of the 3389 patients, 72% (2,423) were censored in care by March 31st 2013, 1% (36) died during follow-up, 2% (70) transferred out of care, and 12% (415) were lost-to-follow-up. In total, patients contributed 3,990 person-years (median 394 days [IQR 170 – 627]) during follow-up.

Of the 3389 patients included in analysis, 67 % (2279/3389) were female, the median age at enrollment was 32 years (IQR 27 – 39), and 3.6 % (113/3389) were obese at ART enrollment (Table 1). The most commonly prescribed initial regimen was TDF, lamivudine (3TC), and EFV (n=1672, 49.3%) followed by AZT, 3TC, and NVP (n=1075, 31.7%), and AZT, 3TC, and EFV (n= 421, 12.2%), and TDF, 3TC and NVP (n=103, 3%) (Table 1). Only 3.6% of participants (n=118) were prescribed other regimens and the vast majority (n=2712, 80%) remained on a single regimen during the entire observation period.

Incidence and predictors of hypertension

A total of 445 participants developed incident hypertension during 3,990 years of total observation time, resulting in a crude incidence of 111.5 per 1000 person years (py) (95% CI 101.9 - 121.7). Of those, 374 (84%) met clinical criteria with two or more consecutive visits with elevated blood pressure, while the remaining 71 (16%) were prescribed an anti-hypertensive medication. The most common anti-hypertensive medications prescribed were propranolol (β-blocker) in 30 of 71 (42%) patients and bendroflumethiazide (thiazide diuretic) prescribed in 21 of 71 (30%) patients.

In univariable cox proportional hazard models, male gender, age 40 years, obesity (BMI 25kg/m^2), and a nadir CD4 100-350 or >350 cells/mm^3 (as compared to a nadir CD4 <100) were associated with incident hypertension (Table 2). In multivariable, male gender (AHR 1.88, 95% CI 1.49 - 2.39), increasing age (AHR 1.36, 95% CI 1.02 - 1.82 for those > 40 years compared to those aged 30 years or less), nadir CD4 count (AHR 0.77, 95% CI 0.60 - 0.99 and AHR 0.64 95%CI 0.41 – 1.00 for a nadir CD4 cell count 100 - 350 and > 350 cells/mm^3 compared to <100 cell/mm^3, respectively), and high baseline body mass index (AHR 2.50, 95% CI 1.56 - 4.01 for those with a BMI 30 kg/m^2 versus normal BMI) were independently associated with increased risk of hypertension (Table 3, Figures 2A-C). Neither use of TDF versus AZT, nor use of NVP versus EFV was associated with risk of hypertension in the multivariate model.

DISCUSSION

In a large cohort of PLWH initiating ART at a publically operated, HIV clinic in rural Uganda, we found high rates of incident hypertension in both genders and across broad ranges of ages. The rates we detected in this cohort appear similar to or higher than that of prior estimates among HIV positive populations in resource-rich settings.[26-28] For example, we estimated an overall incidence of hypertension of 111.5 per 1000 py (95% CI 101.9 - 121.7), which is higher in magnitude than estimates described among PLWH in Norway (29.8 per 1000 py, 95% CI 20.3–42.2),[28] a multi-center study in the United States (64.1 per 1000 py, 95% CI 58.7 - 69.9)[26], and from the D:A:D study cohort which enrolls participants from sites in Europe, the United States, and Australia (72.1/1000py, 95%CI 68.2 – 76.0). Although we cannot make direct comparisons from study to study, our data offer preliminary evidence of higher rates in our patient population than those from resource rich settings.

While prior studies described high prevalence of hypertension among HIV-infected persons in cross-sectional studies in sub-Saharan Africa, [29-32] our results are the first to document

high rates incident hypertension during longitudinal follow-up among initially normotensive PLWH initiating ART. Particularly notable was the magnitude of hypertension incidence in younger groups. These results are compatible with data on cardiovascular outcomes from resource rich areas, which have demonstrated a 40% increased risk of stroke in PLWH versus HIV-uninfected controls, and significantly younger age at the time of stroke for PLWH versus those uninfected.[33-35] Such data, if corroborated elsewhere, should encourage strategies to expand guidelines for screening hypertension irrespective of age among PLWH in similar settings.

Potential mechanisms for increased incidence of hypertension in our study may include HIV associated chronic inflammation, immune suppression, [36] endothelial activation and dysfunction, [37] as well as the direct infection of arterial vascular smooth muscle cells by HIV. [38, 39] Alternatively, incident hypertension in this setting may reflect a "return to health" as individuals gain weight during ART, particularly with advanced pre-ART disease stages. Indeed, a recently presented population-based study suggested a lower prevalence of hypertension in HIV-infected Ugandans compared to the general population.[40] Of note, in our study, antiretroviral therapy did not predict hypertension as shown in some studies. [13, 14] We hypothesize that this might be related to the limited use of protease inhibitors – a class of antiretroviral therapy which have been associated with hypertension (metabolic syndrome), in our study setting. On the contrary, some studies suggests that the detrimental effects of antiretroviral therapy on arterial wall properties leading to arterial stiffening and subsequent hypertension, are not solely due to their metabolic effects but a collection of factors.[41]

Our data reinforce findings by multiple prior studies from resource rich settings that have indicated inverse relationships between hypertension risk and CD4 count nadir.[42-44] While the Strategies for Management of Antiretroviral Therapy (SMART) study was among the first to note increasing cardiovascular disease risk for PLWH with increasing time off of ART,[45] other studies have also identified a increasing risk of coronary artery atherosclerosis [46] and stroke [47] with decreasing CD4 count prior to ART initiation. As late ART initiation in resource-rich settings is often associated with unmeasured confounding factors that might also contribute to hypertension (i.e., methamphetamine and other drugs of abuse), our results – obtained from a very different clinical setting with much lower prevalence of illicit drug use – add support to an immunologic mechanism mediating this relationship. Taken together, these data suggest that immunosuppression and/or viral burden play a role in promoting early vascular damage as evidenced by the association of a low CD4 cell count with subclinical atherosclerotic damage,[36] a processor of hypertension. Our results therefore add support to recent World Health Organization recommendations to initiate ART for all individuals with a CD4 count < 500 cell/mm^3.[48]

This data should be interpreted in the context of the study design. Smoking status and laboratory results of blood glucose, serum creatinine, serum electrolytes and serum lipids were not available for most patients, therefore the contribution of clinical factors known to be associated with hypertension such as diabetes mellitus, chronic kidney disease, hyperlipidemia could not be assessed. Whereas blood pressure measurement can be particularly susceptible to measurement bias, [49] we attempted to mitigated this bias by

choosing a hypertension definition requiring two consecutive visits with elevated blood pressure and/or prescription of an antihypertensive medication. While it is likely that some measurement error remains, there is a low likelihood of consistent over or under-estimation of blood pressure. We also acknowledge that it is likely some patients on other antihypertensive medications that were not available in the clinic pharmacy might have been missed in the clinic electronic database, leading to underestimation of antihypertensive drug prescription and incidence of hypertension. The lack of systematic bias would bias estimates of associations about hypertension risk factors towards the null. Moreover, our findings including identification of both traditional (age, gender, obesity) and non-traditional (nadir CD4 count) are largely consistent with prior studies.

In summary we found that Incident hypertension is common among PLWH initiating ART in rural Uganda, with nominally higher rates than HIV positive populations previously reported elsewhere. Notably, both traditional hypertension risk factors and lower nadir CD4 cell count were associated with increased risk of hypertension. These data reinforce the need for increased attention to screening of and treatment for hypertension in PLWH in sub-Saharan Africa, as well as further attention paid to the epidemiology of non-communicable disease in this aging population.

Acknowledgements

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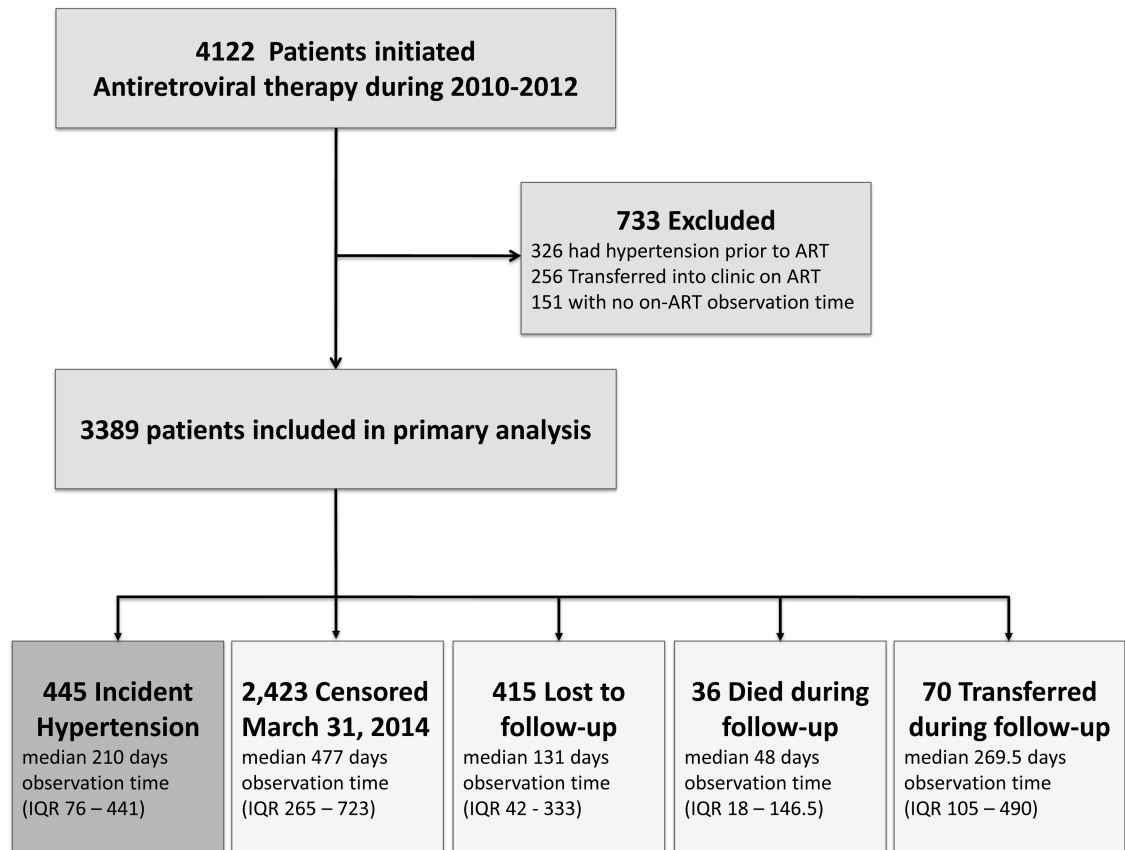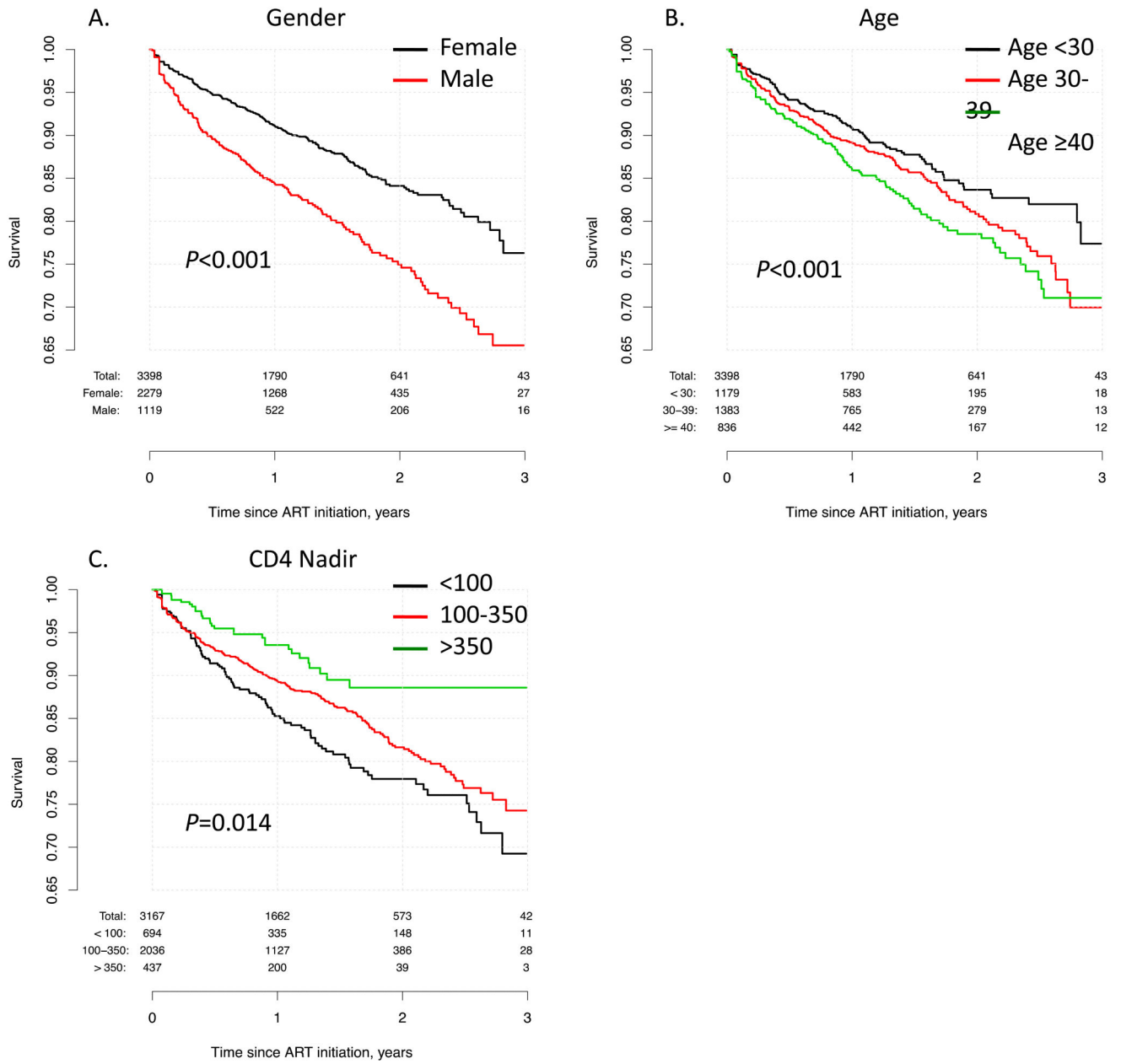
Figure 1.
Study profile

Figure 2A-C.
Kaplan-Meier survival curves demonstrating survival from hypertension by cohort sub-groups

Table 1

Characteristics of the Patients at Baseline and at Last Follow-up.

Characteristic, n (%)	Total Cohort N = 3398	Incident Hypertension during follow-up n=445	Without Hypertension during follow-Up n=2953
Female gender	2279 (67.1)	248 (55.7)	2031 (68.8)
Age group			
< 30	1337 (39.3)	145 (32.6)	1192 (40.4)
30 – 39	1318 (38.8)	181 (40.7)	1137 (38.5)
40	743 (21.9)	119 (26.7)	624 (21.1)
Nadir CD4 cell counts Ψ			
100	694 (20.4)	110 (24.7)	584 (19.8)
101 - 350	2036 (59.9)	263 (59.1)	1773 (60)
> 351	437 (12.9)	31 (7)	406 (13.8)
Missing	231 (6.8)	41 (9.2)	190 (6.4)
BMI ϵ			
< 18.5	593 (18.8)	79 (17.7)	514 (17.4)
18.5 – 24.9	1961 (62.1)	241 (54.2)	1720 (58.2)
25.0 – 29.9	491 (15.5)	72 (16.2)	419 (14.2)
30	113 (3.6)	24 (5.4)	89 (3.0)
Missing	240 (7.1)	29 (6.5)	211 (7.2)
NRTI β			
Zidovudine	1496 (45.7)	239 (53.7)	1257 (42.6)
Tenofovir	1778 (54.3)	180 (40.5)	1598 (54.1)
Other and missing	124 (3.6)	26 (5.8)	98 (3.3)
NNRTI a			
Nevirapine	1178 (36)	210 (47.2)	968 (32.8)
Efavirenz	2093 (64)	209 (47)	1884 (63.8)
Other and missing	127 (3.7)	26 (5.8)	101 (3.4)
Follow-up time, median (IQR)	394 (170 - 627)	207 (74 - 435)	422 (199 - 653)
Total Clinic Visits, median (IQR)	8 (4 - 14)	6 (3 - 9)	8 (5 - 11)

Age groups: At time of ART initiation.

ΨNadir CD4 cell counts: CD4 counts (cells/mm^3) at the time of ART initiation or up to 3 months post ART initiation;

ϵBMI: Body mass index is the weight in kilograms divided by the square of the height in meters (kg/m^2);

βNRTI: Nucleoside reverse transcriptase inhibitors;

aNNRTI: Non-nucleoside reverse transcriptase inhibitors.

Table 2

Hypertension incidence rate (per 1,000 person years) by age group

Age Category	Total Cohort	Males	Females
Age < 30 years	92.2 (47.4 - 179.1)	120.8 (79.5 - 183.5)	86.9 (70.3 - 107.3)
Age 30 – 39 years	110 (66.7 - 181.6)	176.4 (144.3 - 215.7)	80 (65.4 - 97.8)
40 years	134.8 (76.2 - 238.2)	158.8 (127.5 - 197.7)	114.1 (89.8 – 145)

Table 3

Cox proportional hazards models for correlates of incidence hypertension for people with HIV on antiretroviral therapy in Uganda (per 1,000 person years)

Characteristic	Univariate Model HR (95 % CI)	Multivariate Model Adjusted HR (95 % CI)
Female gender	REF	REF
Male gender	1.77 (1.47 - 2.14)	1.88 (1.49 - 2.39)
Age category		
<30	REF	REF
30-39	1.24 (0.99 - 1.56)	1.12 (0.86 - 1.45)
40	1.48 (1.16 - 1.89)	1.36 (1.02 - 1.82)
Baseline BMI[¥]		
<18.5	1.06 (0.82 - 1.37)	0.82 (0.61 - 1.09)
18.5 – 24.9	REF	REF
25.0 – 29.9	1.26 (0.97 - 1.64)	1.55 (1.16 - 2.07)
30	1.95 (1.28 - 2.97)	2.50 (1.56 - 4.01)
Nadir CD4 cell count[μ]		
<100	REF	REF
100 – 350	0.78 (0.62 - 0.7)	0.77 (0.60 - 0.99)
>350	0.49 (0.33 - 0.73)	0.64 (0.41 - 1.00)
Zidovudine-based regimen	REF	REF
Tenofovir-based regimen	1.15 (0.94 - 1.2)	1.24 (0.92 - 1.68)
Nevirapine-based regimen	REF	REF
Efavirenz-based regimen	0.91 (0.75 - 1.12)	0.83 (0.61-1.12)

Abbrevaition HR: Hazard ratio

[μ]Nadir CD4 cell count: CD4 counts (cells/mm^3) at the time of ART initiation or up to 3 months post initiation;

[¥]Baseline BMI: Body mass index is the weight in kilograms divided by the square of the height in meters (kg/m^2) at time of ART initiation.