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Noninfectious Comorbidity in the African Cohort Study

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Background. Noninfectious comorbid diseases (NCDs) contribute to morbidity and mortality in human immunodeficiency virus (HIV)–infected populations in resource-rich countries. With antiretroviral therapy (ART) scale-up in Africa, understanding burden NCD informs public health strategy.

Methods. At enrollment, participants at 11 HIV clinics in Kenya, Uganda, Tanzania, and Nigeria underwent medical history, physical, laboratory, and neuropsychological assessments to identify elevated blood pressure, hypercholesterolemia, dysglycemia, renal insufficiency, and cognitive impairment. Poisson regression models estimated adjusted relative risks (ARRs) and 95% confidence intervals (CIs) for the number of NCDs associated with factors of interest. Logistic regression was used to evaluate each NCD separately among HIV-infected participants.

Results. Among 2720 participants with complete NCD data, 2159 (79.4%) were HIV-infected. Of those, 1426 (66.0%) were taking ART and 813 (37.7%) had at least 1 NCD. HIV infection was associated with more NCDs, especially with ART (ARR, 1.42; 95% CI, 1.22–1.66). In addition to age, body mass index, and program site, ART usage was associated with more NCDs (ARR, 1.50; 95% CI, 1.27–1.78 for virologically suppressed and ARR, 1.38; 95% CI, 1.13–1.68 for viremic) among HIV-infected participants. In participants taking ART, CD4 nadir below 200 cells/mm^3 was associated with more NCDs (ARR, 1.43; 95% CI, 1.06–1.93). ART use was independently associated with hypercholesterolemia and dysglycemia. Program site was significantly associated with all comorbidities except renal insufficiency.

Conclusions. HIV infection was a risk for NCDs, which were common in HIV-infected participants, geographically variable, and largely consistent with metabolic complications of first-line ART.

Keywords. HIV; comorbidity; noninfectious; Africa.

Long-term cohort studies have made important contributions to the understanding of the natural history and pathogenesis of human immunodeficiency virus (HIV) [1–3]. In resource-rich settings, cohorts have demonstrated that antiretroviral therapy (ART) has decreased HIV-associated morbidity and mortality [4–6]. Despite this, multiple cohorts in these settings have revealed that HIV-infected individuals have a shorter life expectancy than the general population [7–9] and may be at increased risk for noninfectious comorbidities [6, 10] including, but not limited to, cardiovascular disease, hypertension, renal failure, and diabetes [10–15]. Potential contributors may include ART exposure and toxicity, chronic immune activation and inflammation, and concomitant risk factors such as substance abuse [11, 16, 17].

The extent to which HIV and its treatment interact with noninfectious comorbidities in sub-Saharan Africa is largely unknown. The impact of these noninfectious comorbidities in the African setting is potentially distinct given a higher burden of endemic coinfections that impact both HIV-infected and HIV-uninfected populations [18]. Social and behavioral differences may play a role as well.

We established a large clinic-based cohort in 4 African countries (Kenya, Uganda, Tanzania, and Nigeria) to study HIV disease characteristics and long-term outcomes in a multinational, multi-subtype African context. The African Cohort Study (AFRICOS) has a planned 15-year duration and provides an opportunity to investigate the extent and consequences of noninfectious comorbidities in HIV-infected individuals, initially in cross-sectional fashion but ultimately with longitudinal analysis utilizing the cohort's prospective repository of data and specimens.

METHODS

Study Design and Participants

AFRICOS, established in 2013, is a systematic longitudinal cohort study enrolling HIV-infected and HIV-uninfected adults at 11 clinics across 5 geographically distinct programs supported

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by the president's Emergency Plan for AIDS Relief (PEPFAR) in Kenya, Tanzania, Uganda, and Nigeria (Figure 1). Most HIV-infected study participants were invited to the study based on random selection from existing clinic patient lists (stratified by gender and ART status) or new enrollees to the clinic, while a minority (less than 5%) are recruited from other HIV studies performed by our group locally to facilitate long-term follow-up. HIV-uninfected participants are recruited from individuals undergoing HIV counseling and testing at the clinics.

Recruitment and enrollment began 21 January 2013 and is ongoing up to a maximum of 3600 participants (3000 HIV infected and 600 HIV uninfected). Individuals were eligible if they were aged ≥18 years and consented to data and specimen collection. An additional inclusion criterion for HIV-infected individuals was the ongoing receipt of HIV care at the enrolling clinic. We excluded individuals who were pregnant at enrollment.

All participants provided written informed consent. The institutional review boards of the Walter Reed Army Institute of Research, Makerere University School of Public Health, Kenya Medical Research Institute, Tanzania National Institute of Medical Research, and Nigerian Ministry of Defence approved the study.

Procedures

On enrollment, participants were administered a medical history and physical exam, completed a broad demographic and behavioral questionnaire, and underwent phlebotomy. For HIV-infected participants, serum chemistry and blood cell counts were performed, CD4 T-lymphocyte count and HIV RNA ("viral load") were enumerated, and fasting glucose and cholesterol levels were ascertained. All participants underwent a brief battery of neuropsychological tests including the International HIV Dementia Scale (IHDS), which includes evaluation of memory (registration and recall), motor speed (finger tapping), and manual dexterity (Luria sequence) [19].

To ensure comparability of data across sites, standard operating procedures for vital signs were followed, and laboratory measures were performed at laboratories that were accredited by the College of American Pathologists or had successfully completed external quality assurance. Study staff who performed neuropsychological testing underwent twice-yearly recertification through quality assurance visits after competency testing with initial certification.

Data Collection and Definitions

Data were entered and verified in the Clinplus platform (DZS Software Solutions, Bound Brock, NJ). Only baseline enrollment visit data were included in this cross-sectional analysis. Study participants enrolled as of 3 August 2016 were eligible for inclusion in these analyses.

The study database was used to identify participants with noninfectious diseases (NCDs) according to prespecified definitions. Elevated blood pressure was defined as a systolic

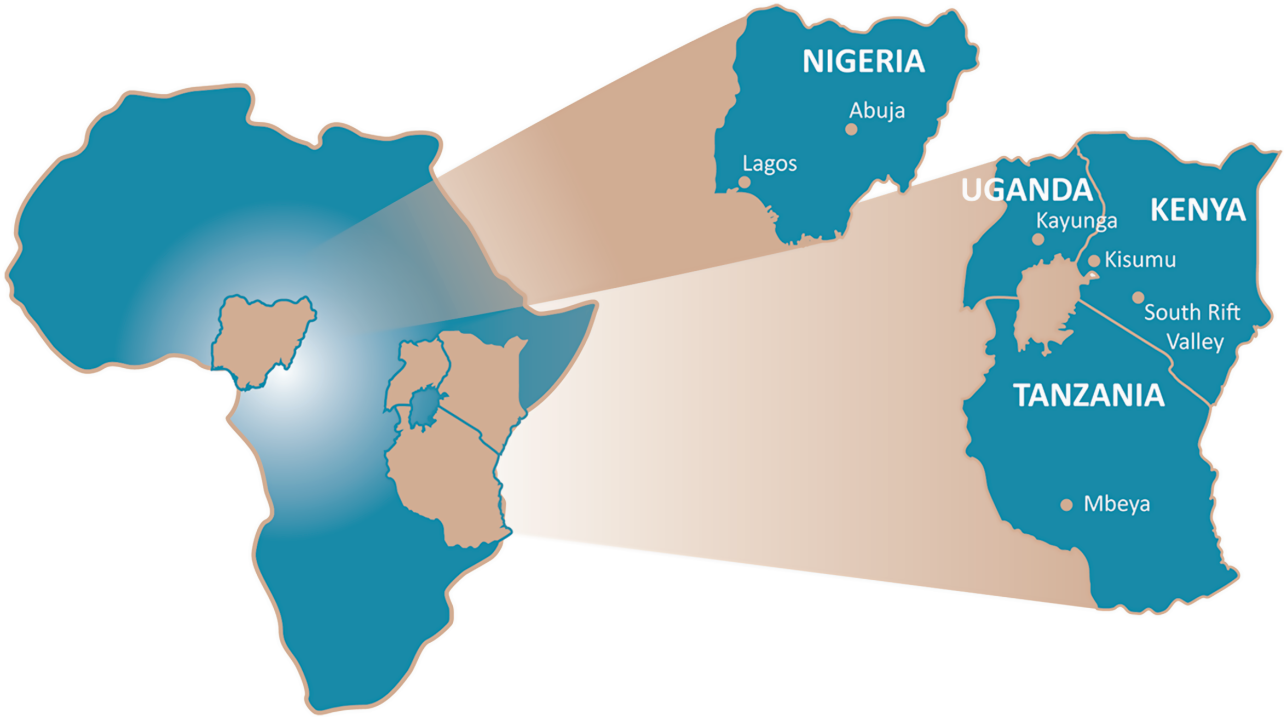

Figure 1. Map of African Cohort Study sites. Kayunga, Uganda: Kayunga District Hospital; South Rift Valley, Kenya: Kericho District Hospital, AC Litein Mission Hospital, Kapkatet District Hospital, Tenwek Mission Hospital, Kapsabet District Hospital, Nandi Hills District Hospital; Kisumu, Kenya: Kisumu West District Hospital; Mbeya, Tanzania: Mbeya Zonal Referral Hospital; Abuja, Nigeria: Defence Headquarters Medical Center; Lagos, Nigeria: 68th Nigerian Army Reference Hospital.

blood pressure measurement >139 mm Hg, a diastolic blood pressure measurement >89 mm Hg, or receipt of antihypertensive medications, with abnormal blood pressures repeated for confirmation during the study visit. Hypercholesterolemia was defined as a total fasting cholesterol >199 mg/dL or receipt of lipid-lowering medications. Dysglycemia was defined as a fasting glucose >99 mg/dL, nonfasting glucose >199 mg/dL, or receipt of hypoglycemic medications. Renal insufficiency was defined as an estimated glomerular filtration rate (GFR) <60 mL/min/1.73 m^2, calculated using the Modification of Diet in Renal Disease equation based on serum creatinine captured at entry [20]. Cognitive impairment was defined as having an IHDS score that was at least 2 standard deviations lower than the mean score of HIV-uninfected participants in the region. Since educational attainment was substantially different between Nigeria and East African countries, we examined them separately, yielding the 2 standard deviation cutpoint of <6 in East Africa and <7 in Nigeria.

Demographic variables, including sex, age, education level, and clinical care site, were collected upon enrollment. Body mass index (BMI) was calculated using participants' height and weight, then categorized as underweight (<18.5), normal (18.5–24.9), or overweight (≥25). Anemia was defined as hemoglobin <13 g/dL for males or <12 g/dL for females [21]. CD4 count at enrollment was categorized as <200, 200–349, 350–499, or ≥500 cells/mm^3. Antiretroviral medication use and viral load (VL) stratum were combined into the following categories: not on ART, on ART and VL <50 copies/mL, and on ART and VL ≥50 copies/mL. The 11 enrolling clinics were analyzed by program, with 1 clinic in the Kenya Kisumu West, Uganda, and Tanzania programs; 2 clinics in the Nigeria program; and 6 clinics in the Kenya South Rift Valley program (Figure 1).

Statistical Analyses

Only participants with the clinical and laboratory assessments required to assess all 5 NCDs of interest were included in these cross-sectional analyses. Participants were categorized based on the number of NCDs diagnosed (0, 1, or ≥2). Participant characteristics at study enrollment were compared across these 3 groups using the Fisher exact test for categorical variables and the Kruskal-Wallis test for continuous variables. Univariate and multivariate Poisson regression models were used to estimate unadjusted and adjusted relative risks (ARRs) and 95% confidence intervals (CIs) for number of NCDs associated with prespecified demographic and clinical factors of interest. A secondary analysis was conducted comparing HIV-uninfected participants to HIV-infected participants on ART and HIV-infected participants not on ART. Each of the 5 NCDs were also evaluated separately, using multivariable logistic regression models to estimate adjusted odds ratios and 95% CIs for associations between the same prespecified factors and each NCD. Subgroup analyses were conducted in which the study population was restricted to participants prescribed ART. Due to the smaller sample size of HIV-uninfected participants, only descriptive statistics and the Poisson model examining total NCD count were performed. All analyses were performed using SAS 9.4 (Cary, NC).

Sensitivity Analyses

To assess for the effect of missingness on our results, all analyses were rerun, including those participants with missing values for any NCD. We also assessed the effect of enrollment in prior studies rerunning analyses restricting to participants who were not included in prior studies.

RESULTS

From 21 January 2013 to 3 August 2016, 2727 volunteers were enrolled, including 463 HIV-uninfected participants. A total of 2264 HIV-infected participants were enrolled from the general clinic population with the exception of 124 participants recruited for follow-up from other studies. A total of 379 participants from the HIV-uninfected group and 2159 participants from the HIV-infected group had complete data on NCDs and were included in these analyses. Participants included in these analyses had a median age of 38.5 (interquartile range, 31.6, 46.0) years and 1501 (59%) were female (Supplementary Table 1). Across the entire analyzed population, 1414 (56%) had zero NCDs, 786 (31%) had 1 NCD, and 338 (13%) had 2 or more (Supplementary Figure 1). Adjusting for program site, age, gender, BMI, anemia, and education, we found HIV infection to be associated with more NCDs (ARR, 1.42; 95% CI ,1.22–1.66 for individuals on ART and ARR, 1.14; 95% CI, 0.95–1.36 for untreated individuals; Supplementary Table 2).

Among HIV-infected participants, median CD4 count was 384.0 cells/mm^3 and 1426 (66.0%) were taking ART at the time of enrollment (Table 1). Of those taking ART, 1245 (87.3%) had a viral load less than 1000 copies/mL and 1004 (70.4%) were suppressed below 50 copies/mL. Most ART-treated volunteers were on standard first-line therapy including a nonnucleotide reverse transcriptase inhibitor (NNRTI), with only 7.4% taking a protease inhibitor.

NCDs were common in the HIV-infected group, with 37.7% having at least 1 comorbidity and 10.0% having 2 or more. The most common comorbidity was hypercholesterolemia (19.1%) followed by elevated blood pressure (13.0%), dysglycemia (9.9%), cognitive impairment (5.7%), and renal insufficiency (1.3%).

We noted differences across program sites ($P < .001$; Table 1), with the programs in Kayunga, Uganda, and Kisumu West, Kenya, having the lowest prevalence of NCDs and Nigeria the highest (Figure 2). In unadjusted comparisons, we noted associations between a higher number of comorbidities and older age (RR, 1.97; 95% CI, 1.47–2.66 for 40–49 years and RR, 2.74; 95%

CI, 2.03–3.71 for >50 years), higher BMI (RR, 1.72; 95% CI, 1.52–1.96), more years of education (RR, 1.30; 95% CI, 1.12–1.51), and taking ART (RR, 1.97; 95% CI, 1.68–2.29 for those virologically suppressed and RR, 1.74; 95% CI, 1.44–2.11 for viremic individuals). Lower category of CD4 T-lymphocyte count (RR, 0.78; 95% CI, 0.65–0.93) and anemia (RR, 0.69; 95% CI, 0.60–0.80) were associated with a lower number of comorbidities.

In multivariable models adjusting for age, gender, BMI, and program site (Table 2), ART usage persisted in its association with more NCDs (ARR, 1.50; 95% CI, 1.27–1.78 for those virologically suppressed and ARR, 1.38; 95% CI, 1.13–1.68 for viremic individuals). In this adjusted model, anemia continued to be associated with fewer comorbidities (ARR, 0.78; 95% CI, 0.67–0.91). Evaluating only those taking ART (n = 1426; Supplementary Table 3) and adjusting for age, sex, BMI, and program, CD4 nadir less than 200 cells/mm^3 prior to ART initiation was found to be associated with more NCDs (ARR, 1.43; 95% CI, 1.06–1.93).

Among factors associated with each individual comorbidity, program site was significantly associated with all comorbidities except renal insufficiency (n = 28; Table 3). Male gender demonstrated an association with less hypercholesterolemia. Age was associated with elevated blood pressure, hypercholesterolemia, and meeting criteria for cognitive impairment, whereas more years of education was associated with less cognitive impairment. Anemia was associated with less elevated blood pressure and hypercholesterolemia, and we found an association or trend toward less hypercholesterolemia in CD4 groups less than 500 cell/mm^3. ART use was associated with hypercholesterolemia and dysglycemia.

Evaluating factors associated with individual NCDs among ART-treated participants only (Supplementary Table 4), we observed a trend toward increased cognitive impairment in the group with CD4 nadir below 200 cells/ mm^3 (P = .06) and an adjusted odds ratio of 4.64 (CI, 1.06–20.35; P = .04) for developing cognitive impairment with CD4 nadir 200–350 cells/ mm^3 compared to a nadir greater than 350 cells/mm^3.

There were no significant differences in results when allowing participants with missing NCD values (n = 104) or participants enrolled in prior studies into the analyses.

DISCUSSION

This study characterized key chronic noninfectious comorbidities across 4 countries in sub-Saharan Africa, with a large number of HIV-infected participants represented. The enrollment was majority female, reflective of the overall site clinic populations. Also, the attainment of viral suppression to less than 1000 copies/mL by 87% of those on therapy reflects moderately successful ART implementation at the study sites, although it falls short of the 90% UNAIDS goal [22].

As with studies performed in resource-rich settings, we found HIV infection to be associated with more total NCDs, especially among those taking ART. The study was largely underpowered to detect differences between HIV-infected and HIV-uninfected groups for specific NCDs. Substantial differences in the frequency of NCDs were observed across program sites, even after adjustment for demographic and HIV characteristics in the multivariate model. We cannot entirely rule out variation in site performance of the assessments despite standardization measures taken, but we would highlight that the programs with the least comorbidity in Uganda and Kisumu are the most rural programs in the cohort and the sites in Nigeria are the most urban. These site contrasts may reflect dietary and lifestyle differences. Host genetic differences between east and west African populations should also be considered.

Compared to those not taking ART, positive ART status was associated with increased number of comorbidities, both among participants who were virally suppressed and as well as those failing therapy. This increase was largely mediated by higher rates of hyperglycemia and hyperlipidemia, which are known side effects of NNRTIs [23–26]. However, we are unable to make that specific attribution in this group because few participants were taking non-NNRTI–based regimens. This association between ART and more comorbidities may be modified in the future as ARTs thought to have more favorable metabolic profiles, such as integrase inhibitors [27, 28], are made more widely available in the resource-limited setting.

In this analysis, concurrent anemia emerged as independently associated with fewer NCDs. This may reflect poor underlying nutritional status that is not otherwise captured by other covariates but that may lessen propensity to develop vascular or metabolic comorbidities.

Lower CD4 nadir among those treated with ART was associated with more noninfectious comorbidities, specifically cognitive impairment. Low CD4 nadir is a well-described risk factor for HIV-associated cognitive impairment in resource-rich settings [29, 30], and this association is now demonstrated in this African cohort as well. This observation suggests cognitive benefits for test and start recommendations [31], particularly for programs able to find cases prior to advanced HIV progression.

These analyses leveraged a diverse cohort recruited from PEPFAR-supported clinics in 4 countries to characterize the burden of NCDs and factors associated with their frequency in sub-Saharan Africa, primarily focusing on a large number of HIV-infected participants. We were able to make comparisons in NCDs between HIV-infected and HIV-uninfected study participants; however, the small size and convenience-based enrollment strategy for HIV-uninfected individuals into the cohort is a limitation of that analysis. However, where relevant comparisons are available, the frequencies of NCDs observed

Table 1. Study Population Characteristics at Enrollment

Characteristic	All HIV+ (N = 2159)	No NCDs (N = 1346)	1 NCD (N = 598)	2+ NCDs (N = 215)	*P* Value[a]
Program site					**<.0001**
Kayunga, Uganda	402 (18.6%)	320 (23.8%)	70 (11.7%)	12 (5.6%)	…
South Rift Valley, Kenya	802 (37.1%)	457 (34.0%)	256 (42.8%)	89 (41.4%)	…
Kisumu West, Kenya	361 (16.7%)	250 (18.6%)	80 (13.4%)	31 (14.4%)	…
Mbeya, Tanzania	354 (16.4%)	205 (15.2%)	108 (18.1%)	41 (19.1%)	…
Abuja and Lagos, Nigeria	240 (11.1%)	114 (8.5%)	84 (14.0%)	42 (19.5%)	…
Gender					.7727
Male	887 (41.1%)	552 (41.0%)	242 (40.5%)	93 (43.3%)	…
Female	1272 (58.9%)	794 (59.0%)	356 (59.5%)	122 (56.7%)	…
Age (years)					**<.0001**
18–24	164 (7.6%)	123 (9.1%)	34 (5.7%)	7 (3.3%)	…
25–39	1013 (46.9%)	722 (53.6%)	239 (40.0%)	52 (24.2%)	…
40–49	612 (28.3%)	341 (25.3%)	194 (32.4%)	77 (35.8%)	…
50+	370 (17.1%)	160 (11.9%)	131 (21.9%)	79 (36.7%)	…
Education					**.0002**
Less than primary school	751 (34.8%)	476 (35.4%)	212 (35.5%)	63 (29.3%)	…
Primary school	829 (38.4%)	549 (40.8%)	208 (34.8%)	72 (33.5%)	…
Secondary school or above	577 (26.7%)	320 (23.8%)	177 (29.6%)	80 (37.2%)	…
Missing/Unknown	2 (0.1%)	1 (0.1%)	1 (0.2%)	0 (0.0%)	**…**
Body mass index (kg/m^2)					**<.0001**
18.5–24.99	1357 (62.9%)	912 (67.8%)	340 (56.9%)	105 (48.8%)	…
<18.5	235 (10.9%)	160 (11.9%)	63 (10.5%)	12 (5.6%)	…
>25	567 (26.3%)	274 (20.4%)	195 (32.6%)	98 (45.6%)	…
Anemia					**<.0001**
No	1451 (68.5%)	854 (64.6%)	433 (74.1%)	164 (77.7%)	…
Yes	666 (31.5%)	468 (35.4%)	151 (25.9%)	47 (22.3%)	…
Missing/Unknown	42 (2.0%)	24 (1.8%)	14 (2.4%)	4 (1.9%)	…
Current alcohol use					.3671
No	1755 (81.3%)	1106 (82.2%)	476 (79.6%)	173 (80.5%)	…
Yes	403 (18.7%)	239 (17.8%)	122 (20.4%)	42 (19.5%)	…
Missing/Unknown	1 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	…
Lowest CD4 (cells/mm^3)					**.0001**
500+	249 (11.5%)	174 (12.9%)	58 (9.7%)	17 (7.9%)	…
350–499	265 (12.3%)	182 (13.5%)	69 (11.5%)	14 (6.5%)	…
200–349	605 (28.0%)	390 (29.0%)	159 (26.6%)	56 (26.0%)	…
<200	1038 (48.1%)	598 (44.4%)	312 (52.2%)	128 (59.5%)	…
Missing/Unknown	2 (0.1%)	2 (0.1%)	…	…	…
Enrollment CD4 (cells/mm^3)					**.0408**
500+	691 (32.0%)	412 (30.6%)	195 (32.6%)	84 (39.1%)	…
350–499	486 (22.5%)	309 (23.0%)	138 (23.1%)	39 (18.1%)	…
200–349	536 (24.8%)	334 (24.8%)	141 (23.6%)	61 (28.4%)	…
<200	404 (18.7%)	271 (20.1%)	105 (17.6%)	28 (13.0%)	…
Missing/Unknown	42 (1.9%)	20 (1.5%)	19 (3.2%)	3 (1.4%)	…
Viral load (copies/mL)					**<.0001**
<50	1033 (47.8%)	568 (42.2%)	326 (54.5%)	139 (64.7%)	…
50+	1058 (49.0%)	735 (54.6%)	253 (42.3%)	70 (32.6%)	…
Missing/Unknown	68 (3.1%)	43 (3.2%)	19 (3.2%)	6 (2.8%)	…
Years since HIV diagnosis, mean (SD)					
(n = 2139)[b]	3.7 (3.6)	3.4 (3.5)	4.1 (3.7)	5.0 (3.7)	**<.0001**
ART status					**<.0001**
No	733 (34.0%)	542 (40.3%)	161 (26.9%)	30 (14.0%)	…
Yes	1426 (66.0%)	804 (59.7%)	437 (73.1%)	185 (86.0%)	…
Among participants on ART[c]					
On ART containing tenofovir	794 (55.7%)	466 (57.9%)	240 (54.9%)	88 (47.6%)	**.0364**
On ART containing efavirenz	729 (51.0%)	420 (52.2%)	216 (49.4%)	93 (50.3%)	.7388
On ART containing nevirapine	580 (40.7%)	319 (39.7%)	178 (40.7%)	83 (44.9%)	.3574
On ART containing a protease inhibitor	105 (7.4%)	62 (7.7%)	37 (8.5%)	6 (3.2%)	.0837

Table 1. Continued

Characteristic	All HIV+ (N = 2159)	No NCDs (N = 1346)	1 NCD (N = 598)	2+ NCDs (N = 215)	*P* Value[a]
Duration of ART (years), mean (SD)	3.8 (3.0)	3.6 (2.9)	4.0 (2.9)	4.4 (3.2)	**.0011**
Nadir CD4 (cells/mm^3), mean (SD)	184.4 (138.5)	195.0 (148.1)	177.6 (132.3)	155.1 (100.3)	**.0117**

All data presented as n (%) unless otherwise indicated. Bold indicates *P* value < 05. Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; NCD, noninfectious comorbid disease; SD, standard deviation.

[a]*P* values were calculated using Kruskal-Wallis test for continuous variables and Fisher exact test for categorical variables.

[b]Twenty participants were missing information on date of HIV diagnosis.

[c]Eleven participants were on ART containing rilpivirine, 1 participant was only on tenofovir and lamivudine.

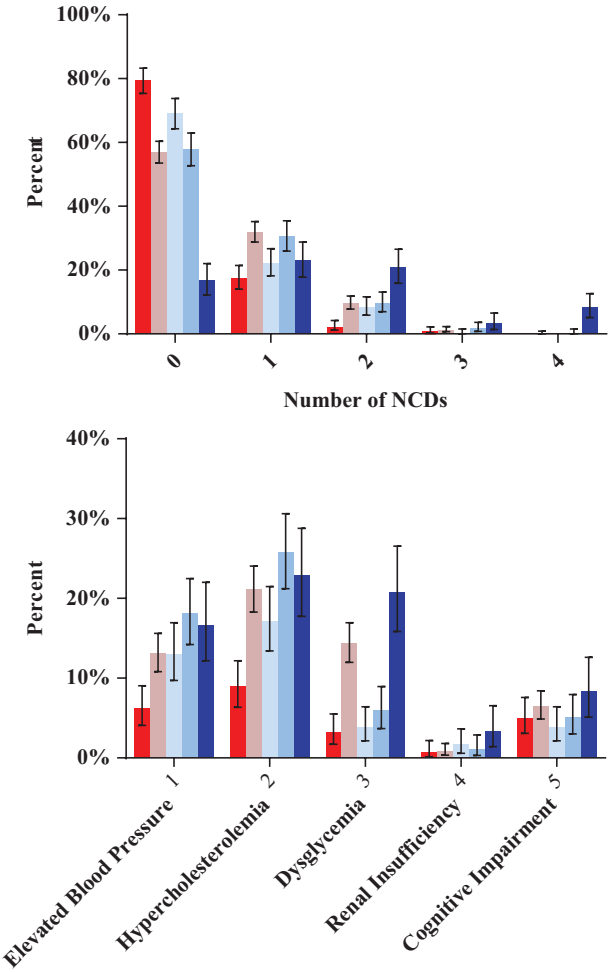

Figure 2. (*A*) Percentage of participants by number of noninfectious comorbid diseases (NCDs) and site. Shown is the distribution of NCDs by site, with the majority of participants with 0 NCDs, although this varies by site. (*B*) Percentage of participants with select NCDs by site . Similar to overall count of NCDs, prevalence of individual NCDs varies by site: Kayunga, Uganda; South Rift Valley, Kenya; Kisumu West, Kenya; Mbeya, Tanzania; Abuja and Lagos, Nigeria. 1: elevated blood pressure (BP); systolic BP >139 or diastolic BP >89 or on hypertension medications. 2: hypercholesterolemia; cholesterol >199 or on cholesterol medications. 3: dysglycemia; fasting glucose >99 or any glucose >199 or on glucose medications. 4; renal insufficiency, glomerular filtration rate <60 by Modification of Diet in Renal Disease Study equation. 5; cognitive impairment, International HIV (human immunodeficiency virus) Dementia Scale <6 for East Africa or <7 for Nigeria. Abbreviation: NCD, noninfectious comorbid disease.

Table 2. Unadjusted and Adjusted Relative Risk for Select Factors and Number of Noninfectious Comorbid Diseases

Factor	Unadjusted Relative Risk (95% CI)	Adjusted Relative Risk (95% CI)
Program site		
Kayunga, Uganda	Reference group	…
South Rift Valley, Kenya	2.31 (1.86–2.88)[a]	1.98 (1.57–2.50)[a]
Kisumu West, Kenya	1.64 (1.27–2.12)[b]	1.38 (1.06–1.80)[b]
Mbeya, Tanzania	2.32 (1.82–2.96)[a]	2.04 (1.57–2.65)[a]
Abuja and Lagos, Nigeria	2.99 (2.33–3.83)[a]	3.16 (2.39–4.18)[a]
Gender		
Female	Reference group	…
Male	0.96 (0.85–1.09)	0.98 (0.85–1.12)
Age (years)		
18–24	Reference Group	…
25–39	1.14 (0.85–1.54)	0.98 (0.72–1.33)
40–49	1.97 (1.47–2.66)[a]	1.60 (1.18–2.18)[b]
50+	2.74 (2.03–3.71)[a]	2.31 (1.68–3.16)[a]
Education		
Less than primary school	Reference group	…
Primary school	0.95 (0.82–1.10)	0.93 (0.79–1.09)
Secondary school or above	1.30 (1.12–1.51)[a]	0.92 (0.78–1.10)
Body mass index (kg/m^2)		
18.5–24.99	Reference group	…
<18.5	0.91 (0.73–1.14)	0.97 (0.77–1.21)
>25	1.72 (1.52–1.96)[a]	1.48 (1.29–1.70)[a]
Anemia		
No	Reference group	…
Yes	0.69 (0.60–0.80)[a]	0.78 (0.67–0.91)[b]
Missing/Unknown	0.97 (0.63–1.48)	1.03 (0.66–1.59)
Enrollment CD4 (cells/mm^3)		
500+	Reference group	…
350–499	0.85 (0.72–1.01)	0.89 (0.75–1.05)
200–349	0.94 (0.81–1.10)	0.94 (0.80–1.11)
<200	0.78 (0.65–0.93)[b]	0.87 (0.72–1.06)
Missing/Unknown	1.11 (0.74–1.66)	1.00 (0.66–1.52)
Viral load group		
Not on ART	Reference group	…
On ART, virally suppressed (<50 copies/mL)	1.97 (1.68–2.29)[a]	1.50 (1.27–1.78)[a]
On ART, viremic (>50 copies/mL)	1.74 (1.44–2.11)[a]	1.38 (1.13–1.68)[b]
Missing/Unknown	1.48 (1.02–2.15)[b]	1.26 (0.85–1.87)

N = 2159. Abbreviations: ART, antiretroviral therapy; CI, confidence interval.

[a]*P* value <.001.

[b]*P* value <.05.

Table 3. Adjusted Analyses of Factors Associated With Specific Noninfectious Comorbid Disease

Factor	Elevated Blood Pressure N = 281 OR (95% CI)	Hypercholesterolemia N = 413 OR (95% CI)	Dysglycemia N = 213 OR (95% CI)	Renal Insufficiency N = 28 OR (95% CI)	Cognitive Impairment N = 124 OR (95% CI)
Program site					
Kayunga, Uganda	Reference group	…	…	…	…
South Rift Valley, Kenya	2.05 (1.25–3.37)[a]	1.93 (1.27–2.92)[a]	4.25 (2.29–7.88)[b]	1.09 (0.25–4.69)	1.78 (1.00–3.16)
Kisumu West, Kenya	2.22 (1.29–3.81)[a]	1.44 (0.91–2.29)	0.93 (0.42–2.05)	2.09 (0.47–9.29)	0.84 (0.40–1.76)
Mbeya, Tanzania	3.15 (1.83–5.42)[b]	2.86 (1.80–4.57)[b]	1.52 (0.71–3.24)	0.89 (0.18–4.54)	1.55 (0.75–3.18)
Abuja and Lagos, Nigeria	3.57 (1.93–6.63)[b]	2.80 (1.65–4.76)[b]	9.40 (4.61–19.16)[b]	2.68 (0.56–12.89)	3.55 (1.65–7.61)[a]
Gender					
Female	Reference group	…	…	…	…
Male	1.28 (0.95–1.73)	0.70 (0.54–0.90)[a]	1.28 (0.92–1.79)	1.40 (0.61–3.22)	0.78 (0.52–1.18)
Age (years)					
18–24	Reference group	…	…	…	…
25–39	1.05 (0.53–2.06)	1.06 (0.63–1.79)	0.64 (0.32–1.28)	1.44 (0.17–11.78)	1.03 (0.39–2.71)
40–49	1.71 (0.86–3.38)	1.89 (1.11–3.20)[a]	1.00 (0.49–2.02)	3.27 (0.40–26.90)	2.76 (1.06–7.22)[a]
50+	4.29 (2.15–8.57)[b]	2.91 (1.68–5.05)[b]	1.67 (0.80–3.46)	3.23 (0.35–29.66)	2.19 (0.80–6.02)
Education[c]					
Less than primary school	Reference group	…	…	…	…
Primary school	1.05 (0.75–1.47)	1.21 (0.90–1.62)	0.79 (0.53–1.17)	1.58 (0.54–4.65)	0.42 (0.26–0.67)[b]
Secondary school or higher	0.95 (0.65–1.39)	1.30 (0.94–1.81)	0.78 (0.52–1.18)	1.94 (0.61–6.19)	0.38 (0.26–0.65)[b]
BMI (kg/m^2)[d]					
18.5–24.99	Reference group	…	…	…	…
<18.5	0.83 (0.49–1.41)	0.84 (0.54–1.29)	1.15 (0.69–1.93)	…	1.54 (0.89–2.65)
>25	2.57 (1.90–3.46)[b]	1.43 (1.10–1.85)[a]	1.70 (1.21–2.39)[a]	1.51 (0.64–3.59)	0.93 (0.59–1.48)
Anemia					
No	Reference group	…	…	…	…
Yes	0.64 (0.45–0.89)[a]	0.62 (0.46–0.83)[a]	0.77 (0.53–1.12)	1.35 (0.57–3.21)	1.09 (0.70–1.68)
Missing/ Unknown	0.63 (0.21–1.91)	1.07 (0.49–2.33)	0.90 (0.26–3.17)	3.84 (0.68–21.80)	1.54 (0.43–5.49)
Enrollment CD4 (cells/mm^3)					
500+	Reference group	…	…	…	…
350–499	0.99 (0.69–1.42)	0.72 (0.52–0.98)[a]	0.84 (0.54–1.31)	0.54 (0.14–2.08)	1.14 (0.67–1.93)
200–349	0.91 (0.63–1.31)	0.87 (0.64–1.18)	1.01 (0.67–1.53)	1.13 (0.40–3.23)	0.91 (0.53–1.57)
<200	0.67 (0.43–1.05)	0.52 (0.35–0.78)[a]	1.40 (0.89–2.20)	1.05 (0.34–3.25)	1.43 (0.82–2.51)
Missing/Unknown	0.61 (0.20–1.83)	0.67 (0.31–1.46)	2.22 (0.88–5.62)	3.53 (0.61–20.41)	0.93 (0.21–4.19)
Viral load group					
Not on ART	Reference group	…	…	…	…
On ART, virally suppressed (<50 copies/mL)	1.15 (0.81–1.62)	2.62 (1.91–3.61)[b]	1.94 (1.29–2.93)[a]	0.40 (0.14–1.12)	1.08 (0.67–1.75)
On ART, viremic (>50 copies/mL)	1.08 (0.71–1.63)	2.05 (1.40–3.00)[b]	1.56 (0.97–2.53)	1.11 (0.42–2.95)	1.21 (0.69–2.10)
Missing/Unknown	0.38 (0.13–1.13)	2.58 (1.34–4.97)[a]	2.18 (0.83–5.73)	0.53 (0.06–4.90)	1.14 (0.32–4.07)

N = 2159. Elevated blood pressure (BP): systolic BP >139 or diastolic BP >89 or on hypertension medications. Hypercholesterolemia: cholesterol >199 or on cholesterol medications. Dysglycemia: fasting glucose >99 or any glucose >199 or on glucose medications. Renal insufficiency: glomerular filtration rate <60 by Modification of Diet in Renal Disease Study equation. Cognitive impairment, International HIV (human immunodeficiency virus) Dementia Scale <6 for East Africa or <7 for Nigeria.

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; CI, confidence interval; OR, odds ratio.

[a] *P* value <.05.

[b] *P* value <.001.

[c] Two participants with Missing/Unknown Education data were included in the "Less than Primary School" reference group.

[d] There were 235 participants with BMI <18.5, of which none had renal insufficiency and were regrouped to the reference group BMI 18.5–24.99.

in this study's HIV-uninfected comparison group are generally consistent with published estimates from other HIV-uninfected populations in sub-Saharan Africa. We found elevated blood pressure in 19.3% of HIV-uninfected AFRICOS participants, and studies in Malawi, South Africa, Tanzania, and Nigeria have reported a prevalence of hypertension in HIV-uninfected populations of 8.0%–27. 9% [32–35]. Maganga and colleagues reported glucose metabolism disorders in 7.2% of an HIV-uninfected population in Tanzania [36], similar to our estimate of 7.1% with dysglycemia among uninfected AFRICOS enrollees. Renal insufficiency with GFR <60 mL/min/1.73 m^2 was seen in 0.3% of uninfected AFRICOS participants [37, 38].

Prospective enrollment likely introduced some selection bias in the HIV-infected group despite high rates of participation in

the study. Comparing basic demographics, we do see a higher proportion of males in our analysis than that in the overall clinic population sampled (41.1% vs 35.1%, $P < .0001$), and the cohort was on average slightly younger, with a mean age of 40 years (range, 18 – 76) in the cohort vs 41 years (range, 16–94) in the overall clinic population. We adjusted for age and gender in these analyses; however, these populations may also differ in unmeasured ways that limit the generalizability of our findings. The small number of study participants who were recruited from prior studies may be particularly more prone to bias; however, excluding them in the multiple regression analyses did not change our findings.

A further limitation is that these cross-sectional analyses did not evaluate important long-term outcomes of comorbid disease processes, such as myocardial infarction, heart failure, and cerebrovascular accident. However, ongoing prospective data collection will enable future analyses of such events. Some comorbidity definitions were adapted to suit the cross-sectional nature of these analyses, such as elevated blood pressure defined by a single-day measurement as opposed to hypertension that requires serial blood pressure measurements for diagnosis. Our definition for cognitive impairment likely selected only the most severe cases due to the use of a 2-standard deviation threshold and comparison to co-enrolled HIV-uninfected participants rather than normative data typically acquired from a healthy cognitively asymptomatic population. It is also possible that some members of our comparative cohort experienced cognitive impairment from head injuries, substance use, or other factors. Additionally, statistical power to evaluate for risk factors for renal insufficiency was limited since few participants experienced renal dysfunction defined by a GFR <60 mL/min/1.73 m^2; however, the observed associations were robust to analyses that used a higher threshold. Finally, the overall model for comorbidities includes somewhat heterogeneous diseases, and underlying biological mechanisms likely vary.

Our data add substantially to the field by documenting a substantial frequency of noninfectious comorbidities in a large cohort across 4 African countries, with more than 37% of HIV-infected study participants meeting criteria for at least 1 NCD. Among HIV-infected participants, AFRICOS cohort prevalence of NCDs is generally less than older, highly treated HIV cohorts in resource-rich settings [39, 40]. However, as the HIV-infected population in Africa ages and ART increasingly scales up across the continent, it will be increasingly important for HIV treatment models to address evaluation and treatment of common NCDs in the comprehensive care of HIV-infected individuals. Future comparison of noninfectious comorbidity to a larger HIV-uninfected control population will enrich the understanding of HIV-associated noninfectious risks in Africa. Additional work in this cohort includes direct comparison of NCD data with a large Western HIV cohort and assessment of markers of immune inflammation to elucidate pathogenesis pathways in the African context. Pursuit of this work will be further advanced by evaluation of accumulating longitudinal data on the incidence of definitive clinical outcomes.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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