Infectious and Noninfectious Multimorbidity Among HIV Clinic Clients in the African Cohort Study

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ABSTRACT - updated

Background

The frequency and complexity of multimorbidity in the increasingly treated African HIV epidemic is not comprehensively described.

Methodology

The African Cohort Study (AFRICOS) prospectively enrolls adult HIV clinic clients and uninfected adults at 11 PEPFAR supported facilities in Kayunga, Uganda; South Rift Valley and Kisumu West, Kenya; Mbeya, Tanzania and Abuja and Lagos, Nigeria. We evaluated infectious comorbidities (ICOs) at baseline: HBV, HCV and syphilis by screening serologies, pulmonary TB by Xpert MTB/RIF, and cryptococcosis by serum CrAg if CD4+ count ≤ 200. Baseline noninfectious comorbidities (NICOs) included elevated blood pressure (SBP>139 or DBP>79), impaired fasting glucose (IFG) (>99 mg/dl), renal insufficiency (GFR<60 mL/min), hypercholesterolemia (total cholesterol >199 mg/dl), anemia (hemoglobin <11 mg/dl), and cognitive impairment (International HIV Dementia Scale < 1.5 SD below the mean). We compared those with no comorbidities to those with two or more comorbidities using descriptive statistics and investigated determinants of NICOs employing multivariate Poisson regression.

Results

Between January 2013 and December 2014, 1071 HIV infected adults enrolled in Kayunga (21%), South Rift Valley (42%), Kisumu West (15%), Mbeya (15%), and Nigeria (7%). Participants were 59% female with mean age 40 years and mean CD4+ count 417 cells/[mm3]. Among the 72% taking antiretroviral therapy (ART), mean duration was 4.2 years, 67% were suppressed to < 50 copies/mL, and 78% had exposure to thymidine analogues. Rates of smoking and IDU were low (3.3 and 0.2%). Reactive serologies for hepatitis B, C, and syphilis were identified in 4.9%, 1.5% and 5.7%. Nineteen (1.9%) had positive Xpert assays and 8/153 (5.2% of those with CD4+ count ≤ 200) had cryptococcal antigenemia. The most common NICOs were elevated blood pressure (16.8%), anemia (14.2%) and impaired fasting glucose (10.4%). 47% had ≥1 comorbidity and 14% had ≥2. 12% had ≥1 ICO and 40% had ≥1 NICO. Those with ≥2 comorbidities had significantly higher age, lower CD4+ count (current and at diagnosis), higher body mass index (BMI), and, among those on ART, lower CD4+ nadir than those with no comorbidities. Multivariate regression revealed independent association of age (p<0.0001), CD4+ count (p=0.02) and female gender (p=0.01) with total NICOs. There was a nonsignificant trend toward an association of higher BMI with total NICOs.

Conclusions

The cohort demonstrates considerable HIV associated multimorbidity in a largely rural African context. Body mass and CD4+ T cell count are potentially modifiable predictors of NICOs. Future analyses will prospectively assess the impact of expanded ART eligibility on these outcomes.

INTRODUCTION

- Cohorts in resource rich settings have described increased prevalence of noninfectious comorbidities among HIV infected individuals
- Non-AIDS defining illnesses a major cause of morbidity and mortality
  - Pathogenesis linked to immune inflammation persisting despite antiretroviral therapy (ART)
  - Confounded by possible ART effects, concomitant risk factors (e.g., substance use) in Western populations
- Impact of comorbidities potentially distinct in the African setting
  - Higher burden of endemic co-infections impacting HIV infected and uninfected populations
  - Social and behavioral differences
  - Noninfectious comorbidity less comprehensively described

METHODS

The African Cohort Study (RV 329: AFRICOS)

- MHRP prospective observational HIV focused cohort
- Broad primary objective: "To longitudinally assess the impact of clinical practices, biological factors and socio-behavioral issues on HIV infection and disease progression in an African context."
- Enrolling adult volunteers, HIV infected and uninfected, at HIV clinical care and treatment sites. (Figure 1):

Figure 1. AFRICOS Enrollment Sites



  - Kayunga District Hospital, Uganda
  - South Rift Valley, Kenya: Kericho, Kapkatet, Nandi Hills, and Kapsabet District Hospitals and AC Litein, Tenwek Mission Hospitals
  - Kisumu West District Hospital, Kenya
  - Defence Headquarters Medical Center, Abuja, and 68th Nigerian Army Reference Hospital, Lagos, Nigeria
  - Mbeya Referral Hospital, Tanzania
- Visits: Enrollment, 6 monthly follow up, unscheduled visits for acute illness
- Physical exam, questionnaire, demographic, social, and medical history, neurocognitive battery and depression screen
- HIV outcomes: Clinical staging, CD4+ count, viral load, genotype resistance testing at baseline and virologic failure
- Laboratory comorbidity characterization
  - Syphilis, HBV, HCV serologic screening
  - Tuberculosis
    - Sputum for Xpert® MTB/RIF
    - Interferon gamma release assay in ART naïve
  - Cryptococcal antigen screening (for CD4+ ≤ 200)
  - Malaria
    - Thin and thick film slides (read prospectively if febrile)
    - Dried blood spot
  - For women: cervical cancer screening (visual inspection +/-Pap)
  - Fasting glucose, lipids
- Cryopreservation of serum, plasma, PBMC

Analysis methods

- Defined prevalent Infectious Comorbidities (ICOs) and Noninfectious Comorbidities (NICOs) at enrollment visit for updated cohort population (Table 1)

Table 1. Comorbidity Definitions

Infectious Comorbidities		Noninfectious Comorbidities	
Hepatitis B	Reactive HBsAg	Elevated blood pressure	SBP>139 or DBP>79
Hepatitis C	Reactive HCV Ab	Impaired fasting glucose	Fasting glucose >99 mg/dl
Syphilis	Reactive RPR/VDRL	Renal insufficiency	GFR <60 mL/min
Pulmonary tuberculosis	Positive Xpert MTB/RIF	Hypercholesterolemia	Total cholesterol > 199 mg/dl
Cryptococcosis	Positive Serum CrAg*	Anemia	Hemoglobin < 11 mg/dl
		Cognitive impairment	IHDS < 6 (1.5 SD below mean)**

*Serum CrAg evaluated in those with CD4+≤200
**IHDS = International HIV Dementia Score

- Compared characteristics of volunteers with two or more comorbidities to those with no comorbidities employing descriptive statistics
  - Chi square or Fisher exact test for categorical variables
  - Two-sided T test for continuous variables
- Developed multivariate Poisson regression model for determinants of NICOs

RESULTS

- From January 2103 to December 2014 1071 HIV infected adults enrolled
  - Kayunga (21%), South Rift Valley (42%), Kisumu West (15%), Mbeya (15%), and Nigeria (7%)
  - 59% female, mean (SD) age 40.0 (10.5) years
- Comorbidity frequency (Table 2)

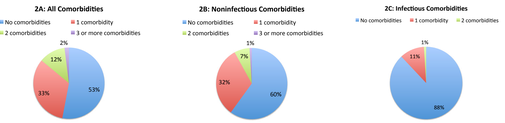
Table 2. Comorbidity Frequencies (n=1071)

Infectious Comorbidities		Noninfectious Comorbidities	
Hepatitis B	4.9%	Elevated blood pressure	16.8%
Hepatitis C	1.5%	Impaired fasting glucose	10.4%
Syphilis	5.7%	Renal insufficiency	1.3%
Pulmonary tuberculosis	1.9%	Hypercholesterolemia	2.6%
Cryptococcosis*	5.2%	Anemia	14.2%
		Cognitive impairment	5.0%

*Serum CrAg evaluated in those with CD4+≤200 (n=153)

- Most common infectious comorbidities: syphilis and hepatitis B
- Most common noninfectious comorbidities: elevated blood pressure, anemia and impaired fasting glucose
- Multimorbidity common: 47% with at least one comorbidity, 14% with two or more (Figure 2)

Figure 2. Multimorbidity Frequency (n=1071)



- Those with two or more comorbidities had significantly higher age (p<0.0001), lower current CD4+ count (p=0.0011), lower CD4+ count at diagnosis (p=0.0143), and higher body mass index (p<0.0001) than those with no comorbidities (Table 3)

Table 3. Multimorbidity and Volunteer Characteristics on Enrollment

	One comorbidity n=356	Two or more comorbidities n=147	No comorbidities N=568	All HIV+ N=1071
Female, n (%)	208 (54)	92 (62.6)	336 (59.2)	636 (59.4)
Age (years), mean (SD) **	**40.9 (10.5)**	**43.4 (10.5)**	**38.6 (10.3)**	**40.0 (10.5)**
Taking ART, n (%)	255 (71.6)	97 (66.0)	414 (72.9)	766 (71.5)
Highest WHO stage III or IV, n (%)	183 (51.4)	84 (57.1)	304 (53.5)	571 (53.3)
CD4 at diagnosis (cells/mm³), mean (SD)**	**179.2 (134.6)**	**161.2 (104.0)**	**193.0 (141.9)**	**184.4 (135.4)**
Current CD4 (cells/mm³), mean (SD)**	**407.9 (235.6)**	**364.8 (220.6)**	**436.3 (232.8)**	**416.9 (233.2)**
Viral load group (n=995):				
<50 copies/mL, n (%)	183 (51.4)	71 (48.3)	278 (48.9%)	532 (49.7)
50-999 copies/mL, n (%)	33 (9.3)	14 (9.5)	69 (12.1)	116 (10.8)
≥1000 copies/mL, n (%)	123 (34.6)	52 (35.4)	172 (30.3)	347 (32.4)
ART duration (years), mean (SD)*	4.4 (2.6)	4.1 (2.6)	4.1 (2.8)	4.2 (2.7)
Exposure to thymidine analogue, n (%)*	201 (78.8)	70 (72.2)	328 (79.2)	599 (78.2)
CD4 nadir (cells/mm³), mean (SD)*.**	**169.7 (122.8)**	**146.8 (91.3)**	**181.2 (142.1)**	**173.1 (130.7)**
Smoking, n (%)	15 (4.2)	4 (2.7)	16 (2.8)	35 (3.3)
IDU, n (%)	0 (0)	1 (0.7)	1 (0.2)	2 (0.2)
Alcohol, n (%)	55 (15.4)	24 (16.3)	80 (14.1)	159 (14.8)
Body Mass Index group, <18.5, n (%)**	**48 (13.5)**	**22 (15.0)**	**55 (9.7)**	**125 (11.7)**
18.5-24.99, n (%)	**218 (61.2)**	**66 (44.9)**	**381 (67.1)**	**665 (62.1)**
25-29.99, n (%)	**69(19.4)**	**43 (29.3)**	**88 (15.5)**	**200 (18.7)**
≥30, n (%)	**19 (5.3)**	**14 (9.5)**	**40 (7.0)**	**73 (6.8)**

*Among those on ART (n=766) **p<0.05 2+ comorbidities vs. No comorbidities

- Among volunteers taking ART, those with two or more comorbidities had lower CD4+ nadir (p=0.0045) than those with no comorbidities
- Rates of potentially confounding substance use were low
- In multivariate model: older age, female gender, and current CD4+ count independently associated with total number of noninfectious comorbidities, with a trend displayed for higher BMI (Table 4)

Table 4. Modelling Noninfectious Multimorbidity: Total NICOs

Variable	Univariate Estimate	Univariate P-Value	Multivariate Estimate	Multivariate P-value
Intercept			-1.8279	<.0001
Age	**0.0214**	**<.0001**	**0.0249**	**<.0001**
Gender (M, ref=F)	-0.1672	0.0631	**-0.2743**	**0.0063**
BMI	**0.0251**	**0.0072**	0.0178	0.0785
Current CD4	-0.0004	0.0608	**-0.0005**	**0.0183**
CD4 Nadir	-0.0001	0.5764		
Taking ART	-0.0197	0.8371		
VL Group	0.0958	0.2695		
Time since HIV diagnosis	-0.0068	0.5940		

Multivariate Poisson model for total number of noninfectious comorbidities

DISCUSSION

- Enrollment data demonstrates substantial objectively ascertained multimorbidity in a largely rural African cohort
  - Reveals prevalence of infectious and noninfectious comorbidities that are not routinely assessed in HIV care in resource limited settings
  - Chronic conditions predominate
- Impact of CD4+ count may reflect influence of HIV disease progression on multimorbidity
  - Implications for implementation of guidelines initiating ART at higher CD4+ count
- Traditional risk factors are also associated with noninfectious comorbidity in this setting
- Analysis limitations
  - Burden of ICOs likely underestimated by evaluation of single timepoint given episodic nature of endemic infections
  - Single measurements identifying NICOs and screening serologies identifying ICOs limit accuracy of definitions
  - Differing underlying pathogenesis of varying NICOs may confound identification of risk factors (e.g., increased risk of anemia among females may not apply to other NICOs)

CONCLUSIONS

- Multimorbidity among HIV infected individuals is common in this African setting, and is more common with advanced HIV disease
- HIV associated (CD4+ count) and non-associated (BMI, age) factors are likely contributing to the burden of noninfectious comorbidities
- Prospective analysis will facilitate more comprehensive measurement of comorbidity and enable assessment of impact of expanded ART eligibility on comorbidity outcomes

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