Clinical predictors cannot replace biological predictors in HIV-2 infection in a community setting in West Africa

Annabelle J. Gourlay [a,*], Carla van Tienen [b], Sangeeta S. Dave [c], Tim Vincent [d], Sarah L. Rowland-Jones [e], Judith R. Glynn [a], Hilton C. Whittle [a], Maarten F. Schim van der Loeff [f,g]

[a] Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT, UK
[b] Erasmus Medical Centre, Medical Microbiology & Infectious Diseases, Rotterdam, the Netherlands
[c] Centre for Sexual Health and HIV Research, Research Department of Infection and Population Health, University College London, London, UK
[d] Medical Research Council, Fajara, Banjul, The Gambia
[e] Nuffield Department of Medicine, University of Oxford, John Radcliffe Hospital, Oxford, UK
[f] Department of Infectious Diseases, Health Service of Amsterdam, Amsterdam, the Netherlands
[g] Department of Internal Medicine, Division of Infectious Diseases, Tropical Medicine and AIDS, Center for Infection and Immunity Amsterdam (CINIMA), Academic Medical Center, Amsterdam, the Netherlands

ARTICLE INFO

SUMMARY

Objective: To identify clinical predictors of mortality in HIV-2-infected individuals that may be used in place of CD4 count or plasma viral load (PVL) to guide treatment management in resource-limited settings.
Methods: A prospective community cohort study of HIV-infected and HIV-negative individuals in a rural area of Guinea-Bissau has been ongoing since 1989. In 2003 participants were invited for a clinical examination and blood tests. They were followed-up for vital status until 2010. Antiretroviral treatment (ART) became available in 2007. Cox regression was used to examine the association of clinical measures (World Health Organization (WHO) stage, body mass index (BMI), mid-upper arm circumference (MUAC), and WHO performance scale) measured in 2003 with subsequent mortality.
Results: In 2003, 146 HIV-2-infected individuals (68% women; mean age 56 years) were examined. Over the next 7 years, 44 (30%) died. BMI < 18.5 kg/m^2 was associated with a crude mortality hazard ratio (HR) of 1.9 (95% confidence interval (CI) 1.0–3.9, $p = 0.08$); adjusted for age and sex, HR 1.8 (95% CI 0.9–3.8, $p = 0.1$). MUAC <230 mm in women and <240 mm in men was also associated with an elevated mortality HR, though statistical evidence was weak (crude HR 2.2, 95% CI 0.9–5.3, $p = 0.1$). WHO clinical stage and WHO performance scale were not associated with mortality ($p = 0.6$ and $p = 0.2$, respectively, for crude associations).
Conclusions: Baseline BMI, MUAC, WHO stage, and WHO performance scale were not strong or statistically significant predictors of mortality among HIV-2-infected individuals. CD4 count and PVL are more reliable tools, when available, for the management of HIV-2-infected patients in the community setting.

© 2012 International Society for Infectious Diseases. Published by Elsevier Ltd. All rights reserved.

1. Introduction

Human immunodeficiency virus type 2 (HIV-2) is mostly restricted to West Africa, the highest prevalence having been observed in Guinea-Bissau.[1] The mortality rate of HIV-2-infected subjects is approximately two times higher than that of HIV-negative subjects.[2–5] This contrasts with an ≥8-fold increased mortality rate in HIV-1-infected individuals compared to HIV-negative individuals.[6,7] It is thought that a large proportion of HIV-2-infected individuals do not progress to AIDS,[8,9] or progress more slowly than HIV-1-infected individuals.[8,10] However HIV-2 can progress to AIDS with similar clinical features to those in HIV-1-infected individuals.

In low-income settings, clinical measures may offer practical criteria for the management of HIV-infected patients and for the decision to start antiretroviral treatment (ART). CD4 count and plasma viral load (PVL) predict mortality with HIV-2 infection,[2,5,11–13] but laboratory testing for these markers is often not feasible.

Clinical predictors of mortality with HIV-1 infection, such as body mass index (BMI)[14–17] and World Health Organization (WHO) clinical stage,[18,19] have been documented. Whether they also predict mortality with HIV-2 infection is less clear, as the few studies conducted among HIV-2-infected individuals were mostly hospital-based and limited to patients with more advanced

* Corresponding author.
  E-mail address: annabelle.gourlay@lshtm.ac.uk (A.J. Gourlay).

disease.[2,14,20] Population-based studies are therefore needed to further investigate the role of clinical measures in the management of HIV-2 infection. In this study we explore the utility of clinical predictors for mortality in HIV-2-infected adults in a community cohort in Guinea-Bissau.

2. Methods

2.1. Study setting

The study was conducted in the rural area of Caio in north-western Guinea-Bissau. Caio consists of a string of settlements in cashew forest, divided into 10 zones. Villagers mostly work as subsistence farmers. A large number of male villagers leave to work in Guinea-Bissau's main commercial centers, or abroad in Senegal, Portugal, and France. This results in a high ratio of women to men in the remaining population. A health center is located in the central zone of Caio.

2.2. Participants

An HIV survey was first conducted among adults (aged ≥15 years) in the community in 1989–1991.[21] All HIV-positive individuals (HIV-1 or HIV-2) identified plus an equal number of HIV-negative individuals, frequency-matched on age, gender, and village zone, were invited to enroll in a cohort. Participants were invited for a physical examination and blood test in 1991, 1996, 2003, and 2006. Another population serological survey was conducted in 1997–1998, and newly identified HIV-positive individuals and a similar number of HIV-negative individuals were added to the cohort.[22]

2.3. 2003 clinical study

All cohort members were invited to participate in the 2003 study round. After obtaining informed consent, a physical examination was done and medical history and a blood sample were taken. The field workers and physicians were unaware of participant HIV status. Treatments were prescribed as indicated.

2.4. Follow-up of vital status

Vital status was determined annually in a community-wide census. People who were temporarily absent were visited up to three times by field workers. If they remained in close contact with their families, and were expected back, they were considered to be alive and resident in Caio. For people who had permanently left and whose whereabouts were unknown by their family, date of leaving the village (last known to be alive) was recorded and the subject was considered lost to follow-up. Deaths were considered to be accurately recorded, even if they occurred abroad, since the community strictly practises death rituals and family links are very strong. When an individual dies outside Caio, their body or a symbolic mat is sent back to the village. Field workers were unaware of participant HIV status. Census information up to July 2010 was used to determine vital status.

2.5. Laboratory procedures

Laboratory procedures for HIV testing, PVL, and CD4 are described in Leligdowicz et al.[23] In brief, screening for HIV antibodies was done using ICE HIV 1.2.O (Murex Diagnostics), and if positive, samples were tested with two monospecific ELISAs (Wellcozyme HIV Recombinant I and ICE HIV-2, Abbott Murex). Indeterminate serology was resolved using nested-PCR.

2.6. Ethics and ART

Ethical approval was granted by the London School of Hygiene and Tropical Medicine Ethics Committee, the Gambia Government/ MRC Laboratories Joint Ethics Committee, and the Research Committee of the Ministry of Health of Guinea-Bissau.

ART became available in Caio in 2007. From this time, participants were offered ART if they had undergone pre- and post-test counseling, had obtained their HIV test results, were HIV-infected, and were eligible. Co-trimoxazole prophylaxis was offered to HIV-infected patients aware of their status who had symptoms or CD4 <28%. All participants received free care from a physician who was permanently based at the project.

2.7. Statistical methods

All results were double-entered and verified in Access 2000 (Microsoft, Redwood, WA, USA). Statistical analyses were done using Stata version 11.1 (StataCorp, College Station, TX, USA).

BMI was calculated by weight (kg) divided by squared height (m), and grouped into a binary variable based on the suggested WHO cut-off of 18.5 kg/m² for malnourished adults.[24] Mid-upper arm circumference (MUAC) was categorized using a cut-off of 230 mm for women and 240 mm for men.[24]

Based on information from the 2003 clinical examination, history, and laboratory data, individuals were assigned a WHO clinical stage (2006 revision[25]). The staging system and algorithm are hierarchical: individuals are assigned to the highest stage (most advanced disease) indicated by their symptoms. Most conditions were diagnosed clinically as diagnostic facilities were limited (Appendix A). Physicians also classified individuals according to the WHO performance scale, a subjective assessment of health status, ranging from 1 (asymptomatic) to 4 (symptomatic and bedridden over 50% of the day).

Differences between groups for categorical variables were analyzed using the Chi-square test, or Fisher's exact test; t-tests were used to compare normally distributed continuous variables and Wilcoxon rank sum tests for not normally distributed variables. Person-time was calculated from date of examination in 2003 to death, or date permanently moved out of the area (no further information available for the subject), or date ART started, whichever came first. Individuals were classified according to their baseline HIV serostatus.

Kaplan–Meier plots were used to explore survival differences and log-rank tests to compare survival probabilities. Cox regression was used to obtain hazard ratios (HR) for the effect of HIV status and other explanatory variables on mortality. To examine the predictive effect of each clinical measure in its own right on mortality, crude mortality HRs were calculated, then adjusted a priori for age and sex. The predictive effects independent of CD4% and PVL were also explored by further adjusting for these markers.

3. Results

3.1. Participants

Five hundred and forty-seven eligible individuals identified in January 2003 from the demographic database were visited in their homes. Twenty-six (5%) individuals had died, 97 (18%) were not present, two (0.4%) had permanently moved away, and 15 (3%) refused to participate. Four hundred and seven were recruited into the study, of whom five (1%) declined to be tested; hence 402 individuals were included (Figure 1). Of the 402 participants, 146 (36%) were HIV-2-infected and 197 (49%) were HIV-negative. There were 29 HIV-1-infected and 30 HIV-1/2 dually-infected
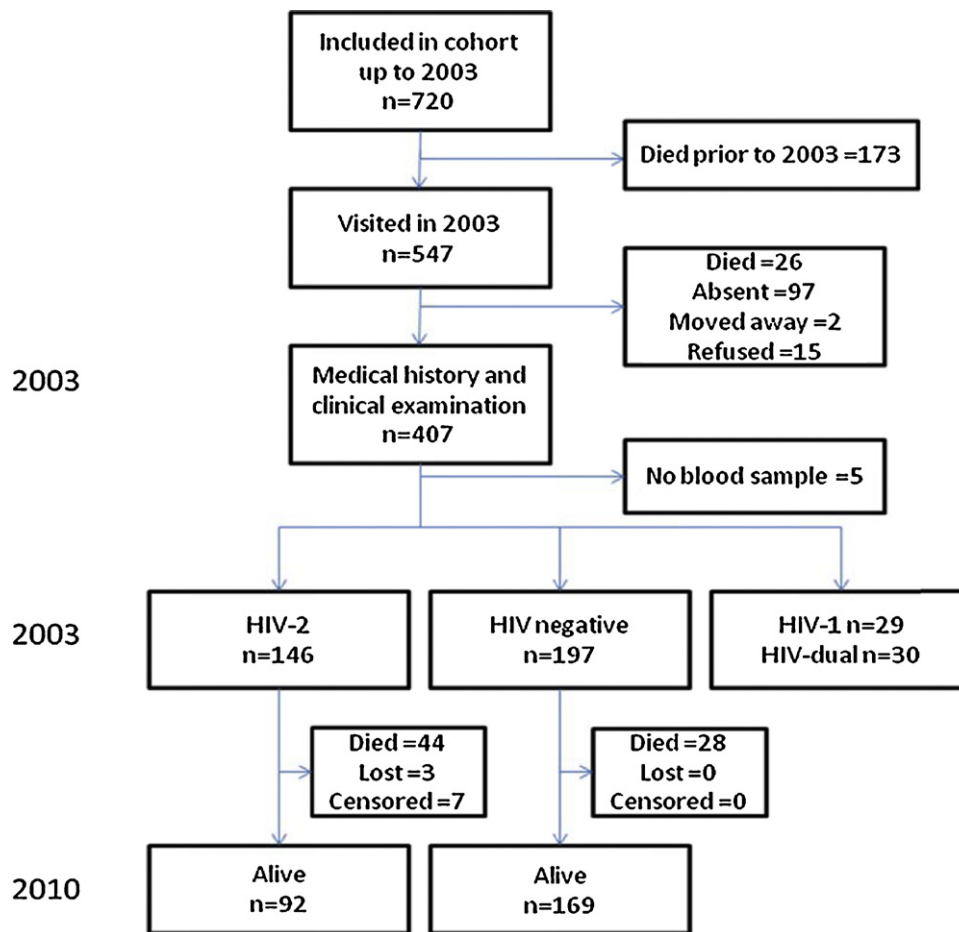
Figure 1. Flow-chart of a community cohort of HIV-infected and HIV-negative individuals in Guinea-Bissau, examined in 2003 and followed-up until 2010.

individuals; these were excluded from the current analysis because of small numbers.

3.2. Characteristics at baseline

The characteristics of study participants in 2003 are presented in Table 1. Seventy one percent of participants were female. The sex distribution of HIV-2-infected subjects was similar to that of HIV-negative subjects, but they were older ($p = 0.01$).

Median BMI and mean MUAC observed in HIV-2-infected and HIV-negative individuals were well above the cut-offs and were similar in the two groups (BMI $p = 0.6$, MUAC $p = 0.4$). Seventeen percent of HIV-2-infected individuals had BMI <18.5 kg/m^2, compared to 11% of HIV-negative subjects ($p = 0.1$). An even smaller proportion of individuals had MUAC below the cut-off: 8% in HIV-2-infected subjects compared to 5% in HIV-negative individuals ($p = 0.2$).

The majority of HIV-2-infected individuals were in WHO clinical stage 1; the proportions in stage 2 and stage 3/4 were higher than those in HIV-negative individuals ($p = 0.05$). WHO clinical stage was associated with CD4% ($p = 0.004$). HIV-2-infected and HIV-negative individuals had similar distributions according to the WHO performance scale ($p = 0.4$).

HIV-2-infected individuals had a median PVL of 1124 copies/ml (interquartile range (IQR) 50–6792) and a median CD4 of 31% (IQR 26–38%). Only 4% were in the lowest CD4% category (Table 1), and 29% had undetectable PVL (<100 copies/ml). There was little correlation between BMI and CD4, or MUAC and CD4% among HIV-2-infected individuals ($r = 0.1$ for both).

Of the 37 stage-defining conditions[25] (grouping mucocutaneous manifestations), only nine were observed (Table 2). Some of the conditions could not be diagnosed given limitations in diagnostic facilities, and some conditions were excluded from the algorithm (persistent fever because of the very high background prevalence in HIV-negative subjects, and wasting syndrome because its definition incorporates persistent fever). The most commonly observed conditions among HIV-2-infected individuals were peripheral generalized lymphadenopathy (PGL), mucocutaneous manifestations, herpes zoster, pulmonary tuberculosis (PTB), and severe weight loss.

A higher proportion of HIV-2-infected subjects (42%) had PGL compared to HIV-negative subjects (18%, $p < 0.001$). Herpes zoster was also observed in a higher proportion of HIV-2-infected individuals (5%) than HIV-negative subjects (0.5%, $p = 0.009$). Six percent of HIV-2-infected individuals had current or recent PTB (diagnosed by medical history or clinically), compared to 3% of HIV-negative individuals ($p = 0.2$).

Mucocutaneous manifestations and severe weight loss were also common among HIV-negative subjects, and the proportions of individuals with these conditions were only slightly lower than in HIV-2-infected individuals.

The only stage 4-defining condition observed in HIV-2-infected individuals was esophageal candidiasis (one person).

3.3. Overall mortality

Participants were followed-up for a median of 6.2 years (range 0–7.4 years). Only 1% of participants were lost to follow-up. Seven

Table 1
Socio-demographic data, clinical measures, and laboratory markers of HIV-2-infected and HIV-negative participants in a community cohort in Guinea-Bissau in 2003

Characteristics	HIV-2, n (%)[a] (n = 146)	HIV-negative, n (%)[a] (n = 197)	p-Value
Gender			
Male	47 (32)	54 (27)	0.3
Female	99 (68)	143 (73)	
Age (years)			
15–29	4 (3)	23 (12)	0.01
30–44	35 (24)	50 (25)	
45–59	47 (32)	47 (24)	
60+	60 (41)	77 (39)	
Mean (SD)	55.9 (15)	52.8 (18)	0.1
Ethnic group			
Manjako	146 (100)	189 (96)	0.01
Other	0	8 (4)	
Zone			
Central	115 (79)	154 (78)	0.9
Peripheral	31 (21)	43 (22)	
Marital status			
Single	22 (15)	35 (18)	0.3
Married	104 (71)	145 (74)	
Divorced/widowed	20 (14)	17 (9)	
BMI (kg/m^2)[b]			
<18.5	24 (17)	21 (11)	0.1
≥18.5	121 (83)	176 (89)	
Median (IQR)	21.6 (19.7–24.4)	21.8 (19.6–24.3)	0.6
MUAC (mm)[c]			
<230 W or <240 M	12 (8)	10 (5)	0.2
≥230 W or ≥240 M	134 (92)	187 (95)	
Mean (SD)	278.7 (36.5)	282.3 (37.2)	0.4
WHO clinical stage[d]			
1	105 (72)	163 (83)	0.05
2	20 (14)	15 (8)	
3/4	21 (14)	19 (10)	
WHO performance[e,f]			
1	57 (40)	92 (47)	0.4
2	57 (40)	69 (35)	
3/4	30 (21)	34 (17)	
CD4%[g]			
<14	6 (4)	0	<0.001
14-28	41 (30)	5 (3)	
>28	92 (66)	183 (97)	
Median (IQR)	31 (26–38)	40 (36–46)	<0.001
PVL (copies/ml)			
<100	42 (29)		
100–9999	74 (51)		
10 000–99 999	23 (16)		
≥100 000	7 (5)		
Median (IQR)	1124 (50–6792)		

BMI, body mass index; MUAC, mid-upper arm circumference; WHO, World Health Organization; PVL, plasma viral load; SD, standard deviation; IQR, interquartile range.
[a] Unless otherwise indicated.
[b] One missing value.
[c] Cut-offs: 230 mm for women (W) and 240 mm for men (M).
[d] WHO clinical stage assigned using an algorithm based on WHO staging criteria for HIV infection (2006 revision[25]).
[e] Four missing values.
[f] WHO performance scale: 1 (asymptomatic, normal activity), 2 (symptomatic, normal activity), 3 (bedridden <50% of the day), 4 (symptomatic and bedridden >50% of the day).
[g] Sixteen missing values.

Table 2
Distribution of WHO stage-defining conditions in a community cohort in Guinea-Bissau in 2003[a]

Condition	HIV-2, n (%) (n = 146)	HIV-negative, n (%) (n = 197)	p-Value
Stage 1			
PGL	61 (42)	36 (18)	<0.001
Stage 2			
Herpes zoster	7 (5)	1 (0.5)	0.009
Mucocutaneous manifestations	16 (11)	14 (7)	0.2
Stage 3			
Severe weight loss	13 (9)	12 (6)	0.3
Oral candidiasis	2 (1)	0	0.1
Oral hairy leukoplakia	1 (0.7)	1 (0.5)	0.8
Anemia	1 (0.7)	0	0.2
Pulmonary tuberculosis	9 (6)	6 (3)	0.2
Stage 4			
Esophageal candidiasis	1 (0.7)	0	0.2

WHO, World Health Organization; PGL, peripheral generalized lymphadenopathy.
[a] Conditions defined according to WHO clinical staging criteria for HIV-infection.[25] The conditions are listed in Appendix A, with comments on how their diagnosis was handled in the current study. Some individuals had two or more conditions and appear in more than one stage in this table. Fifty-nine HIV-2-infected and 135 HIV-negative individuals had none of the stage-defining conditions listed.

uninfected group, adjusted for age and sex, was 1.9 (95% confidence interval (CI) 1.2–3.1).

3.4. Clinical measures/socio-demographic factors and mortality

Gender was strongly associated with mortality. After adjustment for age, CD4%, and PVL, females experienced 0.3 times the mortality rate of males (95% CI 0.2–0.7). The HR was elevated among the older age groups, with a strong overall effect of age on mortality (p = 0.001 adjusted for sex, CD4%, and PVL) (Table 4).

An increasing trend in mortality HRs was observed with decreasing CD4% in the crude analysis, and adjusted for age, sex, and PVL (p = 0.04). Crude mortality rates also increased with increasing category of PVL. There was evidence for an effect of PVL on mortality after adjustment for age and sex (p < 0.001), and on further adjustment for CD4% (p = 0.02).

HIV-2-infected individuals with BMI <18.5 kg/m^2 had a higher mortality rate than those with BMI ≥18.5 kg/m^2 in the crude analysis (HR 1.9, 95% CI 1.0–3.9, p = 0.08). Adjusted for age and sex, the mortality HR was 1.8 (95% CI 0.9–3.8, p = 0.1), while the effect was weaker on further adjustment for CD4% and PVL (HR 1.2, 95% CI 0.5–3.0, p = 0.6). When other cut-offs of BMI were explored, the strongest effect was observed among individuals with BMI <17 kg/m^2 (crude HR 3.6, 95% CI 1.4–9.5, p = 0.008; adjusted for age and sex, HR 3.6, 95% CI 1.4–9.6, p = 0.02). There was weak evidence for an association between MUAC and mortality in the univariate

Table 3
Follow-up, mortality rates, and mortality hazard ratios for HIV-2-infected and HIV-negative participants in a community cohort in Guinea-Bissau 2003–2010

	HIV-2 (n = 146)	HIV-negative (n = 197)
Number (%) lost to follow-up	3 (2)	–
Number (%) started ART	7 (5)	–
Number (%) of deaths	44 (30)	28 (14)
Total follow-up (years)	775	1114
Mortality rate (95% CI) per 100 PYO	5.7 (4.2–7.6)	2.5 (1.7–3.6)
Crude MHR (95% CI)	2.1 (1.3–3.5)	Ref.
Adjusted MHR[a] (95% CI)	1.9 (1.2–3.1)	Ref.

ART, antiretroviral treatment; PYO, person-years of observation; MHR, mortality hazard ratio; CI, confidence interval.
[a] Adjusted for age and sex.

patients started ART and were censored. The median CD4% of individuals who started ART (26%, IQR 22–32%) was lower than that for individuals who did not start ART (38%, IQR 31–44%) (p = 0.01). In total, 72 subjects (21%) died: 44 (30%) HIV-2-infected individuals and 28 (14%) HIV-negative individuals (Figure 1, Table 3).

HIV-2-infected persons experienced a mortality rate approximately double that of HIV-negative subjects (Table 3). The overall mortality HR for HIV-2-infected subjects compared to the

Table 4

Crude mortality rates and crude and adjusted associations of socio-demographic and clinical factors with mortality, among HIV-2-infected individuals in a community cohort in Guinea-Bissau, 2003–2010

Characteristic	Deaths	PYO	Mortality rate per 100 (95% CI)	Crude HR (95% CI)	p-Value[a]	HR adjusted for age and sex (95% CI)	p-Value[a]	HR adjusted for age, sex, CD4%, and PVL (95% CI)	p-Value[a]
Sex									
Male	22	231.3	9.5 (6.3–14.4)	1	0.002	1	<0.001	1	0.003
Female	22	543.8	4.1 (2.7–6.1)	0.4 (0.2–0.7)		0.3 (0.2–0.6)		0.3 (0.2–0.7)	
Age, years[c]									
<40	1	109.0	0.9 (0.1–6.5)	1	0.004	1	<0.001	1	0.001
40–59	12	309.5	3.9 (2.2–6.8)	3.9 (0.5–30.3)		3.2 (0.4–24.5)		2.2 (0.3–17.2)	
≥60	31	356.7	8.7 (6.1–12.4)	8.2 (1.1–60.1)		8.9 (1.2–65.2)		6.8 (0.9–50.7)	
Marital status									
Single	8	107.6	7.4 (3.7–14.9)	1	0.6	1	0.4	1	0.6
Married	28	560.3	5.0 (3.5–7.2)	0.6 (0.3–1.4)		0.5 (0.2–1.3)		0.6 (0.2–1.6)	
Divorced/widowed	8	107.2	7.5 (3.7–14.9)	0.7 (0.3–1.9)		0.5 (0.2–1.8)		0.7 (0.2–3.1)	
Zone									
Central	34	602.9	5.6 (4.0–7.9)	1	0.7	1	0.7	1	0.3
Peripheral	10	172.3	5.8 (3.1–10.8)	1.1 (0.6–2.3)		1.1 (0.6–2.4)		1.5 (0.7–3.2)	
BMI (kg/m²)									
≥18.5	32	649.7	4.9 (3.5–7.0)	1	0.08	1	0.1	1	0.6
<18.5	11	120.8	9.1 (5.0–16.4)	1.9 (1.0–3.9)		1.8 (0.9–3.8)		1.2 (0.5–3.0)	
MUAC (mm)[d]									
≥230 W or ≥240 M	38	721.7	5.3 (3.8–7.2)	1	0.1	1	0.3	1	0.5
<230 W or <240 M	6	53.5	11.2 (5.0–25.0)	2.2 (0.9–5.3)		1.60 (0.7–3.9)		1.5 (0.6–4.0)	
WHO clinical stage									
1	29	560.7	5.2 (3.6–7.4)	1	0.6	1	0.9	1	0.5
2	7	106.8	6.6 (3.1–13.8)	1.2 (0.5–2.7)		1.2 (0.5–2.8)		1.1 (0.5–2.9)	
3/4	8	107.6	7.4 (3.7–14.9)	1.5 (0.7–3.2)		1.2 (0.5–2.7)		0.6 (0.2–1.6)	
WHO performance									
1	11	311.4	3.5 (2.0–6.4)	1	0.2	1	0.6	1	0.5
2	22	284.6	7.7 (5.1–11.7)	1.9 (0.9–3.9)		1.4 (0.7–2.9)		1.6 (0.7–3.4)	
3/4	11	167.7	6.6 (3.6–11.8)	1.7 (0.7–3.9)		1.0 (0.4–2.4)		1.2 (0.5–3.3)	
CD4%									
>28	17	506.0	3.4 (2.1–5.4)	1	0.001	1	0.001	1	0.08
14–28	19	209.6	9.1 (5.8–14.2)	2.5 (1.3–5.0)		2.0 (1.0–3.9)		1.6 (0.7–3.4)	0.04[b]
<14	5	23.9	20.9 (8.7–50.2)	7.9 (2.9–21.8)		9.7 (3.4–27.4)		4.8 (1.3–17.5)	
PVL (copies/ml)									
<10 000	25	638.9	3.9 (2.6–5.8)	1	<0.001	1	<0.001	1	0.07
10 000–99 999	14	112.2	12.5 (7.4–21.1)	3.0 (1.6–5.9)		3.3 (1.7–6.5)		1.9 (0.8–4.5)	0.02[b]
≥100 000	5	24.1	20.8 (8.6–49.9)	7.5 (2.8–20.3)		4.8 (1.7–13.2)		3.8 (1.3–11.3)	

PYO, person-years observation; CI, confidence interval; HR, hazard ratio; PVL, plasma viral load; BMI, body mass index; MUAC, mid-upper arm circumference; WHO, World Health Organization.

[a] Likelihood ratio test (LRT).
[b] LRT for trend.
[c] Age analyzed as a time-varying variable.
[d] Cut-offs: 230 mm for women (W) and 240 mm for men (M).

analysis (HR 2.2, 95% CI 0.9–5.3, p = 0.1), and no evidence for an association in the adjusted analyses.

The crude mortality rate increased with each (higher) WHO stage, though the association was weak (p = 0.6). Crude mortality rates were also higher in categories 2 and 3/4 of the WHO performance scale compared to category 1, but with no evidence of a trend.

4. Discussion

4.1. Key findings

This is the first study to analyze clinical predictors of mortality in HIV-2-infected individuals in a community setting, with excellent follow-up. We did not identify any clinical measures that were strong predictors of mortality: there was only weak statistical evidence for an association between BMI or MUAC and mortality, and no statistical evidence to support an association between WHO stage or performance scale and mortality, once adjusted for age and sex. These findings suggest that, in a community-based setting, these clinical measures are less reliable than CD4 count or viral load for guiding treatment decisions in HIV-2-infected patients.

Our findings also demonstrate that a high proportion of HIV-2-infected individuals in this cohort, many of whom were infected at least since 1989 or 1997, did not show clinical signs of disease progression: a majority were in WHO clinical stage 1 and had normal BMI or MUAC. These clinical findings support the observations of long-term low PVL observed among individuals in this cohort.[12] We observed a mortality rate in HIV-2-infected individuals approximately two times that of HIV-negative individuals, which is consistent with earlier reports from this cohort[5,12] and other study sites.[3,26]

CD4% and PVL were strong predictors of mortality among HIV-2-infected subjects in this analysis, consistent with the results of previous studies,[2,5,11,12] and showing that the failure to find an association with clinical predictors was not simply due to lack of power.

4.2. Clinical predictors

BMI was not strongly associated with mortality, in contrast to a clinic-based study in The Gambia, which reported that BMI was a strong predictor of mortality in patients with HIV-2 infection.[14] The Gambian study was conducted among patients with more advanced disease who attended a clinic, whereas individuals in

this community setting were often asymptomatic. This suggests that while BMI may be a useful alternative to CD4 count or PVL for HIV-2 patient management in a clinic-based setting, it may be less important in a community-based setting. Lack of power may also explain the failure to detect an effect, especially given the small number of individuals and events below the cut-offs defined. The cut-off chosen reflects published guidelines for the identification of malnutrition. We also explored a range of alternative cut-offs between 17 kg/m^2 and 21 kg/m^2, and found a stronger effect among patients with BMI <17 kg/m^2; however less than 5% of HIV-2-infected subjects were in this category.

MUAC may serve as another inexpensive and easily measured proxy for nutritional status,[24] but we found only weak evidence for an association with mortality among HIV-2-infected individuals in this cohort. MUAC <200 mm was associated with an increased risk of death in an urban cohort of HIV-positive (HIV-1, HIV-2, and dual) and HIV-negative TB patients in Guinea-Bissau,[27] however the majority of participants were HIV-negative, and results among advanced HIV-positive patients with TB are probably not generalizable.

WHO clinical stage was not associated with mortality in HIV-2-infected individuals in this study. This result may suggest that clinical stage is not as useful in evaluating the prognosis of HIV-2-infected as HIV-1-infected patients. However, a significant association between WHO stage and mortality among HIV-2-infected individuals was found in another study from a Gambian clinic.[2] Limitations to the staging algorithm used in the current analysis may explain the difference between the studies. The algorithm was based on only a subset of the stage-defining criteria. Identification of most stage 4-defining conditions requires diagnostic procedures that were not available in this setting, although this is the reality in many rural clinics. Only one stage 4-defining condition was identified, though more may have been present that could not be diagnosed. As a result, there may be more individuals in stage 4 who were categorized in earlier stages, diluting the predictive effect. Small numbers of individuals identified in stage 3/4 may have reduced the power. Kaposi's sarcoma was not identified in HIV-2-infected subjects in this cohort, a result that concurs with other studies that have reported that this condition is relatively rare in HIV-2- compared to HIV-1-infected individuals.[28,29]

We found no evidence for an association between WHO performance scale and HIV-2 infection in this study, nor did we find an association between the performance scale and mortality among HIV-2-infected subjects. WHO performance scale has not previously been investigated in its own right as a potential predictor of mortality in HIV-infection, though a similar performance scale, the Karnofsky score, was an indicator of mortality in HIV-1- and HIV-2-infected patients in Gambian clinics.[2,20]

4.3. Limitations

When this cohort was formed, HIV-infected and HIV-negative individuals were matched on age, but HIV-2-infected individuals were older than HIV-negative subjects in our analysis. This is because HIV-1-infected and HIV dual-infected individuals were excluded from this analysis, and they are younger than HIV-2-infected individuals.

Non-differential misclassification of BMI, MUAC, and WHO performance scale or stage may have diluted the effects observed for each of these exposures. Assessment may have differed between the three study physicians, though this was unlikely to have been systematically biased given the assessments were made without knowledge of the outcome. Such limitations would, however, be the reality in clinical or public health practice.

HIV status at baseline was used in the analysis. Seroconversions to HIV-1/2 dual infection among HIV-2-infected individuals during the follow-up period could have biased the associations for each clinical measure with mortality. Information on seroconversions was only available from one serological survey in 2006, when only 60% of the cohort was re-bled: only three HIV-2-infected individuals had seroconverted to HIV-1/2 dual infection. Other seroconversions could have occurred after 2006, though it is unlikely that these would have affected our conclusions. That the exact dates of seroconversion are unknown for individuals in this cohort is a limitation, as age at seroconversion strongly influences survival in HIV-1 infection.[30]

Censoring subjects on ART may have underestimated the mortality rate in the HIV-2-infected group if these individuals were closer to death than subjects who were not censored. Individuals who started ART had lower CD4% than those who did not, however as only seven individuals had started ART this is unlikely to have introduced a considerable bias and affected our conclusions. It is unlikely that any participants were taking and adhering to ART obtained from outside the study site, as the only other health centers administering ART are located at considerable distances from Caio – in Bissau, the capital, or Senegal – and ART was only introduced in Bissau in 2006.

We did not analyze cause of death, and whether HIV-infected individuals died from HIV-related conditions is unknown. This may be particularly useful to determine in this cohort, where background mortality is high and many participants were relatively old. Cause of death was investigated previously in this cohort using a verbal autopsy:[31] AIDS-related deaths were observed among HIV-1, HIV-2, and HIV-1/2 dually infected individuals and were least frequent among HIV-2-infected people.

Clinical measures were only analyzed at baseline in 2003, as clinical data at subsequent time-points were limited. However, repeated measurements and changes in clinical status over time may still be useful in predicting mortality.

5. Conclusions

In this community-based setting, none of four examined clinical measures at baseline (BMI, MUAC, WHO stage, and WHO performance scale) were useful alternatives to CD4 or PVL in predicting mortality among HIV-2-infected individuals. Where possible, laboratory markers should be used to guide the management of HIV-2-infected individuals in the community-based setting.

Acknowledgements

Conflict of interest: The authors declare no conflicts of interest.

Appendix A

List of conditions used in the WHO clinical staging criteria for HIV infection,[25] with comments of how their diagnosis was handled in the current study.

A.1. Stage 1 conditions

Peripheral generalized lymphadenopathy (PGL): lymph nodes present at two or more sites excluding inguinal; clinical diagnosis.

A.2. Stage 2 conditions

- Herpes zoster: current or in last 5 years.
- Mucocutaneous manifestations: fungal nail infection, dermatitis, or papular rash; clinical diagnosis.
- Moderate weight loss 5–10% body weight: could not be defined.
- Recurrent upper respiratory tract infections, angular cheilitis, recurrent oral ulceration: not observed among HIV-2-infected individuals in this study.

A.3. Stage 3 conditions

- Severe weight loss: $\geq$10% weight loss (physician assessment) and BMI <18.5 kg/m^2.
- Oral candidiasis: clinical diagnosis.
- Oral hairy leukoplakia: clinical diagnosis.
- Anemia: hemoglobin <8 g/dl.
- Pulmonary tuberculosis: current or recent; clinical diagnosis or medical history.
- Chronic diarrhea >1 month: duration could not be defined.
- Unexplained persistent fever: patient recall of fever or night sweats >1 month, excluding cases where malarial parasites were detected. Excluded from the clinical staging algorithm due to the high background prevalence observed in HIV-negative subjects (31%) (38% in HIV-2-infected subjects).
- Severe bacterial infection, acute necrotizing ulcerative gingivitis/periodontitis: not observed among HIV-2-infected individuals in this study.

A.4. Stage 4 conditions

- Esophageal candidiasis: oral candidiasis plus pain on swallowing.
- HIV wasting syndrome: excluded from the clinical staging algorithm as persistent fever is used in the definition of wasting.
- Kaposi's sarcoma, Pneumocystis pneumonia, recurrent bacterial pneumonia, extrapulmonary tuberculosis, cytomegalovirus disease, central nervous system toxoplasmosis, HIV encephalopathy, extrapulmonary cryptococcosis: not observed among HIV-2-infected individuals in this study.
- Chronic herpes simplex >1 month: duration could not be defined.
- Disseminated non-tuberculous mycobacteria infection, progressive multifocal leukoencephalopathy, chronic cryptosporidiosis, chronic isosporiasis, disseminated mycosis, recurrent non-typhoid Salmonella bacteremia, lymphoma, invasive cervical carcinoma, atypical disseminated leishmaniasis, HIV-associated nephropathy/cardiomyopathy: no facilities to diagnose these conditions.

References

1. Schim van der Loeff MF, Aaby P. Towards a better understanding of the epidemiology of HIV-2. *AIDS* 1999;**13**(Suppl A):S69–84.
2. Schim van der Loeff MF, Jaffar S, Aveika AA, Sabally S, Corrah T, Harding E, et al. Mortality of HIV-1, HIV-2 and HIV-1/HIV-2 dually infected patients in a clinic-based cohort in The Gambia. *AIDS* 2002;**16**:1775–83.
3. Poulsen AG, Aaby P, Larsen O, Jensen H, Naucler A, Lisse IM, et al. 9-year HIV-2-associated mortality in an urban community in Bissau, West Africa. *Lancet* 1997;**349**:911–4.
4. Whittle H, Morris J, Todd J, Corrah T, Sabally S, Bangali J, et al. HIV-2-infected patients survive longer than HIV-1-infected patients. *AIDS* 1994;**8**:1617–20.
5. Berry N, Jaffar S, Schim van der Loeff M, Ariyoshi K, Harding E, N'Gom PT, et al. Low level viremia and high CD4% predict normal survival in a cohort of HIV type-2-infected villagers. *AIDS Res Hum Retroviruses* 2002;**18**:1167–73.
6. Morgan D, Mahe C, Mayanja B, Okongo JM, Lubega R, Whitworth JA. HIV-1 infection in rural Africa: is there a difference in median time to AIDS and survival compared with that in industrialized countries? *AIDS* 2002;**16**:597–603.
7. Sewankambo NK, Gray RH, Ahmad S, Serwadda D, Wabwire-Mangen F, Nalugoda F, et al. Mortality associated with HIV infection in rural Rakai District, Uganda. *AIDS* 2000;**14**:2391–400.
8. Marlink R, Kanki P, Thior I, Travers K, Eisen G, Siby T, et al. Reduced rate of disease development after HIV-2 infection as compared to HIV-1. *Science* 1994;**265**:1587–90.
9. Schim van der Loeff M., Poulin N., Sarge-Njie R., Whittle H., Geskus RA, et al. A comparison of the progression of HIV-1 and HIV-2 infection. Results of a Markov model based on CD4 counts, in AIDS. Abstract CDC0240. XVIIIth International AIDS Conference, Vienna, Austria, 2010.
10. Jaffar S, Wilkins A, Ngom PT, Sabally S, Corrah T, Bangali JE, et al. Rate of decline of percentage CD4+ cells is faster in HIV-1 than in HIV-2 infection. *J Acquir Immune Defic Syndr Hum Retrovirol* 1997;**16**:327–32.
11. Hansmann A, Schim van der Loeff MF, Kaye S, Awasana AA, Sarge-Njie R, O'Donovan D, et al. Baseline plasma viral load and CD4 cell percentage predict survival in HIV-1- and HIV-2-infected women in a community-based cohort in The Gambia. *J Acquir Immune Defic Syndr* 2005;**38**:335–41.
12. Schim van der Loeff MF, Larke N, Kaye S, Berry N, Ariyoshi K, Alabi A, et al. Undetectable plasma viral load predicts normal survival in HIV-2-infected people in a West African village. *Retrovirology* 2010;**7**:46.
13. Alabi AS, Jaffar S, Ariyoshi K, Blanchard T, Schim van der Loeff M, Awasana AA, et al. Plasma viral load, CD4 cell percentage, HLA and survival of HIV-1, HIV-2, and dually infected Gambian patients. *AIDS* 2003;**17**:1513–20.
14. van der Sande MA, Schim van der Loeff MF, Aveika AA, Sabally S, Togun T, Sarge-Njie R, et al. Body mass index at time of HIV diagnosis: a strong and independent predictor of survival. *J Acquir Immune Defic Syndr* 2004;**37**:1288–94.
15. Lindan CP, Allen S, Serufilira A, Lifson AR, van de Perre P, Chen-Rundle A, et al. Predictors of mortality among HIV-infected women in Kigali, Rwanda. *Ann Intern Med* 1992;**116**:320–8.
16. Mekonnen Y, Dukers NH, Sanders E, Dorigo W, Wolday D, Schaap A, et al. Simple markers for initiating antiretroviral therapy among HIV-infected Ethiopians. *AIDS* 2003;**17**:815–9.
17. Castetbon K, Anglaret X, Toure S, Chene G, Ouassa T, Attia A, et al. Prognostic value of cross-sectional anthropometric indices on short-term risk of mortality in human immunodeficiency virus-infected adults in Abidjan, Cote d'Ivoire. *Am J Epidemiol* 2001;**154**:75–84.
18. Morgan D, Maude GH, Malamba SS, Okongo MJ, Wagner HU, Mulder DW, Whitworth JA. HIV-1 disease progression and AIDS-defining disorders in rural Uganda. *Lancet* 1997;**350**:245–50.
19. Malamba SS, Morgan D, Clayton T, Mayanja B, Okongo M, Whitworth J. The prognostic value of the World Health Organisation staging system for HIV infection and disease in rural Uganda. *AIDS* 1999;**13**:2555–62.
20. Whittle H, Egboga A, Todd J, Corrah T, Wilkins A, Demba E, et al. Clinical and laboratory predictors of survival in Gambian patients with symptomatic HIV-1 or HIV-2 infection. *AIDS* 1992;**6**:685–9.
21. Wilkins A, Ricard D, Todd J, Whittle H, Dias F, Paulo Da Silva A. The epidemiology of HIV infection in a rural area of Guinea-Bissau. *AIDS* 1993;**7**:1119–22.
22. Tienen C, Schim van der Loeff MS, Zaman SM, Vincent T, Sarge-Njie R, Peterson I, et al. Two distinct epidemics: the rise of HIV-1 and decline of HIV-2 infection between 1990 and 2007 in rural Guinea-Bissau. *J Acquir Immune Defic Syndr* 2010;**53**:640–7.
23. Leligdowicz A, Yindom LM, Onyango C, Sarge-Njie R, Alabi A, Cotten M, et al. Robust Gag-specific T cell responses characterize viremia control in HIV-2 infection. *J Clin Invest* 2007;**117**:3067–74.
24. World Health Organization. Physical status: the use and interpretation of anthropometry. *World Health Organ Tech Rep Ser* 1995;**854**:345–69.
25. World Health Organization. WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children. Geneva: WHO; 2007.
26. Holmgren B, da Silva Z, Vastrup P, Larsen O, Andersson S, Ravn H, et al. Mortality associated with HIV-1, HIV-2, and HTLV-I single and dual infections in a middle-aged and older population in Guinea-Bissau. *Retrovirology* 2007;**4**:85.
27. Gustafson P, Gomes VF, Vieira CS, Samb B, Naucler A, Aaby P, et al. Clinical predictors for death in HIV-positive and HIV-negative tuberculosis patients in Guinea-Bissau. *Infection* 2007;**35**:69–80.
28. Ariyoshi K, Schim van der Loeff M, Cook P, Whitby D, Corrah T, Jaffar S, et al. Kaposi's sarcoma in the Gambia, West Africa is less frequent in human immunodeficiency virus type 2 than in human immunodeficiency virus type 1 infection despite a high prevalence of human herpesvirus 8. *J Hum Virol* 1998;**1**:193–9.
29. Martinez-Steele E, Awasana AA, Corrah T, Sabally S, van der Sande M, Jaye A, et al. Is HIV-2-induced AIDS different from HIV-1-associated AIDS? Data from a West African clinic. *AIDS* 2007;**21**:317–24.
30. Todd J, Glynn JR, Marston M, Lutalo T, Biraro S, Mwita W, et al. Time from HIV seroconversion to death: a collaborative analysis of eight studies in six low and middle-income countries before highly active antiretroviral therapy. *AIDS* 2007;**21**(Suppl 6):S55–63.
31. Cooper M, Schim van der Loeff MS, Mcconkey S, Cooper S, Vincent T, Whittle H. Cause of death among people with retroviral infection in rural Guinea-Bissau. *Trop Doct* 2010;**40**:181–3.