Mortality and immunovirological outcomes on antiretroviral therapy in HIV-1 and HIV-2-infected individuals in the Gambia

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Objectives: This study's objective was to assess outcomes in HIV-1 and HIV-2 infected antiretroviral therapy (ART)-naïve patients starting ART in the Gambia, West Africa.

Design: A cohort design was used to estimate survival in ART patients and determine whether survival and time to virologic failure varied across patient subgroups.

Methods: Mortality, virologic failures and $CD4^+$ cell recovery were assessed in a clinical cohort of patients from the Genito-Urinary Medicine (GUM) clinic of the MRC Laboratories in the Gambia. Kaplan–Meier estimates of survival were determined for mortality and virologic failure. A Cox proportional hazards model was used to identify baseline demographic, clinical, immunologic and virologic factors associated with increased risk of death.

Results: The overall Kaplan–Meier estimate of survival to 36 months was 73.4% (66.5, 80.3). Survival was marginally higher in HIV-2-infected patients compared to HIV-1-infected patients; it was significantly higher in patients with a baseline $CD4^+$ lymphocyte cell count of greater than 50 cells/μl compared to those with a baseline $CD4^+$ count of less than 50 cells/μl. $CD4^+$ cell recovery was faster in HIV-1-infected individuals compared to HIV-2-infected patients up to 24 months, although this did not result higher mortality in the latter group. No differences in virologic failure were observed by HIV type.

Conclusion: HIV-1 and HIV-2-infected patients receiving ART in a clinical setting in the Gambia had good survival to 36 months. HIV-2-infected patients did as well as HIV-1-infected patients in terms of long-term immunological and virological responses and overall survival.

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Introduction

As of 2007, an estimated 33 million people were living with HIV/AIDS globally, among whom two-thirds resided in sub-Saharan Africa [1]. Overall, coverage with antiretroviral therapy (ART) on the continent is thought to be 30% [1,2] whereas in the Gambia, West Africa, coverage is estimated at just 19% [3]. In Africa, a large

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proportion of HIV-infected patients present for ART at an advanced stage, mortality is high during the first 6 months of treatment and loss to follow-up (LTFU) on treatment is typically elevated [4–9]. Most data on ART programmes in Africa are from HIV-1 mono-infected populations in East and Southern Africa, with relatively little from West Africa and a dearth of reporting on HIV-2 infection. HIV-2 is endemic in West Africa including the Gambia, where the prevalence of HIV-1 and HIV-2 was estimated to be 2.8 and 0.9%, respectively, in 2006 [10]. The presence of HIV-2 infection complicates both diagnostic algorithms and treatment programmes due to intrinsic resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs), creating an additional burden to ART programmes in West Africa. Many previous studies reporting ART outcomes of HIV-2-infected individuals have used multiple or suboptimal regimes, thus limiting their power to assess the ability of optimal ART regimens to control HIV-2 infection, or to provide a valid comparison with HIV-1 treatment [11–17]. Data on virological outcomes on ART are also scarce because of limited availability of viral load testing in resource-limited settings, particularly for HIV-2 infection for which there is no commercially available viral load assay.

The current study is one of the first to compare mortality, LTFU, immunological and virological outcomes among ART-naive HIV-1 and HIV-2-infected patients initiating standardized treatment regimens in West Africa.

Methods

Antiretroviral therapy clinical protocol

The study was carried out at the Genito-Urinary Medicine (GUM) clinic of the MRC Laboratories in Fajara, the Gambia, which has offered confidential HIV testing and clinical care since 1987 and has been a national ART referral centre since October 2004. The clinic is near the capital city of Banjul, but draws patients from throughout the country. HIV-infected patients aged at least 15 years were invited to join a sero-prevalent prospective cohort, which as of August 2009 had approximately 2000 HIV-positive adults in active follow-up, among whom around 400 were on ART. All clinical services are offered free of charge to patients.

Eligibility for ART at the GUM clinic conforms to the World Health Organization's (WHO's) 2006 guidelines [8], which are WHO clinical stage 4 disease or $CD4^+$ lymphocyte count below 200 cells/μl or $CD4^+$ lymphocyte count below 350 cells/μl with WHO stage 2 or 3 disease. Patients eligible for ART attend four pretreatment counselling sessions with a trained counsellor. Patients' clinical and social histories are reviewed by a national Eligibility Committee, which approves initiation of ART. Patients receive a standardized ART drug regimen following national first-line ART treatment guidelines: zidovudine, lamivudine, nevirapine for HIV-1 and zidovudine, lamivudine, lopinavir/ritonavir for HIV-2 infection. At each clinic visit, patients' clinical condition, WHO clinical stage, weight and self-reported adherence are assessed by a physician. Patients deemed to be nonadherent are offered additional counselling. $CD4^+$ lymphocyte counts and HIV viral load are measured at baseline, 12 weeks, 24 weeks and thereafter every 6 months or as clinically indicated. Patients who miss a clinic visit or do not collect their ART drugs are visited at home by a field worker and invited to return to the clinic.

Study participants

Analyses were conducted on HIV-1 and HIV-2 mono-infected ART-naive patients who initiated ART between 1 October 2004 and 1 April 2009. We included follow-up data through 15 April 2009; thus study patients contributed a maximum of 55 months to the cohort. Inclusion criteria for the study were: at least 15 years old, ART-naive at initiation, mono-infected with HIV-1 or HIV-2, and have a $CD4^+$ lymphocyte count, viral load, WHO clinical stage, and weight within 1 year of starting ART. Ninety-one percent of measurements were taken within 3 months before starting ART.

Statistical analysis

In analyses of $CD4^+$ lymphocyte recovery and percentage of patients with detectable HIV RNA (>400 copies/ml), data were grouped into seven discrete intervals that centred around 3, 6, 12, 18, 24, 30 and 36 months. Measurements closest to the centre of the interval were selected; each patient contributed either one or no measurement to each interval. Population-averaged linear regression models were used to investigate changes in $CD4^+$ lymphocyte counts from baseline and percentage of patients with detectable viral load by HIV type and baseline covariates. Two types of virologic failure were examined: incomplete viral response and viral rebound. Incomplete viral response was defined as less than 1 $\log_{10}$ decline in HIV RNA after 12 weeks or detectable viral load after 6 months on ART. Analysis was restricted to patients with a baseline viral load of 4000 copies/ml or greater (94.7% of patients) and available data at 12 weeks or 6 months (69.6% of patients). Viral rebound was defined as two consecutive measurements above 1000 copies/ml taken at least 42 days apart, in patients with complete viral suppression by 365 days after starting ART (67.8% of patients). Patients with complete viral suppression who discontinued ART but were known to be alive were included in the viral rebound category (four patients). Kaplan–Meier estimates were used to assess survival in strata defined by viral response by 6 months and viral rebound. These estimates were then examined by strata defined by

baseline factors (age, sex, HIV type, viral load, CD4 lymphocyte count, weight and WHO clinical stage) to determine whether risk of viral rebound differed by these factors.

Kaplan–Meier estimates of survival were determined for mortality. Data for all patients were included regardless of adherence, change in ART regimen or subsequent discontinuation of ART. For the mortality analysis, patients who were alive and in care on 15 April 2009, had transferred to another ART facility, had discontinued ART but were known to be alive on 15 April 2009 were right-censored on the date of their last clinic visit. Patients who had died were followed through their date of death; six patients whose date of death was unknown were followed through their last recorded clinic visit. Patients who had not attended the clinic for at least 3 months after their last scheduled appointment were considered LTFU and statistically treated as deaths on their last recorded clinic visit. For the analysis of death or virologic failure, patients were followed through the first occurrence of virologic failure, death or LTFU. Patients known to be alive on 15 April 2009 but in treatment default were classified as virologic failures on their last recorded clinic visit. All survival analyses were stratified by baseline $CD4^+$ lymphocyte count category ($<50 \times 10^6$ cells/μl versus $\geq 50 \times 10^6$ cells/μl) and by HIV type to assess differences in survival by strata. Univariate and multivariable analyses were performed using Cox proportional hazards models to identify factors associated with mortality. The analyses were stratified into mortality up to and after 6 months to satisfy the proportional hazards assumption.

Laboratory protocol

Screening for HIV-1 and HIV-2 infection was done using a protocol described in detail elsewhere [18]. Briefly, samples were screened with the ICEHIV-1.O.2 capture enzyme immunoassay (Murex Diagnostics Ltd., UK). Reactive samples were further tested with type-specific enzyme-linked immunosorbent assays (ELISA) (Wellcozyme HIV recombinant-1 and ICE*-HIV-2 test, both Murex); samples strongly reactive in only one type-specific ELISA were assigned a serological diagnosis. Dually reactive samples were further tested using Pepti-Lav 1–2 (Sanofi Diagnostics, Pasteur, France), and assigned a diagnosis if clear bands were present indicating either HIV-1 or HIV-2 mono-infection. Samples with clear HIV-1 and HIV-2 bands in the Pepti-Lav assay were assigned dual HIV-1/HIV-2 status following confirmation with specific polymerase chain reactions (PCRs) [19,20]. A second confirmatory serum sample taken 2–8 weeks later was retested using the same algorithm. Patients with inconclusive tests or discordant results at the two time-points were classified as indeterminate and not used in the current analysis. HIV-1 and HIV-2 RNA quantification was done using an in-house chemiluminescence-based enzyme-linked oligonucleotide quantitative PCR (qPCR) assay, targeting the HIV-1 and HIV-2 long terminal repeat regions, with 100–1 000 000 copies/ml as the limit of detection, as detailed elsewhere [19,21].

Ethics

The study was approved by the Joint Gambian Government/MRC Ethics Committee.

Results

In total, 412 mono-infected HIV-1 and HIV-2 patients were identified as receiving ART between 12 October 2004 and 1 April 2009. Of these, 53 were excluded due to missing baseline data or prior exposure to ART. The final data set included 359 patients. There were no differences in sex, HIV type, baseline age or baseline $CD4^+$ lymphocyte count among patients excluded due to missing data and those in the final data set (data not shown). Baseline characteristics of HIV-1 and HIV-2-infected patients are shown in Table 1. Significant differences between HIV-1 and HIV-2-infected patients were observed for baseline age, median $CD4^+$ lymphocyte count, proportion with HIV RNA greater than 100 000 copies/ml, and proportion with WHO clinical stage 3 or 4.

Mortality

A total of 62 (17.3%) patients died on ART, 12 (3.3%) were LTFU, 7 (1.9%) defaulted from treatment but were known to be alive at the end of follow-up, and 27 (7.5%) voluntarily transferred to another ART facility (Table 2). Median months of follow-up after starting ART was significantly shorter in HIV-1-infected patients compared to HIV-2-infected patients (12.1 versus 20.3; P-value = 0.02) and crude mortality on ART was significantly higher in HIV-1-infected patients compared to HIV-2-infected patients [120.9 per 1000 person-years of observation (PYO) versus 64.2 per 1000 PYO; P value = 0.05].

Overall, the 12, 24 and 36-month Kaplan–Meier survival estimates [95% confidence interval (CI)] were 81.8% (76.8, 86.8), 74.7% (68.1, 81.3) and 73.4% (66.5, 80.3) (Fig. 1). Survival was greater for HIV-2-infected patients than HIV-1-infected patients; however, this difference was not statistically significant (Log rank P value = 0.0962) (Fig. 1). Three HIV-2-infected patients whose initial regimen included NNRTIs switched to appropriate, non-NNRTI containing regimens within 3 months of ART initiation. Twelve, 24 and 36-month HIV-2 survival estimates excluding these three patients differed less than 0.5% from estimates including all HIV-2 patients. Survival was significantly lower for patients with a baseline $CD4^+$ lymphocyte cell count less than 50×10^6 compared to those with a baseline $CD4^+$ lymphocyte cell

Table 1. Baseline characteristics of antiretroviral therapy initiators attending the MRC Gambia GUM clinic.

	HIV-1 ($n=308$)	HIV-2 ($n=51$)	*P* value of difference by HIV type
Median age in years (IQR)	35 (29–42)	42 (32–48)	0.003
Sex [*N* (%) male]	102 (33.1)	19 (37.3)	0.561
Median months in follow-up before starting ART (IQR)	7.6 (4.0–24.4)	9.5 (4.9–38.6)	0.213
Median CD4 cell count per μl (IQR)	110.0 (50.0–200.0)	140.0 (50.0–310.0)	0.042
Number (%) with CD4 cell count (cells/μl)			
<50	77 (25.1)	10 (19.6)	
50–199	155 (50.5)	27 (52.9)	
200–349	72 (23.5)	11 (21.6)	
≥350	3 (1.0)	3 (5.9)	0.072
Median HIV RNA, $\log_{10}$, copies/ml (IQR)	5.4 (4.7–5.9)	4.9 (4.2–5.4)	0.003
Number (%) with HIV RNA ≥100 000 copies/ml	210 (68.2)	25 (49.0)	<0.008
Weight [*N* (%) <45 kg]	73 (23.7)	12 (23.5)	0.981
WHO clinical stage[a]			
1	87 (28.2)	18 (35.2)	
2	69 (22.4)	15 (29.4)	
3	113 (36.7)	14 (27.5)	
4	39 (12.7)	4 (7.8)	
Haemoglobin <8.0 g/100 ml	31 (10.1)	4 (7.8)	0.622
Number (%) initial antiretroviral regimen			
ZDV/3TC/NVP	232 (75.3)	1 (1.9)	
ZDV/3TC/LPVr	6 (1.9)	45 (88.2)	
ZDV/3TC/EFV	32 (10.4)	2 (3.9)	
d4T/3TC/NVP	25 (8.1)	0 (0)	
d4T/3TC/EFV	7 (2.3)	0 (0)	
Other	6 (1.9)	3 (5.8)	

ART, antiretroviral therapy; d4T, stavudine; EFV, efavirenz; GUM, Genito-Urinary Medicine; IQR, interquartile range; LPV/r,lopinavir/ritonavir; NVP, nevirapine; ZDV, zidovudine; 3TC, lamivudine.
[a]0.059 is the *P* value of the difference in stage 1 or 2 versus stage 3 or 4 by HIV type.

count of at least 50×10^6 ($P < 0.001$) (data not shown). Stratum of baseline HIV RNA (>100 000 copies versus <100 000 copies) was not a significant predictor of survival (data not shown).

In multivariate analysis several baseline factors were significantly associated with increased risk of death by 6 months: $CD4^+$ lymphocyte count below 50 cells/μl, haemoglobin below 8.0 g/dl, male sex, weight less than 45 kg, being a GUM clinic patient for less than 12 months before starting ART and started ART in 2007 or 2008 (Table 3). Male sex and starting ART in 2007 or 2008 were the only factors significantly associated with increased risk of death after 6 months.

CD4 cell recovery

In a linear regression model of $CD4^+$ cell count recovery from baseline, increases were faster in HIV-1-infected patients up to 24 months of follow-up, compared to HIV-2-infected patients, controlling for baseline $CD4^+$ cell count (Fig. 2 and data not shown). In multivariate analysis, $CD4^+$ cell recovery was significantly associated with HIV-1 infection [mean 90.0 cells, standard deviation (SD) 32.3], months on treatment (mean 7.2 cells, SD 1.3)

Table 2. Crude follow-up and retention among antiretroviral therapy initiators attending the GUM clinic.

	HIV-1 ($N=308$)	HIV-2 ($N=51$)	All patients ($N=359$)	*P* value[a]
Number (%) died	56 (18.1)	6 (11.8)	62 (17.3)	0.26[a]
Number (%) lost to follow-up (LTFU)	11 (3.6)	1 (1.9)	12 (3.3)	0.99[a]
Number (%) alive but no longer taking ART	6 (1.9)	1 (1.9)	7 (1.9)	1.0[a]
Number (%) transferred to another facility	22 (7.1)	5 (9.8)	27 (7.5)	1.0[a]
Number (%) died, defaulted or LTFU within 1 month of starting ART	16 (5.2)	0 (0.0)	16 (4.5)	0.14[a]
Median follow-up in months[b] (IQR)	12.1 (4.9–30.4)	20.3 (10.0–33.0)	14.0 (5.5–30.5)	0.05[b]
Median number of consultations per month (IQR)	1.0 (0.8–1.5)	1.1 (0.9–1.3)	1.0 (0.8–1.3)	0.80[c]
Number (%) with missed appointment by ≥90 days on ART [c]	35 (11.4)	5 (9.8)	40 (11.1)	0.74[a]
Total person-years of follow-up in cohort	463.1	93.5	559.5	
Mortality rate per 1000 person-years[a]	120.9	64.2	111.4	0.05[b]

ART, antiretroviral therapy; GUM, Genito-Urinary Medicine; IQR, interquartile range.
[a]*P* value of Chi-squared for difference in distribution of outcome by HIV type.
[b]*P* value of Log rank test for difference in Kaplan–Meier curves by HIV type.
[c]*P* value of Kruskal–Wallis difference in median value by HIV type.

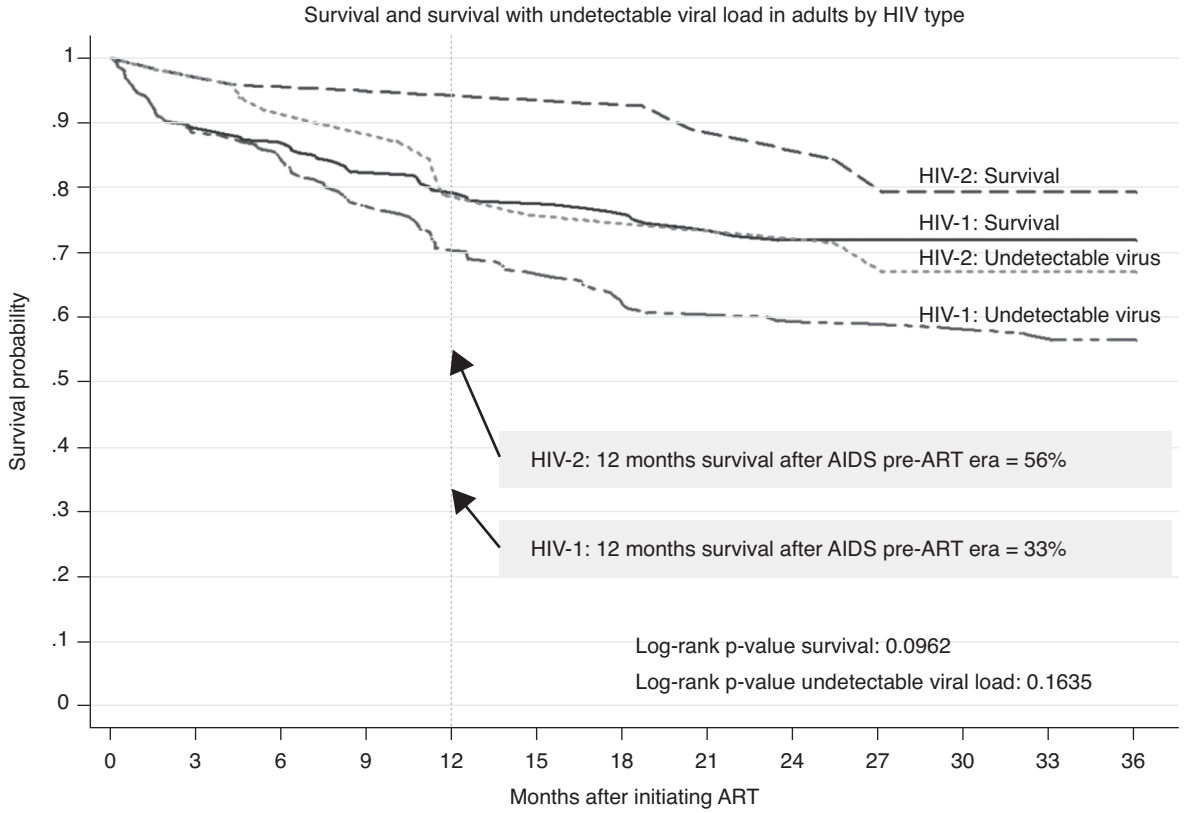

Fig. 1. Probability of survival and survival with undetectable viral load up to 36 months following antiretroviral therapy initiation in HIV-1 and HIV-2-infected individuals. Arrows indicate the probability of survival at 12 months in the same cohort prior to the availability of ART [18]. ART, antiretroviral therapy.

and an interaction between months on treatment and HIV-1 (mean −2.9 cells, SD 1.5); baseline viral load and $CD4^+$ cell count were not associated with $CD4^+$ cell recovery (analysis not shown). In multivariate analysis increases in $CD4^+$ cell count from baseline were positively associated with $\log_{10}$ baseline viral load (mean 75.4 cells, SD 23.8), baseline $CD4^+$ cell count (mean 2.5 cells, SD 1.2) and months on treatment (mean 6.6 cells, SD 0.5).

Virologic failure

The percentage of patients with undetectable viral load at 6, 12, 24 and 36 months were 81.7, 80.7, 89.1 and 81.4%, respectively. In total, 210 HIV-1-infected patients (67.9%) and 38 (74.5%) of HIV-2-infected patients had an 8–12-week and/or a 6-month plasma viral load measurement with which to assess viral response to ART. Missing viral response data were partly due to patients dying before providing a post-baseline blood sample. The Kaplan–Meier estimate of survival to 36 months was significantly lower in patients with incomplete viral response compared to patients with viral suppression by 6 months (66.2 versus 88.7%; *P* value log-rank test = 0.0071, data not shown).

In 233 patients with virologic response by 6 months, 158 had subsequent viral load measurements with which to assess viral rebound. Twenty-three (17.6%) and five (18.5%) of HIV-1 and HIV-2-infected patients, respectively, experienced viral rebound by 36 months. The Kaplan–Meier estimate of survival to 36 months was significantly lower in patients with viral rebound compared to patients without rebound (82.9 versus 96.3%; *P* value log-rank test = 0.0265, data not shown). Only male sex was significantly associated with risk of virologic rebound (hazard ratio 1.78, 95% CI 1.0–3.1, data not shown).

Discussion

The study reports on baseline characteristics and medium-term outcomes in a clinical cohort of HIV-1 and HIV-2-infected ART patients in the Gambia. Our study is one of few to report on mortality, LTFU, immunological and virological outcomes for ART in a cohort of HIV-1 and HIV-2-infected patients. To date, most studies of ART outcomes on HIV-2-infected patients have been limited by small sample size, report

Table 3. Cox proportion hazard models of baseline factors and risk of death in antiretroviral therapy initiators, stratified by death before and after 6 months.[a]

	Death by 6 months				Death after 6 months			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	Hazard ratio for death (95% CI)	*P* value	Hazard ratio for death (95% CI)	*P* value	Hazard ratio for death (95% CI)	*P* value	Hazard ratio for death (95% CI)	*P* value
CD4 cell count <50 cells/μl	3.1 (1.6–5.9)	0.001	2.3 (1.2–4.5)	0.0155	2.3 (0.9–5.8)	0.0693	–	
HIV RNA (log_{10} copies/ml)	1.4 (0.9–2.2)	0.1402	–		1.2 (0.7–1.9)	0.6001	–	
WHO clinical stage 3 or 4[b]	2.6 (1.3–5.4)	0.0077	–		0.9 (0.4–2.4)	0.9345	–	
HIV-1[c]	3.1 (0.7–12.9)	0.120	–		1.3 (0.4–3.5)	0.72	–	
Haemoglobin <8.0 g/100 ml	4.8 (2.3–9.8)	<0.0001	6.2 (2.8–13.8)	<0.0001			2.8 (0.9–8.4)	0.0634
Age ≥45 years	1.5 (0.7–3.0)	0.3184	–		1.6 (0.6–4.1)	0.3706	–	
Male	2.0 (1.0–3.9)	0.0365	4.9 (2.5–10.8)	<0.0001	2.2 (0.9–5.8)	0.0996	2.5(1.2–5.6)	0.0184
Weight <45 kg	3.6 (1.9–7.0)	0.0001	3.9 (1.8–8.2)	0.0004	1.2 (0.4–3.7)	0.7849	–	
In cohort <12 months prior to ART	5.1 (1.8–14.6)	0.0021	3.7 (1.1–9.3)	0.0145	0.7 (0.3–2.0)	0.6874	–	
Started ART in 2007 or 2008[d]	2.5 (1.2–5.1)	0.0165	2.8 (1.3–6.0)	0.0076	6.6 (2.4–17.9)	0.0002	5.9 (2.5–14.4)	<0.0001

[a]360 patients are in the model of 6-month survival, 262 patients in the model of after 6 months survival.
[b]Referent is WHO stage 1 or 2.
[c]Referent is HIV-2.
[d]Referent is started on ART in 2004, 2005, 2006 or 2009.

only on immunological outcomes, or include a substantial subset of patients not initiating WHO-recommended first-line therapy [8,12–14,17,22–27]. Here we report outcomes from a cohort in which 88.2% of HIV-2-infected patients initiated ART on a first-line therapy of zidovudine, lamivudine and lopinavir-ritonavir, for which there is observational evidence of high treatment efficacy [23,28]. Baseline immunological and demographic characteristics of our cohort were similar to other ART cohorts in sub-Saharan Africa, in which the majority of patients initiate ART at an advanced stage, at 35–40 years of age [9,29], and are predominantly female [29].

Overall patient survival in our cohort was 81.8% at 12 months, which is within the range of 74–92% reported in a recent review of mortality in ART programmes in sub-Saharan Africa [30]. However, that review excluded LTFU from survival estimates; our estimates represent a minimum survival rate because LTFU was statistically treated as death. Early mortality contributed substantially to overall mortality and patient attrition in our cohort, with 58.9% of deaths occurring by 6 months; however, high early mortality was limited to HIV-1-infected patients. High rates of early mortality among HIV-1-infected adults in ART programmes in sub-Saharan Africa are common [4,7,30,31] and elevated compared to rates in Europe and North America, even when controlling for baseline immunodeficiency [4]. In the current study, low $CD4^+$ lymphocyte count at baseline tripled the risk of death by 6 months. This suggests that many HIV-infected patients were not accessing ART early enough in their disease to benefit from therapy.

In the current study male sex and operational covariates were independently associated with increased mortality. Higher mortality in male ART patients has been reported in some studies [22,32,33], but not others [31,34]. Some studies suggest that sex differences in mortality are mostly explained by late presentation rather than poor adherence [35,36]. However, in this study, sex differences in mortality are likely due to poorer adherence among men; in multivariate modelling male sex remained a risk factor for mortality while controlling for baseline factors that would largely account for late presentation (i.e. CD4 cell count, HIV RNA, haemoglobin, weight and clinical stage). Calendar year was also associated with increased risk of death, particularly after 6 months of treatment. It is plausible that increased publicity for alternative therapy in the Gambia during 2007 and 2008 may have led to an increase in ART defaults. Use of traditional medicines has been a reason for ART default in other programmes in sub-Saharan Africa [37]. Other explanations for poorer ART outcomes during this period, including changes in the patient population or the clinical setting, were not investigated.

The study found that $CD4^+$ cell recovery was slower in HIV-2-infected patients compared to HIV-1-infected

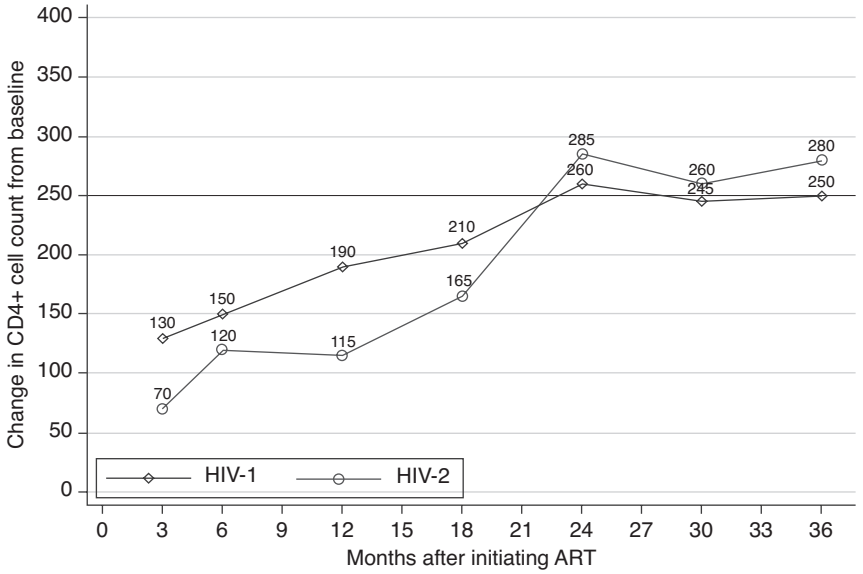

Fig. 2. CD4$^+$ T-cell recovery up to 36 months in HIV-1 and HIV-2-infected individuals initiating antiretroviral therapy. ART, antiretroviral therapy.

patients, despite higher median baseline CD4 cell count; this is consistent with previous findings [12,14,17,24]. These differences may be attributed to sub-optimal ART regimens for HIV-2, particularly reduced susceptibility of HIV-2 to certain protease inhibitors [38,39], longer duration of infection in HIV-2 patients at ART initiation [14] and older age. However, in our data, age was not associated with CD4$^+$ cell recovery. Furthermore, slower CD4$^+$ T-cell reconstitution was observed in our cohort despite 88.2% of HIV-2-infected patients commencing a boosted lopinavir-based regime. In HIV-1 infections persistent T-cell activation despite viraemic control by ART is associated with incomplete CD4$^+$ cell recovery [40]. Viral replication (below the current limit of detection) may contribute to this process. Thus even boosted protease inhibitor-based regimes may allow ongoing low-level HIV-2 viral replication, which takes longer to control than in HIV-1-infected individuals on ART. In this study, despite differences in the rate of CD4 recovery, cumulative CD4$^+$ T-cell gains had equalized in HIV-2 and HIV-1-infected patients by 24 months, there was no difference in virologic suppression by HIV type and overall mortality was lower in HIV-2 compared to HIV-1. Thus, slower CD4$^+$ cell recovery in HIV-2-infected patients does not seem to equate to worse virological and clinical outcomes compared to HIV-1-infected patients.

In the current study, no baseline factors were associated with virologic response and only male sex was associated with virologic rebound. Primary drug resistance at baseline cannot be excluded as a reason for virologic failure, as viral genotyping was not carried out. However, HIV-1 drug resistance surveillance indicates that transmitted resistance in Africa is less than 5% [41], and may be lower in the Gambia where ART only became available in October 2004. It seems reasonable to assume, therefore, that poor adherence was the primary cause of virologic failure in this cohort.

The current study possesses several strengths including a sizeable cohort, the inclusion of both HIV-1 and HIV-2-infected ART-naive individuals, analysis of virologic and immunologic data and low LTFU. Some limitations should, however, be considered during interpretation. Firstly, we were unable to determine whether virologic failures and deaths were due to poor adherence or drug failures, although we presumed that most were due to the former. Secondly, our analysis of virologic failure excluded patients who died before providing a postbaseline viral load, which may have lead to an underestimation of virologic failure. However, nearly 60% of deaths occurred by 6 months; most of these were likely due to advanced disease at baseline rather than virologic failure. In addition, given the absence of a commercially available and validated assay to quantify HIV-2 RNA loads, we used an in-house assay for HIV-2 and HIV-1 RNA quantification [19,21]. An evaluation of nine such HIV-2 qPCR assays found our in-house assay was highly reproducible at all viral loads and reliably detected low level viraemia [42]; it was also a sensitive predictor of disease progression and mortality in both HIV-1 and HIV-2-infected individuals [43,44]. However, the assay tended to over quantify RNA levels [42], thus we may have overestimated the number of individuals failing to achieve viral suppression to less than 400 copies/ml.

Thirdly, information on cause of death and reasons for patients stopping ART was not collected. Such data may have identified modifiable elements of the HIV

treatment programme that directly or indirectly contributed to these deaths and/or treatment abandonment within the Gambian context. Finally, ART outcomes reported here may not be generalizeable to programmes that do not require pretreatment counselling, lack active follow-up of patients, charge fees for clinical services and drugs or lack immunologic and virological monitoring.

Another issue worthy of consideration is the high degree of genetic diversity of HIV-1 infections in West Africa. In the GUM cohort, approximately 50 and 18% of infections are due to CRF02_AG and CRF49_cpx, respectively, with several other subtypes (A, B, C, D, F, G, CRF06_cpx, CRF09_cpx and CRF11_cpx) each representing 1–5% of infections ([45] and TdS, unpublished data). ART outcomes may differ by HIV-1 subtype, possibly due to rates at which drug resistance mutations accumulate [46] and could potentially explain the HIV-1 ART failures we observed. Research indicates that initial immunological and virological responses to ART in HIV-1 infections with subtypes CRF02_AG, A, C and D are largely comparable to infections caused by subtype B [47,48]. Future work examining ART responses to other HIV-1 subtypes, particularly CRF49_cpx, would be valuable.

In summary, HIV-1 and HIV-2-infected patients receiving ART in the Gambia had good survival to 36 months. HIV-2-infected patients did as well as HIV-1-infected patients in terms of long-term immunological and virological responses and overall survival. Improvements in the performance of the ART programme should be directed at earlier diagnosis and ART commencement, reducing early mortality and improving adherence to therapy.

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Conflicts of interest

There are no conflicts of interest to declare for any of the authors.

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