Table 2. Univariable and multivariable regression models evaluating the effect of baseline CD4 cell counts stratum on mortality.

	Regression on the cumulative incidence function (CIF)[a]			
	Univariate analysis (N=908)		**Multivariate analysis* (N=907)**	
bCD4[b]	**Crude sHR (95% CI)**	**p value**	**Adjusted sHR (95% CI)**	**p value**
≥ 500	1		1	
<500	1.40 (1.02-1.91)	0.035	1.49 (1.07-2.07)	0.017
Cox regression model				
	Univariate analysis (N=908)		**Multivariate analysis* (N=907)**	
bCD4[b]	**Crude HR (95% CI)**	**p value**	**Adjusted HR (95% CI)**	**p value**
≥ 500	1		1	
<500	1.63 (1.19-2.23)	0.002	1.44 (1.03-2.02)	0.033

Note: *[a]Fine-Gray regression for competing risks endpoints; [b]baseline CD4 cell count; *multivariate model adjusted for the following confounding variables (using a 10% change in estimate methods): age, sex and fCD4*

Death cumulative incidence at one year was 8.8% (95% CI=6.3-11.8) among HIV-1 patients and 29.9% (95% CI=24.4-35.7) after five years of follow up. In HIV-2 patients, cumulative incidence at one year and five years were 4.4% (95% CI=1.8-8.9) and 21.6% (95% CI=14.1-30.3), respectively. Cumulative incidences were 6.2% (95% CI=1.1-17.9) and 53.2% (95% CI=30.9-71.2) for HIV-D patients **(Figure 1.3)**. **Table 3** presents the univariable and multivariable analysis of the association between HIV serotype and mortality. The sHR were adjusted on age, sex, education level and inclusion period. Comparing HIV-2 infection, HIV-1 and HIV-D infection were associated with a higher risk of death: the respective asHR were 1.66 (95% CI=1.14-2.43) and 2.15 (95% CI=1.25-3.73). The risk of death was not statistically different between HIV-D infected patients and HIV-1 mono infected patients: asHR=1.36 (95% CI=0.84-2.21). Similar results were obtained using classic Cox regression.

Table 3. Univariable and multivariable regression models evaluating the effect OF HIV serotype on mortality.

	Regression on the cumulative incidence function (CIF)[a]			
	Univariate analysis (N=908)		**Multivariate analysis* (N=907)**	
HIV serotype	**Crude sHR (95% CI)**	**p value**	**Adjusted sHR (95% CI)**	**p value**
HIV-2	1		1	
HIV-1	1.24 (0.85-1.80)	0.267	1.66 (1.26-2.81)	0.008
HIV-D	1.88 (1.02-3.44)	0.041	2.15 (1.24-3.73)	0.006
Cox regression model				
	Univariate analysis (N=908)		**Multivariate analysis* (N=907)**	
HIV serotype	**Crude sHR (95% CI)**	**p value**	**Adjusted sHR (95% CI)**	**p value**
HIV-2	1		1	
HIV-1	1.45 (0.98-2.13)	0.061	1.80 (1.21-2.68)	0.004
HIV-D	2.05 (1.10-3.84)	0.025	2.23 (1.18-4.22)	0.013

The effect of beta 2 microglobulin (β2m) on mortality was evaluated in a subpopulation of 263 individuals. The characteristics of patients included for the analysis of β2m are summarized in **Table 1**. The β2m level was dichotomized with the median value as the cut-off point: ≥ 2.85 mg/l or <2.85 mg/l. Cumulative incidence of death varied with the level of β2m: after ten years, the cumulative incidence of death was 51.0% (95% CI=40.2-60.7) in case of

baseline β2m level ≥ 2.85 and 10.6% (95% CI=4.6-19.5) in case of baseline β2m level <2.85 **(Figure 1.4)**. Crude and adjusted sHR and 95% CI for the association between β2m ≥ 2.85 mg/l and mortality are presented in **Table 4**. After adjustment on age and sex, Plasma β2m was associated with mortality. PLHIV who presented with baseline β2m ≥ 2.85 mg/l had more than three times higher mortality than people who presented with baseline β2m<2.85 mg/l: asHR=3.26 (95% CI=2.03-5.25). The association was similar for HIV-1 infection (asHR=3.31; 95% CI=1.77-6.20) and HIV-2 infection (asHR=3.22; 95% CI=1.37-7.55) as well as for HR obtained with classic proportional hazard model.

Table 4. Univariable and multivariable regression models evaluating the effect of β2m level on mortality.

	Regression on the cumulative incidence function (CIF)[a]			
	Univariate analysis (N = 908)		**Multivariate analysis* (N = 907)**	
β2m level	**Crude sHR (95% CI)**	**p value**	**Adjusted sHR (95% CI)**	**p value**
<2.85	1		1	
≥ 2.85	3.48 (2.18-5.54)	<0.001	3.26 (2.03-5.25)	<0.001
Cox regression model				
	Univariate analysis (N=908)		**Multivariate analysis* (N=907)**	
β2m level	**Crude HR (95% CI)**	**p value**	**Adjusted HR (95% CI)**	**p value**
<2.85	1		1	
≥ 2.85	3.53 (2.15-5.83)	<0.001	3.39 (2.16-5.31)	<0.001

Note: *[a]Fine-Gray regression for competing risks endpoints, *multivariate model adjusted for the following confounding variables (using a 10% change in estimate methods): age and sex*

DISCUSSION

We conducted a prospective cohort study on a population of 908 ART-naïve Gambian PLHIV followed between 1992 and 2010 with an average exposure time of 2.5 years. We described pre-ART mortality and estimated the association of bCD4, HIV serotype and β2m level using competing risks estimation methods and classical methods.

After adjustment, mortality was influenced by CD4 stratum, HIV serotype and β2m level.

In this study, we recruited and followed a significant ART-naïve population over two decades. Our observational cohort reflects the real-life conditions in Sub-Saharan Africa over secular time, offering a powerful basis for generalizability across different contexts.

Our mortality rate was similar to those found in Sub-Saharan Africa although some authors reported lower values related to the differences in methods of survival analysis [7-11,20]. However, the exposure times in these studies were relatively short. In developed countries like North American and European countries, mortality among ART naïve PLHIV is lower than what has been found in our cohort: it was lower than 0.7/100 PY in the stratum "350-499" and lower than 0.5/100 PY in the stratum "≥ 500" [1,2]. In EuroSIDA, the mortality rate was 1.4/100 PY in a population with ≥ 350 CD4/µL while in CASCADE, cumulative incidences were 10% and 44% at five years and ten years after seroconversion, respectively [3,6].

After adjustment, our study found a 49% increase in mortality in the stratum of baseline CD4 350-499 compared with the stratum CD4 ≥ 500. A difference in mortality by CD4 cell count stratum was previously reported in one study [16] but not in others [13,18,34-36]. Importantly, these studies used a different methodology, considering the time spent in a specific CD4 cell count stratum instead of baseline CD4 cell count only. These studies have contributed to the debate on the best moment to initiate ART without bringing about a clear consensus. A systematic review including 24 studies with three RCT was in favor of initiating ART at 350-500 CD4/µL [19] and supported the WHO guidelines for ART initiation issued in 2013 [37]. In 2015, the results of two major RCTs confirmed those of HPTN 052 and recommended initiation of ART regardless CD4 cell count and clinical stage [12]. In these RCTs, a composite measure of the primary endpoint was death, AIDS event or serious non-AIDS event. The authors argued there was a clinical benefit from early initiation of ART, although the differences in mortality were not statistically significant [13-15].

One major limitation of RCTs is external validity: this is particularly the case for HPTN 052 which was conducted in a population of serodiscordant couples (SDC). The PLHIV in SDC are known to have an important social support and a high risk perception that might contribute to good adherence and good results [38-40]. More generally, international RCTs are conducted under optimal conditions that do not

reflect those found in real-life: additional technical, financial and social supports are given in order to maximize adherence. This may explain in part the low number of events and deaths in these trials, and their inability to show statistically significant differences in mortality. In Sub Saharan Africa, it is usually through RCTs or other clinical research settings that it is possible to obtain frequent measures of CD4 cell count and even viral load among ART-naïve PLHIV. Significant loss to follow up has already been reported in these PLHIV and it is important to take into account this parameter [41-44]. For these reasons, real-life data are necessary to support the results of RCTs: this is crucial to convince decision-makers that results of RCTs can be reproduced in resource-poor settings and even scaled up.

In this analysis, based on real-life data, we showed that ART initiation at CD4 cell count ≥ 500 would reduce mortality compared to initiating at a CD4 cell count of 350-499. We have chosen to consider baseline CD4 cell count as the main exposure variable and to adjust for CD4 cell count measurements during follow up. The first visit and baseline CD4 cell count determine future clinical management of PLHIV in Sub Saharan Africa. Before ART initiation, consecutive visits usually depend on the wellbeing of the patient and are often irregular. Our study offers insight into the natural history of HIV in ART-naïve patients in Sub Saharan Africa under real-world conditions.

Our observation that mortality was higher in HIV-1 and HIV-D infected than in HIV-2 infected patients has previously been reported [20-23]. HIV-2 is less virulent with a slower progression than HIV-1. The underlying mechanisms are not fully understood yet, but some authors linked it to the virus-cell interactions during surface envelope Glycoprotein engagement of cell receptors, the difference in the humoral response or genomic differences [45-48]. We found that mortality of HIV-D patients was higher than that of HIV-1 patients but the difference was not statistically significant as it was the case of the majority of previous studies [23,25,27]. This is in contradiction with the results of Esbjörnsson et al. who reported an inhibition of HIV-1 disease progression by contemporaneous HIV-2 infection and a lower mortality in HIV-D patients [26,28]. It was important to produce valid estimations of mortality by HIV serotype in West Africa where both viruses remain endemic.

Through this study, we also found that the plasmatic level of β2m was strongly associated with death, similarly in HIV-1 and HIV-2 infected patients. The role of immune activation (IA) in HIV disease progression and death was previously reported by studies from different contexts [31,49-55]. However, these studies were cross-sectional, of short duration or mainly concerned PLHIV in advanced disease stages. Two studies conducted in Rwanda and Zambia did not find a role of β2m in mortality of HIV patients [56,57]. Our study confirmed the role of IA in HIV-1 and HIV-2 disease progression and mortality even in PLHIV with high CD4 cell count and followed for 18 years. There is little data examining these relationships in the context of high prevalence of both IA and HIV infection. In addition to HIV disease progression, IA has been recognized as the main risk factor for non-AIDS related morbidity and mortality in PLHIV even under effective ART [29,58-60]. As a result, IA has become a therapeutic target and specific therapies are being developed [29,61]. Our study can contribute to inform the best usage of such therapies in Sub Saharan Africa. Moreover, we used β2m as soluble marker of IA. β2m has already been shown to be suitable marker for a general IA in HIV infection and is stable for long-term storage of plasma samples and freeze-thawing [62]. This low cost and easily quantifiable marker has a public health interest in contrast with cellular markers which are usually preferred in research contexts.

However, our study presents some limitations: potential confounders such as body mass index (BMI), hemoglobin level and viral load were not collected although their roles in mortality were not unanimously recognized [31,33]. The effect of β2m level was evaluated in a subpopulation of the cohort with a possibility of selection bias. However, the selection of this subpopulation preceded the event and was not related to any of our exposure variables, minimizing a possibility of such bias. Moreover, a significant proportion were lost to follow up. In sensitivity analyses, if we considered all those lost to follow up as deceased, the effects of our exposure variables were underestimated (toward the null), while considering them all as alive did not significantly change the associations (supplementary results). It is more likely that the lost to follow-up remained alive for several reasons. Firstly, they were younger, were more frequently working, had a higher level of education and were more frequently infected by HIV-2. Secondly, the procedures of the study described in the methods were very effective to report deaths even if they occurred out of hospital. Thirdly, the existence of alternative therapeutic options (traditional medicine and then ART programs in surrounding countries) was considered the main reason of lost to follow up.

CONCLUSION

In this observational cohort of ART-naïve Gambian PLHIV followed for two decades, we demonstrated that mortality was higher in those with baseline CD4 cell count of 350-499 compared to those with a baseline CD4 ≥ 500. We confirmed that mortality is lower in HIV-2 infection than in HIV-1 and HIV-D infections with no argument of the inhibition of HIV-1 progression by HIV-2 co-infection. Using a soluble marker of IA with potential public health interest, we found a strong and durable association between β2m and mortality. These data are scare in Sub Saharan Africa and provide a picture of real-life long-term differences in mortality. They clearly indicate that early

ART initiation and lower levels of IA would reduce mortality in a context of high prevalence of HIV and IA.

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AUTHORS' CONTRIBUTIONS

AD, HT, VKN and AJ conceived the work.

AD, GT, MT and AS coordinated data collection and quality control.

AS realized beta-2-microglobulin measurements.

MT realized viral load measurements.

AD and HT realized the analysis and the interpretation of the data.

AD realized the first draft of the manuscript.

HT, VKN, GT, MT, AS, AJ and SM revised the consecutive drafts.

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