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Mortality and survival patterns of people living with HIV-2

Boris Tchounga[1,2,3], **Didier K Ekouevi**[1,2,3,4], **Eric Balestre**[1,2], and **François Dabis**[1,2]

[1]Université de Bordeaux, ISPED, Centre INSERM U1219-Bordeaux Population Health, Bordeaux, France

[2]INSERM U1219 – Centre Inserm Bordeaux Population Health, Université de Bordeaux, Bordeaux, France

[3]Programme PACCI, site de recherche ANRS, Abidjan, Côte d'Ivoire

[4]Université de Lomé, Département de Santé Publique, Lomé-Togo

Abstract

Purpose of review—People living with HIV-2 infected usually initiate antiretroviral therapy (ART) at an advanced period in the course of their infection after a long asymptomatic period characterized by high CD4 cell count and thus at a relatively advanced age. In the new international context of early and universal ART initiation, the aim was to review survival patterns among HIV-2 infected patients, either on ART or not.

Recent findings—Very few reports were published on mortality in people living with HIV-2 during the last five years. People living with HIV-2 experience high mortality rates although lower than people living with HIV-1 before ART initiation. They seem to survive longer regardless of the conditions of ART use. Mortality is associated with late presentation, male gender, CD4 count <500 cell/μl, high plasma viral load, hemoglobin rate <8 g/dl) and body mass index < 18 Kg/m^2.

Summary—People living with HIV-2 initiate ART later than HIV-1 and HIV duals, resulting in higher disease progression and mortality rate. The clinical management of HIV-2 infected patients should now include early diagnosis and treatment initiation as per international guidelines. Further research needs to explore the "what to start" question and document specific causes of death in people living with HIV-2 and enrolled in care in Africa.

Keywords

HIV-2; survival; mortality; antiretroviral therapy

Introduction

Human immune deficiency virus type 2 (HIV-2) is endemic in West Africa and has spread elsewhere in countries with historical and socioeconomic ties to this region (1,2). In West

Corresponding author: Pr François DABIS, MD, PhD, Centre de Recherche INSERM U.1219, Institut de Santé Publique, Epidémiologie et Développement (ISPED), Université de Bordeaux, ISPED, CS61292, 33076 BORDEAUX Cedex - FRANCE, Tel: 33 (0) 5. 57.57.14.36, Francois.Dabis@u-bordeaux.fr.

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Africa, HIV-2 infection accounts for 10% to 20% of all HIV infections, with a significant proportion of coinfections with both HIV-1 and HIV-2 (3,4). In the last decade, many studies reported a consistent decline in the prevalence of HIV-2 infection in West Africa, especially in the Gambia and Guinea Bissau but the reasons of these epidemiological changes remain unclear (5,6). However, new HIV-2 infections are still diagnosed.

Cohorts of people living with HIV-2 are less common worldwide than for those living with HIV-1 (3,7). Clinically, people living with HIV-2 experience a longer asymptomatic latency period and a slower disease progression than those infected with HIV-1 (8). In addition, their biological progression is characterized by a slower T lymphocyte CD4 (CD4) depletion (9,10) and a lower plasma viral load (VL) compared to HIV-1 (11,12). However, HIV-2-infected patients can develop AIDS disease (13,14) and death (15,16), if they do not receive any antiretroviral therapy (ART).

The consolidated 2013 World Health Organization (WHO) guidelines recommended to initiate ART among HIV-2 infected patients with either three nucleoside reverse transcriptase inhibitors (NRTIs) or two NRTIs plus one protease inhibitor (PI) (17). However, the application of these guidelines could lead to the unavailability of effective second-line agents in areas with limited access to ART, since phenotypic cross-resistance with PIs as well as NRTIs is a significant issue for HIV-2 (18,19). More recently, the 2015 WHO guidelines recommended ART initiation in all people living with HIV, including those infected with HIV-2, regardless of CD4 count or clinical disease progression (20). The general aim of these guidelines was to reduce HIV transmission and improve survival, since both benefits of early ART initiation have now been clearly demonstrated (21). However, the strict implementation of these recommendations could be challenging, since people living with HIV-2 usually present with high CD4 counts for a long period of time. Furthermore, the full impact evaluation of such guidelines will have to rely on the measurement of disease-free survival or its counter-measures, loss to follow up and mortality. This review aims to report on the mortality rates, survival patterns and their socio-demographic, clinical and biological predictors among people living with HIV-2 infected either with ART or not.

Search strategy and selection criteria

Considering the limited number of publications on the epidemiology of HIV-2 infection, we have not restricted the period of the review.

Eligibility criteria

All studies, regardless of design, place or language restrictions, were considered if they met the following three selection criteria: 1) data on HIV-2 infected patients clearly disaggregated; 2) data on mortality (death or survival), 3) abstract, article and oral or poster presentation available. We included all studies reporting treatment outcomes, mortality or survival among HIV-2 only and HIV-1/HIV-2 dually infected patients. We excluded case series with less than five patients.

Search strategy and study selection

We developed a sensitive search strategy that combined terms for HIV-2 and mortality.

("hiv-2"[MeSH Terms] OR "hiv-2"[All Fields] OR "hiv 2"[All Fields]) AND ("mortality"[Subheading] OR "mortality"[All Fields] OR "mortality"[MeSH Terms])

Searches were conducted in the following databases: MEDLINE via PubMed and EMBASE. Additional articles were identified from references cited in published papers. We also searched the abstracts available from International AIDS Society (IAS) conferences, Conferences on Retroviruses and Opportunistic Infections (CROI) and International Conferences for AIDS in Africa (ICASA) in the preceding 12 months. Searches were completed up to December 2015.

Outcome measures and data analysis

The outcomes of interest were mortality and survival estimates at different time points. We looked also for factors associated with mortality or survival. We described each relevant study, and analyzed the outcomes reported in each study. When possible, we used the reported data to compute 95% confidence intervals (CI) for mortality estimates.

Mortality estimates in people living with HIV-2

Mortality before ART initiation

It is often stated that about 80% of people living with HIV-2 behave like HIV-1 long-term non-progressors (LTNP) and elite controllers, keeping high CD4 cell count (≥500 cells/mm^3) and low or undetectable viral load (≤100 copies/mL) for up to five to ten years (22,23). Several reports on pre-ART mortality among people living with HIV-2 were available, primarily from West Africa, with most data available from the Gambia (24–26) and Guinea Bissau (16,27–29) with overlapped populations over the time. None of these reports was published during the last 12 months (Table 1). There was only one systematic review, published in 2014 and analyzing data on mortality according to HIV type (30*). The main conclusions drawn from these papers is that compared to people living with HIV-1, those living with HIV-2 and followed in the same settings have a lower crude mortality rate (35.3 [CI: 32.0–38.7] vs 22.0 [CI: 19.7–24.3] per 100 person-year respectively after 10 years of follow up), and survived longer (3.2 years in median vs. 1.8 years; log rank test p= 0.0006) (25,27,30*). In the Gambia, 666 subjects infected with HIV-2- and 746 with HIV-1 were followed up from May 1986 to December 1997; the survival rates were 66.1%, 57.2% and 40.0% at one, two and five years, respectively among people living with HIV-2 higher than the 58.4%, 48.0% and 29.4% figures documented in people living with HIV-1 (25). More recently in 2011, the same trends were reported in a rural community of Bissau: the mortality rate was estimated at 4.1 (3.4–5.0) per 100 person-years (PY) among the 285 people living with HIV-2 versus 9.6 (7.1–12.9) among 117 people living with HIV-1, while it was as low as 1.6 (1.5–1.8) among 4,797 HIV negative subjects (28). Another study from the Gambia in 2011 reported no difference in terms of mortality according to HIV type when adjusted on CD4 count strata (≤100 vs >100 cells/mm^3). This is consistent with a previous report in 2002 suggesting that in the same setting the lower pre-ART mortality risk in people living with HIV-2 compared to HIV-1 was no longer observed when the CD4 count decreased below 500 cells/mm^3 (25).

Thus, without ART, people living with HIV-2 experience moderately higher mortality than HIV-negative individuals and survive longer than people living with HIV-1 when their CD4 cell counts are high (>500 cells/mm^3). Based on these findings, the question of when to start ART in people living with HIV-2 with high CD4 count could be discussed.

Mortality of people living with HIV-2 receiving ART

Mortality and loss to follow up are the most important outcomes to evaluate the impact of ART in sub-Saharan Africa settings. With the rapid scaling up of ART, mortality has been widely explored in HIV-1 infected patients receiving ART (31–33) but not so much in the context of HIV-2 infection. Indeed, some papers have described immune recovery and viral suppression (34*,35), but just a few of them described mortality and survival patterns of cohorts so far (36–39) (Table 2).

Considering the difference in pathogenicity between HIV-1 and HIV-2, a lower mortality rate could be expected in people living with HIV-2 on ART compared to those living with HIV-1. In Europe, the $ACHIE_2VE$ collaboration which is a pooled dataset of seven cohorts has reported vital status information on 170 people living with HIV-2 among which 44 (26%) received a triple NRTI regimen and 126 (74%) a PI boosted by ritonavir (PI/r) based regimen (36). None of these 170 patients receiving the two WHO recommended HIV-2 treatment options died during the first 12 months of treatment. A previous report from the ANRS CO5 HIV-2 Cohort followed up in France and included in the $ACHIE_2VE$ collaboration, had indicated that the initial CD4 cell count level was a predictor of survival. Thus, patients initiating ART with a median CD4 count of 136 cells/ml, showed a median CD4 cell increase of 41 cells/ml at month 12, and five (8.1%) deaths were reported after 21 months of follow up (40). Another report in the same cohort but focusing only on patients starting a lopinavir/r-based ART regimen for a median duration of 105 weeks (inter-quartile range [IQR] [39–132]), reported two deaths among 18 patients classified at CDC stage A (41). These results obtained in the European context with wide ART availability and use indicate that when treated with recommended ART regimens, people living with HIV-2 have a lower immune recovery than HIV-1 patients and a low overall mortality.

An analysis was recently conducted among people living with HIV-2 followed-up in the cohort collaboration of the international epidemiologic database to evaluate AIDS in West Africa (IeDEA-WA) (37*). This data set consisted of 5,193 people living with HIV-2 or with both HIV-1 and HIV-2, followed up in seven countries (Benin, Burkina Faso, Cote d'Ivoire, Guinea-Bissau, Mali, Senegal, and Togo). Among the 1,825 HIV-2 mono-infected patients who initiated ART between February 1997 and September 2014 and were followed up till December 2014, the median CD4 count at ART initiation was 263/mm^3 ((IQR [159 – 429]). The estimated risks of death after six, 12 and 24 months on ART were 4.1 (CI: 3.2–5.1), 5.5% (CI: 4.4–6.5) and 7.7% (CI; 6.4–8.9), respectively (37*). In addition, patients lost to follow-up were censored after their last contact and the estimated risk of loss to follow-up after six, 12 and 24 months on ART were 10.9% (CI: 9.4–12.3), 16.7% (CI: 14.9–18.4) and 25.7% (CI; 23.7–27.7), respectively (37*).

Another cohort from the Gambia have included 51 HIV-2 and 308 HIV-1 ART-treated individuals with a median follow up duration of 20.3 months (IQR: 10.0–33.0) and 12.1

months (IQR: 4.9–30.1), respectively. The crude mortality rate while on ART was significantly lower in HIV-2 infected patients compared to the HIV-1 ones (64.2 versus 120.9 per 1,000 person years; p=0.05). The survival probability was 96.0% at 12 months, 89.1% at 24 months, and 79.5% at 36 months for people living with HIV-2 on ART whereas it was 79.7%, 72.0% and 72.0 at the same time points for people living with HIV-1 (38).

In an urban district hospital in Burkina-Faso, Harries and colleagues investigated mortality among 4,255 people living with HIV who initiated ART and were followed up for a median of 22.6 months (IQR: 7.7–39.4). In this population, after a median follow-up on ART of 23 months (IQR: 8–34), the mortality hazard ratios were 1.41 (CI: 0.83–2.41) and 1.32 (CI: 0.80–2.17) for patients living with HIV-1 and those living with HIV-2 respectively, with no statistical significance (39). The possible explanation could be the administration of inappropriate ART regimen, and the relatively small number of people living with HIV-2 in the cohort, leading to a lack of statistical power (39).

Factors associated with mortality among HIV-2 patients

As in the general population, the advanced age at diagnosis and at treatment initiation plays an important role in the mortality of people living with HIV-2, either on ART or ART-naïve. Many studies including a meta-analysis on pre-ART HIV-2 infected individuals, identified age ≥45 years as the main explanatory factor for mortality among HIV-2 infected individuals (25,28,30*). This effect of an older age seems to be not specific to HIV-2 infected individuals, since similar but higher mortality rates have also been reported in older HIV-1 infected patients. In addition, older age has been shown to be associated with clinical progression to AIDS among ART-naïve HIV-2 infected individuals, emphasizing the importance of early diagnosis and treatment initiation (13). Low CD4 cell count and high plasma viral load are also associated with disease progression and mortality among HIV-2 infected patient (13,27,29), and are usually worse in HIV-2 infected men than women, explaining a part of the sex difference observed in mortality (25,30*). Regarding people living with HIV-2 on ART, the IeDEA West Africa collaboration identified male gender (adjusted hazard ratio [aHR]: 1.9; CI: 1.4–2.8; p<0.001), age >=50 years (aHR: 1.44; CI: 0.9–2.1), CD4 count at ART initiation <200 cells/mm3 (aHR: 3.3; CI: 1.3–7.8), body mass index <18 Kg/m^2 (aHR= 2.1; 95%CI [1.2–3.4], p-value =0.005) and haemoglobin rate <10 g/dL (aHR 2.4; 95%CI [1.3–4.4]; p-value =0.005) as factors associated with higher mortality (p=0.001) (37). In the Gambia, Peterson and colleagues identified CD4 cell count <50 per µl (aHR = 2.3; CI: 1.2–4.5] p=0.02), haemoglobin level <8.0g/dl (aHR: 6.2; CI: 2.8–13.8; p<0.001), weight <45kg (aHR: 3.9; CI: 1.8–8.2; p<0.001) and male gender (aHR: 4.9; CI: 2.5–10.8; p<0.001) as factors associated with mortality among people living with HIV-2 and receiving ART (38). Finally, mortality in people living with HIV-2 either ART naïve and on ART seems to be associated to the same factors than in HIV-1 mortality, including age, sex, clinical and laboratorial baseline characteristics (38,39,42,43). However, the role of immune activation in the mortality and sex difference among HIV-2 infected individuals remain unclear and further investigation are needed (44).

Reliability of mortality estimates among people living with HIV-2 on ART

Data on mortality and survival among people living with HIV-2 remain limited in size and quality. When available, they are usually presented as crude mortality rates (34*–36,40), and very few are using the most appropriate statistical methods (25,39). Most of the cohorts lacked power to detect any statistical difference when investigating factors associated with mortality and some of them lumped together HIV-2 and HIV-1 + HIV-2 dually reactive patients. The few studies including people living with HIV-2 on ART with survival analyses did not describe high early mortality figures as observed in HIV-1 infected patients (45). In the report of the IeDEA West Africa collaboration, the largest ever for ART-treated people living with HIV-2, mortality seems underestimated because of the high number of patients lost to follow as already described in HIV-1 patients in the West Africa region (46). No cohort of HIV-2 infected patients reported having implemented an active search in case of loss to follow up as often done for HIV-1 patients (47). Finally the causes of death have not been usually reported in the studies we reviewed, and the all-cause mortality is probably insufficient to provide an insight of what could be an HIV-2 specific mortality pattern.

Conclusion

Despite the low disease progression, the rate of death for people living with HIV-2 receiving ART is elevated, especially for those enrolled and followed in the West African context. Thus, it cannot be considered very different from what is known for patients infected with HIV-1 or dual infection and living in the same environment. One of the reasons explaining the high rate of mortality among people living with HIV-2 is the late presentation, characterized by the older age at ART initiation (eight to ten years difference between HIV-2 and HV-1) with low CD4 count and high plasma viral load (34*,38,39). Other reasons that need to be further investigated are poor adherence and more importantly the use of ineffective ART regimens against HIV-2 either by inaccurate diagnosis or non-compliance with guidelines. There is a need to better document the causes of death among people living with HIV-2 and to explore further treatment adherence and viral resistance on ART. The low mortality hypothesis often formulated for HIV-2 patients seems to hold in the pre-ART era but not beyond, due to a combination of factors. Now that the when to start question has been normalized irrespective of the HIV type (20), the question of what to start remains for HIV-2 patients (34*) and is likely to be the last frontier to improve their prognosis.

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Key points

Before ART initiation, people living with HIV-2 with CD4 count ≥500 cells/mm^3 survive longer than HIV-1 and HIV1+2 dually infected patients.

People living with HIV-2 on ART experience high mortality, although lower than compared to HIV-1 individuals owing mostly but not entirely to the age difference at ART initiation.

Data on mortality among people living with HIV-2 remain scarce, emphasizing the need for more collaborative works to estimate the survival and mortality patterns among people living with HIV-2.

Table 1

Mortality among ART-naïve people living with HIV-2

Author Year	Period Country	Population size	Median age years [IQR]	Women (%)	Initial CD4 median [IQR]	Number of deaths	Mortality rate/100 PY	Mortality hazard ratio	Survival probability
Van Der Loeff 2002 (25)	1986–1997 Gambia	**666 HIV-2**	**35 [16–70]**	**60%**	**325 [130–590]**	**342 (51.4%)**	**22.0 (19.7–24.3)**	**0.5 [0.28–0.88]**	**57.2%**
		746 HIV-1	30 [15–68]	46%	210 [70–401]	423 (56.7%)	35.3 (32.0–38.7)	Ref	48.0%
		107 HIV-Dual	32 [19–72]	55%	230 [110–510]	63 (58.9%)	41.7 (31.4–52.0)	1.27 [0.51–3.7]	40.3%
Togun T 2011 (26)	2004–2009 Gambia	**103 HIV-2**	– NA	NA	NA	**15 (14.6%)**	**21.9 [18.3–26.2]**	**0.73 [0.4–1.2]**	NA
		647 HIV-1	– NA	NA	NA	96 (14.8%)		Ref	NA
		40 HIV-Dual	– NA	NA	NA	7 (17.5%)		1.07 [0.5–2.3]	NA
Van Der Loeff 2010 (27)	1991–2009 Guinea-Bissau	**133 HIV-2**	**47 [36–60]**	**68%**	**25 [18–32]**[$]	**66 (50%)**	**4.5 (3.6, 5.8)**	**1.9 (1.3, 2.8)**	NA
		158 HIV-neg	49 [38–62]	73%	NA	49 (31%)	2.1 (1.6, 2.9)	Ref	NA
Tienen C 2011 (28)	1989–2009 Guinea Bissau	**285 HIV-2**	**44 [34–58]**	**64%**	**NA**	**111 (39%)**	**4.1 [3.4–5.0]**	**2.6 [2.1–3.2]**	NA
		117 HIV-1	31 [25–42]	55%	NA	43 (40%)	9.6 [7.1–12.9]	7.3 [5.3–10.0]	NA
		53 HIV-Dual	47 [35–60]	86%	NA	24 (45%)	8.8 [4.3–7.9]	6.6 [4.4–9.9]	NA
		4,797 HIV-neg	25 [20–43]	58%	NA	783 (16%)	1.6 [5.9–13.1]	Ref	NA
Gourlay A 2012 (29)	2003–2010 Guinea Bissau	**146 HIV-2**	**56 Sd = 15**	**68%**	**31 [26–38]**[$]	**44 (30%)**	**5.7 [4.2–7.6]**	**1.9 (1.2–3.1)**	NA
		197 HIV-neg	53 Sd = 18	73%	40 [36–46][$]	28 (14%)	2.5 [1.7–3.6]	Ref	NA
Prince PD 2014 (30*)	Gambia Guinea Bissau	**1949 HIV-2**	– NA	NA	NA	**666 (34%)**	NA	**Ref**	NA
		1270 HIV-1	**– NA**	**NA**	**NA**	**586 (46%)**	**NA**	**1.9 [1.4–2.4]**	**NA**

HIV-Dual: HIV-1 and HIV-2 dually reactive individuals; **HIV-neg**: HIV-negative individuals; **NA**: not available; **Ref**: reference value; **PY**: person-years of observation. Sd: standard deviation;

[$]: CD4 count expressed in %

Table 2

Mortality and survival among people living with HIV-2 on ART.

Study Author, year	Country Population size	Median age	Men (%)	Baseline CD4 count	Follow up duration on (months)	ART regimens	Estimate of mortality	Survival Month 12
Ekouevi 2014 (34*)	Systematic review (17 studies) HIV-2 (n=976)	44 [42–48]	NR	165 [138–203]	NR	NR	37/771 (4.8%)	NR
Drylewicz 2010 (35)	West Africa (5 countries) HIV-2 (n=270)	43 [36–50]	46%	148 [77–232]	11 [6–13]	PI-based regimen (71%) (31% on boosted PI)	3/270 (1%)	NR
Benard, 2011 (36)	Europe (6 countries) HIV-2 (n=170)	46 [39–52]	51%	191 [90–275]	20 [8–36]	PI-based regimen (74%) (61% on boosted PI) 3NRTIs (26%)	Month 12: 0/170 (0%)	NR
Tchounga 2015 (37*)	West Africa (7 countries) HIV-2 (n=1825)	45 [38–52]	40%	185 [95–297]	28.8 [9.8–58.9]	PI-based regimen (66%) 3NRTIs (9%) NNRTIs-based (14%)	Month 6: 4.1% [3.2–5.1] Month 12: 5.5% [4.4–6.5] Month 24: 7.7% [6.4–8.9]	NR
Peterson 2011 (38)	Gambia HIV-2 (n=51)	42 [32–48]	37%	140 [50–310]	20 [10–33]	PI-based regimen (88%) (100% on boosted PI) 3 NRTIs (6%) NNRTI-based (5%)	64.2/1000 pyo	96% (89–100)
Harries, 2010 (39)	Burkina-Faso HIV-2 (n=91	44 [37–50]	39%	208 [103–459]	23 [8–34]	PI-based regimen (70%) (27% on boosted PI) 3NRTIS (1%) NNRTI-based (29%)	1.32 [0.80–2.17]$	NR

ART: antiretroviral therapy; **PI**: protease inhibitors; **NRTI**: nucleoside reverse transcriptase inhibitors; **NNRTI**: non-nucleoside reverse transcriptase inhibitors; **NR**: not reported; **pyo**: person-year of observation.

$: Estimate risk of mortality