HIV-2 in West Africa. Epidemiological studies
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Mortality of HIV-1, HIV-2 and HIV-1 / HIV-2 dually infected patients in a clinic-based cohort in The Gambia, West Africa

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Mortality of HIV-1, HIV-2 and HIV-1 / HIV-2 dually infected patients in a clinic-based cohort in The Gambia, West Africa

ABSTRACT

Objective: To assess and compare the mortality rate of patients with HIV-1, HIV-2 or both infections (HIV-D) in the same population.

Design: Clinic-based cohort study

Methods: HIV-seropositive subjects aged 15 years and above who attended the MRC clinics in Fajara between May 1986 and September 1997 were recruited. Clinical assessment using the Karnofsky score, CDC staging, and WHO staging, as well as CD4 counts, were done at baseline. Patients were invited to attend the clinic every 3 months; if they did not attend, they were visited at home by field workers to ascertain survival status. No patient was on antiretroviral therapy during the study period.

Results: Data from 1519 HIV-positive adult patients were analysed. Seven hundred and forty-six patients had HIV-1, 666 HIV-2, and 107 patients had HIV-D infection. Eight hundred and twenty-eight (55%) subjects died, and 161 (11%) were lost to follow up. The median follow-up time was 12 months (range 0 to 128). CD4 counts were available for 894 patients. Compared to HIV-1, the adjusted Hazards Ratio (HR) for mortality in the CD4 category ≥ 500 /μL was 0.50 for HIV-2 (95% Confidence Interval (CI): 0.28-0.88), and 1.27 (95% CI 0.51-3.7) for HIV-D. Among those with CD4 <500 /μL the mortality rates in HIV-2 and HIV-D infection were similar to that in HIV-1.

Discussion: HIV-2 infected patients with CD4 counts ≥ 500 /μL have a significantly lower mortality rate than HIV-1 infected patients. HIV-2 infected patients with advanced disease have the same poor prognosis as patients with HIV-1. Dually infected patients have mortality rates similar to HIV-1.
**HIV-2 in West Africa**

**Introduction**

Survival with the Human Immunodeficiency Virus type 1 (HIV-1) varies with age at infection, with an overall median survival of 11 years in developed countries [1]. Recent data indicate that the survival in Africa may be similar [2]. The other human immunodeficiency virus, HIV-2, is less well studied, but the available evidence indicates a longer survival for patients with HIV-2 infection [3,4].

Two community-based studies and one occupational cohort study from Guinea-Bissau found that the mortality rate of HIV-2 infected subjects was between 2.3 and 6.6 times higher than that of seronegative subjects [5,6,7]. This compares to a mortality rate ratio of 11.9 in men and 13.9 in women, comparing HIV-1 to seronegative subjects in a community-based study in rural Uganda [8].

In West Africa, where both viruses circulate, it is not uncommon for one patient to be infected with both [9]. The clinical course and the associated mortality rate of dual infection with HIV-1 and HIV-2 (HIV-D) has not been described so far, apart from a small study in Côte d'Ivoire in tuberculosis (TB) patients [10], which reported no difference in mortality rates between HIV-1 and HIV-D.

We compared the mortality rates and survival of patients with HIV-D infection with those who had HIV-1 or HIV-2 single infections, in a hospital-based cohort study. This represents a continuation of an earlier study of the same cohort [4].

**Patients and Methods**

**Patients**

The first case of HIV in The Gambia was identified in 1986. In 1995, the prevalence of HIV-1 among pregnant women was 0.5% (95% CI 0.4-0.6%), of HIV-2 1.1% (95% CI 1.0-1.2%), and of HIV-D 0.05% (95% CI 0.03-0.09%) [11]. At the clinic and hospital of
the Medical Research Council (MRC) Laboratories in Fajara, The Gambia (West Africa), subjects are tested for HIV antibodies for a variety of reasons. All blood donors and self-identified female commercial sex workers (CSWs) are routinely tested. Most patients with TB or a suspected sexually transmitted disease (STD), and partners of HIV and STD cases are tested as well. Finally, patients with a clinical presentation suggestive of HIV disease are tested. The study population therefore comprises both healthy and symptomatic patients. The clinic is situated in an urban area near the capital, but attracts patients from the rural areas as well. It is the national referral centre for HIV patients in The Gambia. Patients aged 15 years or older attending the clinic who were HIV-positive upon screening, and who gave informed consent, were included in the study. All patients were counselled before and after HIV testing.

The date of seroconversion was unknown for most patients. The date of the first positive HIV test was taken as the date of enrolment. The clinic started recruiting patients in May 1986, and enrolment for this study closed on 30th September 1997.

Patients who were tested in outside laboratories and not re-tested at the MRC (due to early death or loss to follow-up) were excluded. None of the patients is known to have been on anti-retroviral therapy during the study period. Patients with TB were treated with multidrug therapy according to the national guidelines. Prophylaxis against opportunistic infections or TB was not provided during the period of the study.

Serological diagnosis of HIV infections
Serum was screened by the Wellcozyme HIV 1+2 (Murex Diagnostics Ltd, Dartford, UK) until August 1996, and after that date by the ICEHIV-1.O.2 (Murex). If reactive, samples were re-tested by type-specific ELISA's. For HIV-1 this was the Wellcozyme HIV recombinant-1 (Murex), and for HIV-2 the Wellcozyme HIV-2 (Murex Diagnostics) from the start till April 1996, and after that the ICE*-HIV-2 test (Murex). Samples that were clearly reactive in only one type-specific ELISA were assigned a serological diagnosis accordingly. Samples positive in both ELISA's were further tested by a synthetic peptide-based strip method, Pepti-Lav 1-2 (Sanofi Diagnostics Pasteur, Marne
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la Coquette, France). We interpreted the appearance of a clear band (+) or a very clear band (++) as evidence of infection with the relevant HIV type; samples with clear or very clear lines for both virus types were considered as dually infected. A second, confirmatory serum sample, usually taken 2 to 8 weeks later, was tested in the same way. Samples with at least one positive test result, but inconclusive ELISA and Pepti-Lav results, or with insufficient serum to do all required tests, and patients with two samples having incompatible results were classified as indeterminate. A serological diagnosis was assigned by investigators unaware of the clinical condition of the patient.

PCR confirmation of dual infection

Peripheral blood mononuclear cells (PBMC’s) stored at -70 °C from patients who were serologically dually reactive, were tested by qualitative polymerase chain reaction (PCR), using methods that have been described elsewhere [12,13]. If both the HIV-1 specific PCR and the HIV-2 specific PCR signals were positive, the patient was considered as having dual infection. Cases from whom PBMC’s were not available but in whom the serological pattern was unequivocally suggesting dual infection, were also considered as HIV-D. Finally, some cases positive by PCR for HIV-1 but not for HIV-2, with unequivocal serological evidence of dual infection were considered to be HIV-D, as in HIV-D patients with advanced immunodeficiency the PCR signal for HIV-2 may disappear [14,15]. The HIV status at recruitment was used to classify patients as HIV-1, HIV-2, or HIV-D.

Clinical stage

At the first visit after a positive test result a research clinician took a history and conducted a full physical examination. All patients were given a score on the Karnofsky performance scale, ranging from 10 (moribund) to 100 (asymptomatic and well) [16]. Patients were staged according to the CDC 1993 system [17]. From 1st January 1993 patients were also categorised according to the WHO clinical staging system, ranging from 1 (asymptomatic infection, persistent generalised lymphadenopathy or acute retroviral syndrome), to 4 (AIDS) [18]. Due to limited options for investigations, most diagnoses and staging were clinical rather than laboratory-confirmed.
**CD4 measurement**

The CD4 count was estimated by FACScan (Becton-Dickinson, Oxford, UK). Lymphocyte subset measurements were started routinely in November 1988. These were performed as soon as possible after patient enrolment. In some patients a CD4 count was not available for the first visit, but for a subsequent visit. These were used as baseline CD4 count if the measurement was performed within 3 months of recruitment.

**Follow up**

Patients were invited to attend the clinic at least every three months, regardless of symptoms. Those who failed to do so were visited at home by a fieldworker to ascertain the vital status. A patient was considered lost to follow-up if the study team had no information on his or her vital status at the close of the study. The observation time of patients who were lost to follow-up was censored at the last date they were known with certainty to be alive. Observation time of patients who refused further contact with the study team was censored at the date of their refusal. The observation period closed at 31st December 1997, and we aimed to establish the vital status of all originally recruited patients at that date.

**Outcome**

The cause of death is unknown in the majority of cases, since most patients died at home. For patients who died in the MRC hospital the date of death was extracted from hospital records. For patients dying at home a field worker obtained a date of death by interviewing relatives.

**Data management and statistical analysis**

Data were entered initially in dBASE III PLUS (Ashton-Tate, CA, USA), and later in FoxPro 2.6a for DOS (Microsoft Corporation, WA, USA). Statistical analysis was done using The SAS System (SAS Institute Inc, NC, USA), and Stata version 6.0 (Stata Corporation, College Station, TX, USA).
Continuous data were compared by Wilcoxon test, or by the t-test if approximately normally distributed. Proportions were compared with the $\chi^2$ test or Fisher's exact test, as appropriate. Differences in survival were examined with Kaplan-Meier survival curves, log-rank test, and multivariate analysis by Cox regression. Significance was assessed using the likelihood ratio test.

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

**Results**

*Baseline characteristics*

A total of 1534 adult HIV-infected patients were recruited; from 642 patients (42%) of these only one sample was available for serology. There were 746 HIV-1 infected patients, 666 HIV-2 infected and 107 patients with dual infection (HIV-D); 15 patients with indeterminate HIV infection were excluded from the analysis. PBMC's were available for PCR from 82 of the 107 patients diagnosed as dually infected by serology, and in 73 of these, dual infection was confirmed by PCR. The other nine, who had advanced disease with a median CD4 count of 40/µL (interquartile range (IQR) 30 - 250), tested positive by PCR only for one of the two HIV types.

The characteristics of the patients are shown in Table 1. The annual number of recruited HIV-1 cases increased over the years, but the number of HIV-2 cases stabilised after 1993. HIV-1 infected patients were significantly younger than HIV-2 and HIV-D infected patients on first presentation ($p < 0.0001$ and $p = 0.04$, respectively). A higher proportion of HIV-2 infected patients than of HIV-1 patients were female ($p<0.001$). On average, women were 6 (95% CI 5 - 7) years younger than men at first presentation.

There were significant differences between the 3 types of infection at presentation according to the distribution of the clinical stage by Karnofsky score, by CDC and by WHO classifications ($p = 0.0007$, $p = 0.03$, and $p < 0.0001$ respectively). HIV-1 and
Table 1. Clinical and immunological characteristics of patients at enrolment

<table>
<thead>
<tr>
<th>HIV-1</th>
<th>HIV-2</th>
<th>HIV-D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>746</td>
<td>666</td>
</tr>
<tr>
<td>Number recruited by year (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>May 1986 – Dec 1989</td>
<td>36 (5%)</td>
<td>123 (18%)</td>
</tr>
<tr>
<td>Jan 1990 – Dec 1993</td>
<td>265 (36%)</td>
<td>298 (45%)</td>
</tr>
<tr>
<td>Jan 1994 – Sept 1997</td>
<td>445 (60%)</td>
<td>245 (37%)</td>
</tr>
<tr>
<td>Age, median (range)</td>
<td>30 (15 – 68)</td>
<td>35 (16 – 70)</td>
</tr>
<tr>
<td>Sex, number female (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female commercial sex workers, number (%)</td>
<td>345 (46%)</td>
<td>402 (60%)</td>
</tr>
<tr>
<td>Karnofsky, median (range)</td>
<td>70 (10-100)</td>
<td>80 (10-100)</td>
</tr>
<tr>
<td>Karnofsky ≤ 60 (%)</td>
<td>240 (32%)</td>
<td>189 (28%)</td>
</tr>
<tr>
<td>Karnofsky 70-80 (%)</td>
<td>263 (35%)</td>
<td>196 (29%)</td>
</tr>
<tr>
<td>Karnofsky 90-100 (%)</td>
<td>243 (33%)</td>
<td>281 (42%)</td>
</tr>
<tr>
<td>CDC classification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>239 (32%)</td>
<td>286 (43%)</td>
</tr>
<tr>
<td>B</td>
<td>326 (44%)</td>
<td>240 (36%)</td>
</tr>
<tr>
<td>C</td>
<td>179 (24%)</td>
<td>139 (21%)</td>
</tr>
<tr>
<td>WHO Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>179 (32%)</td>
<td>138 (39%)</td>
</tr>
<tr>
<td>II</td>
<td>23 (4%)</td>
<td>13 (4%)</td>
</tr>
<tr>
<td>III</td>
<td>230 (42%)</td>
<td>142 (41%)</td>
</tr>
<tr>
<td>IV</td>
<td>122 (22%)</td>
<td>57 (16%)</td>
</tr>
<tr>
<td>Median CD4 cell count (^3) per (\mu)L (IQR)</td>
<td>210 (70, 410)</td>
<td>325 (130, 590)</td>
</tr>
<tr>
<td>Number (%) with CD4 cell count (^3) per (\mu)L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;200</td>
<td>221 (46%)</td>
<td>128 (37%)</td>
</tr>
<tr>
<td>200-499</td>
<td>175 (36%)</td>
<td>110 (31%)</td>
</tr>
<tr>
<td>≥500</td>
<td>85 (18%)</td>
<td>112 (32%)</td>
</tr>
</tbody>
</table>

Notes: 1. Missing for four patients; 2. Collected routinely since 1\(^{st}\) January 1993 and available from 969 patients; 3. Available for 894 patients within 3 months of recruitment. HIV-D = co-infected with both HIV-1 and HIV-2. CDC = Centers for Disease Control and Prevention. IQR = inter-quartile range.

HIV-D infected patients tended to present at a similar, more advanced stage of disease than HIV-2 infected patients. CD4 counts were measured in 1126 (74%) patients, and were available within 3 months of their first presentation from 894 (59%) patients. HIV-
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2 infected patients presented with a significantly higher median CD4 count than HIV-1 infected patients (p < 0.001); there was no significant difference in CD4 count between HIV-D and HIV-1 infected patients (p = 0.3, Wilcoxon test). The median CD4 count at presentation was 330 (IQR 160-570) for women and 180 (IQR 60-370) for men (p<0.0001). The median Karnofsky score at presentation was 80 (IQR 70-90) for women and 70 (IQR 50-80) for men (p<0.0001).

Outcome

Overall 161 (11%) of patients were lost to follow-up either because they had moved or emigrated, or had refused further contact with the clinic (Table 2). There were no significant differences in the proportions lost to follow-up between the three types of infection. Those lost to follow-up were younger, more often female, more often sex workers, and had a higher Karnofsky score, better WHO and CDC stages, and a higher CD4 count (data not shown). These differences were highly significant (p < 0.001 in each case).

The median follow-up was 12 months (range 0 – 128). Four hundred and twenty three (57%) HIV-1 infected, 342 (51%) HIV-2 infected and 63 (59%) HIV-D infected patients died (Table 2). The crude mortality rate in HIV-1 was higher than in HIV-2, but similar to that in HIV-D infected patients. The survival of HIV-2 patients was significantly longer than that of HIV-1 (log rank test, p = 0.006). There was no significant difference in survival of HIV-D compared to HIV-1 (p = 0.8) or to HIV-2 (p = 0.13).

Mortality rates stratified by age and sex

When subjects were divided into four age groups, the mortality rate increased with increasing age (Table 3). This effect remained significant after adjusting for sex, CD4 count category, and HIV type: hazards ratio (HR) for patients 25 – 34 years (95% CI) was 1.44 (1.01 – 2.07; p = 0.04), for patients 35 – 44 years 1.47 (1.00 – 2.15; p = 0.05), and for patients aged 45 years and above 1.93 (1.30 – 2.88; p = 0.0012) relative to those aged 15 – 24 years.
Men had a higher mortality rate than women. This effect was significant in HIV-1 and HIV-2 (p < 0.0001 for both; p = 0.06 in HIV-D). After adjusting for age, CD4 count category, and HIV type, the HR (95% CI) for men was 1.63 (1.3 - 2.0; p < 0.0001) compared to women.

**Mortality rates by CD4 category**

Absolute CD4 cell counts were available within three months of the first visit for 894 patients. There were no significant differences between this subgroup and the total patient group in age, sex and mortality rates (data not shown). The mortality rate was inversely related to CD4 count for all three infection types. Figure 1 shows the Kaplan-Meier survival curves for patients in the high (≥ 500 cells/μL), intermediate (200 – 499 cells/μL), and low (< 200 cells/μL) CD4 categories, comparing the three types of infection. The median survival of HIV-1 subjects in the highest CD4 category was 4.9 years (95% CI 3.7 – 8.7); for HIV-2 and HIV-D the median survival could not be calculated due to insufficient data. The median survival for subjects in the lowest CD4 category was 6 months for HIV-1, 8 months for HIV-2, and 6 months for HIV-D.
<table>
<thead>
<tr>
<th>Age Group</th>
<th>HIV-1</th>
<th>HIV-2</th>
<th>HIV-D</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 – 24</td>
<td>10/43.7 (22.9 (8.7-37.1))</td>
<td>9/38.8 (23.2 (8.0-38.3))</td>
<td>0 (0.0 (--))</td>
</tr>
<tr>
<td>25 – 34</td>
<td>140/264.8 (52.9 (44.1-61.6))</td>
<td>46/152.7 (30.1 (21.4-38.8))</td>
<td>14/15.7 (88.9 (42.3-135.5))</td>
</tr>
<tr>
<td>35 – 44</td>
<td>92/124.0 (74.2 (59.0-89.3))</td>
<td>57/118.1 (48.3 (35.7-60.8))</td>
<td>14/19.8 (70.8 (33.7-107.8))</td>
</tr>
<tr>
<td>≥ 45</td>
<td>35/57.2 (61.2 (40.9-81.4))</td>
<td>69/184.0 (37.5 (28.6-46.3))</td>
<td>9/5.8 (154.2 (53.5-254.9))</td>
</tr>
<tr>
<td>Total</td>
<td>277/489.8 (56.6 (49.9-63.2))</td>
<td>181/493.7 (36.7 (31.3-42.0))</td>
<td>37/41.4 (89.4 (60.6-118.2))</td>
</tr>
</tbody>
</table>

Notes: HIV-D = co-infected with HIV-1 and HIV-2. pyo = person-years of observation. 95% CI = 95% Confidence Interval.
Table 4. Mortality rates and mortality hazards ratios of HIV-1, HIV-2, and HIV-D, by CD4, Karnofsky score, CDC stage, and WHO stage.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Mortality rate per 100 pyo (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIV-1</td>
<td>HIV-2</td>
<td>HIV-D</td>
</tr>
<tr>
<td>CD4 cat¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;200/µL</td>
<td>94.1 (80.1 - 108.0)</td>
<td>83.6 (67.8 - 99.4)</td>
<td>91.3 (52.3 - 130.4)</td>
</tr>
<tr>
<td>200-499/µL</td>
<td>20.7 (16.0 - 25.4)</td>
<td>18.4 (13.1 - 23.7)</td>
<td>29.2 (7.6 - 50.8)</td>
</tr>
<tr>
<td>&gt;500/µL</td>
<td>13.3 (8.2 - 18.4)</td>
<td>8.1 (5.0 - 11.2)</td>
<td>18.8 (3.7 - 33.8)</td>
</tr>
<tr>
<td>Karnofsky²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 60</td>
<td>162.9 (141.1 - 184.7)</td>
<td>102.4 (87.0 - 117.7)</td>
<td>152.4 (99.6 - 205.2)</td>
</tr>
<tr>
<td>70-80</td>
<td>34.0 (28.4 - 39.5)</td>
<td>24.1 (19.3 - 28.9)</td>
<td>43.6 (26.2 - 61.1)</td>
</tr>
<tr>
<td>≥ 90</td>
<td>10.0 (7.6 - 12.5)</td>
<td>7.5 (5.8 - 9.2)</td>
<td>9.3 (2.4 - 16.2)</td>
</tr>
<tr>
<td>CDC stage³</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>10.7 (8.1 - 13.3)</td>
<td>8.0 (6.2 - 9.8)</td>
<td>9.6 (3.0 - 16.3)</td>
</tr>
<tr>
<td>B</td>
<td>37.5 (32.2 - 42.8)</td>
<td>28.3 (23.4 - 33.1)</td>
<td>52.7 (33.5 - 71.0)</td>
</tr>
<tr>
<td>C</td>
<td>207 (176 - 239)</td>
<td>125 (103 - 146)</td>
<td>192 (117 - 268)</td>
</tr>
<tr>
<td>WHO stage⁴</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>7.9 (5.2 - 10.7)</td>
<td>4.2 (2.1 - 6.3)</td>
<td>--</td>
</tr>
<tr>
<td>II + III</td>
<td>37.7 (31.1 - 44.3)</td>
<td>29.9 (22.8 - 37.1)</td>
<td>42.2 (22.1 - 62.3)</td>
</tr>
<tr>
<td>IV</td>
<td>206 (167 - 244)</td>
<td>178 (129 - 226)</td>
<td>346 (171 - 522)</td>
</tr>
</tbody>
</table>

Notes: 1. data available for 894 patients; 2. data available for all 1519 patients; 3. data available for 1515 patients; 4. data available for 969 patients; 5. HR adjusted for sex and age. HIV-D = co-infected with HIV-1 and HIV-2. CDC = Centers of Disease Control and Prevention. pyo = person-years of observation. 95% CI = 95% Confidence interval. HR = mortality hazards ratio.
When adjusting for age and sex in a Cox proportional hazards regression there was little difference in mortality rates between HIV-1 and HIV-2 in the low CD4 (<200/µL) and the intermediate (200 - 499/µL) categories (see Table 4). In the high CD4 category (≥500/µL) the HIV-2 mortality rate was significantly lower than that in HIV-1 (HR = 0.50, 95% CI 0.28 – 0.88; p = 0.02). The mortality rate in HIV-D was not significantly different from that in HIV-1 in any of the categories, but was significantly higher than that of HIV-2 in the high CD4 category (p = 0.04).

Mortality rates by Karnofsky score

Karnofsky scores were divided in three categories (≤ 60, 70 - 80, and 90 - 100), according to tertiles. Mortality rates were inversely related to Karnofsky category in all
three infection types (Table 4). They were lower for HIV-2 than for HIV-1 in all three Karnofsky categories; the overall hazards ratio adjusted for age, sex, and Karnofsky score was 0.75 (95% CI 0.64 – 0.87; p < 0.0001). The HIV-D mortality rate was similar to that of HIV-1 in all strata, and the overall hazards ratio of HIV-D relative to HIV-1 was 1.09 (95% CI 0.83 - 1.42; p = 0.5).

Mortality rates by CDC clinical stage

CDC clinical stage was associated significantly with mortality rates in all three infection types (Table 4). The overall hazards ratio, adjusted for sex, age, and CDC stage, of HIV-2 relative to HIV-1 was 0.76 (95% CI 0.65 – 0.88; p = 0.0003). HIV-D mortality rates were similar to those of HIV-1 in each stratum; the overall hazards ratio adjusted
Fig 1c, Kaplan-Meier survival graph comparing HIV-1, HIV-2, and HIV-D in patients with CD4 < 200/µL.

<table>
<thead>
<tr>
<th></th>
<th>Number at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1</td>
<td>221</td>
</tr>
<tr>
<td>HIV-2</td>
<td>128</td>
</tr>
<tr>
<td>Dually infected</td>
<td>29</td>
</tr>
</tbody>
</table>

for sex, age, and CDC stage, of HIV-D relative to HIV-1 was 1.19 (95% CI 0.91 - 1.55; p = 0.2).

Mortality rates by WHO clinical stage

WHO clinical stage at baseline was available for only 930 patients (61%), as this information was only recorded since 1993. Stage was significantly associated with mortality rates in HIV-1 and HIV-2; for HIV-D not enough data were available (Table 4). The overall hazards ratio of mortality rate of HIV-2 relative to HIV-1 was 0.72 (95% CI 0.61 – 0.84; p < 0.0001); and for HIV-D relative to HIV-1: 1.07 (95% CI 0.87 – 1.40).
Restricting analysis to PCR proven HIV-D
We repeated the analyses restricting the group of HIV-D to those with PCR confirmed dual infection status (n = 73); the results were similar to those in the main analysis (data not shown).

Discussion

This is the largest comparative survival study of HIV-1, HIV-2 and HIV-1/HIV-2 dual infection. We found that among patients with CD4 count of 500 cells/µL or higher, those infected with HIV-2 have a significantly lower mortality rate than HIV-1 or HIV-D infected subjects. In the low CD4 range (< 200/µL) there appears to be no difference in mortality rates between HIV-1, HIV-2, or HIV-D. Mortality rates appear to be similar between HIV-1 and HIV-D in all CD4 categories. Mortality rates were significantly higher among older patients (after adjusting for sex, CD4 count, and HIV type), and among males (after adjusting for age, CD4 count, and HIV type). The Karnofsky performance status was a very good predictor of mortality.

To overcome the problem of unknown time since infection, we decided to stratify HIV patients by CD4 count. This is not ideal, as some patients are known to progress to low CD4 counts rapidly and others appear not to progress for > 10 years, both in HIV-1 [19], and in HIV-2 [20,21]. One cannot assume that the time since infection was similar for HIV-1 and HIV-2 patients. The resulting bias will lead to an underestimation of the difference in mortality rates between the two infections [22]. In the same way, a real difference between HIV-1 and HIV-D could exist, although we were unable to detect it. In seroprevalent cohort studies subjects can be categorised into CD4 strata or clinical stages [23,24]. Although the CD4 count does not indicate time since infection, it indicates disease progression, and is a more reliable predictor of AIDS and death in HIV-1 than time since infection [25]. The high CD4 category
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comprises Long-Term Non-Progressors (LTNPs) and recently infected subjects in an unknown case-mix.

We used the HIV serology at enrolment to assign patients to the HIV-1, HIV-2, or HIV-D group. In some patients seroconversion from single infection to HIV-D may have occurred. As HIV-2 has been prevalent for longer than the more recently introduced HIV-1 [26] we assume most seroconversions will have been from HIV-2 → HIV-D. We decided to ignore these seroconversions. This may have lead to a dilution of the differences between HIV-2 and the other two types of infection, and therefore the differences that we found may be underestimates.

Routine CD4 counts were started in November 1988, 2.5 years after the beginning of the study. Reasons for lacking CD4 counts of patients recruited after that date were rapid clinical deterioration and death, early loss to follow-up, non-attendance, or the FACScan being temporarily out-of-service. CD4 counts are lacking from a larger proportion of HIV-2 than HIV-1 patients (p = 0.00005). Those missing data have reduced the power of the study and led to a different distribution of patients among the HIV infection types. However, as CD4 count was the key stratifying factor, it is unlikely to have caused bias.

The losses to follow-up were limited to 11%. Those lost to follow-up were less ill and had a higher CD4 count than those who remained in the study. As the main predictor of death was CD4 count, and the analysis was stratified by CD4 count, the loss to follow-up has reduced the power of the study marginally in the high CD4 category, but is unlikely to have introduced much bias.

There is broad agreement that in some patients HIV-2 can be pathogenic and can cause immunodeficiency and AIDS. However, the excess mortality risk of HIV-2 infected subjects compared to HIV negative subjects appears to be limited [5,6,7]. Because the proportion of HIV-2 subjects in the high CD4 category is much larger in the population at large than in our study population, the contrast between HIV-1 and
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HIV-2 is most appropriately characterised by the differences found in the high CD4 category. The significantly lower mortality rate in HIV-2 in that category (hazards ratio = 0.5, p = 0.02) is compatible with findings of limited excess mortality among HIV-2 infected people [5,6,7]. Our finding that people in the advanced stage of infection (CD4 < 200/μL) have the same high mortality rate, irrespective of HIV type, suggests that HIV-1 and HIV-2 run the same course once the immune system is severely affected. The finding that the prognosis for subjects with CD4 counts ≥ 500/μL is better for HIV-2, coupled with the identification in community-based studies of many old and healthy HIV-2 infected subjects with normal CD4 counts [5,27], suggests that a substantial proportion of HIV-2 infected subjects is not harmed by the infection; others may experience a disease course which is indistinguishable from that of HIV-1.

HIV-D infected patients had a mortality rate similar to HIV-1 in all CD4 categories, although a non-significant trend to worse survival was seen in the category of CD4 ≥ 500/μL. The power to detect significant differences in survival between HIV-1 and HIV-D was limited: given the number of deaths, the study had 90% power to detect as statistically significant a hazards ratio (comparing HIV-D to HIV-1) of 1.56 or greater. Therefore smaller differences cannot be excluded. The poor survival of HIV-D suggests that preceding HIV-2 does not act as a ‘vaccine’ mitigating the disease course of subsequent HIV-1 infection.

The CASCADE study showed that in HIV-1 age at infection is strongly predictive of mortality [1]. In our sero-prevalent study age at enrolment was also significantly associated with mortality. The CASCADE study did not find a significant difference in survival between men and women, nor did several other cohort studies of HIV-1 in Africa [8,28,29], but in our study men had a significantly higher mortality rate than women in both HIV types. Even after adjustment for CD4 count category, HIV type, and age, the mortality hazards ratio for men relative to women was 1.63 (95% CI 1.3 – 2.0). In an occupational cohort study in Tanzania men with HIV-1 had a mortality rate almost twice that of women [30]. In our study men were at a much more advanced stage of infection than women, and perhaps adjusting for CD4 count did not capture
that difference fully. Other potential reasons for this higher mortality rate among males, such as higher viral loads, should be further examined.

The WHO clinical classification does not require sophisticated laboratory support; it is a scoring system taking into account a wide range of clinical conditions. It has been used with success in research settings [23,24], but it is unclear how widespread its use is in general hospitals or health centres. The Karnofsky index is a simple clinical assessment that is made without the need for a laboratory, and which was originally created to assess the prognosis of patients with cancer [16]. It correlated remarkably well with mortality rates, and may be a simple and useful tool for routine clinic settings and home care to classify HIV positive patients.

In conclusion, this study confirms that HIV-2 infection is associated with a lower mortality rate than HIV-1, but shows for the first time that this difference is limited to patients with CD4 counts above 500/μL. Earlier studies demonstrated the lower heterosexual [31,32] and the lower perinatal transmission [11,33]. Asymptomatic HIV-2 patients should be counselled that they have a better prognosis, that they not necessarily get AIDS, and that the risk of transmitting the infection to an infant is much smaller than in HIV-1. Infection with both HIV-1 and HIV-2 carries the same prognosis as single HIV-1 infection.

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References


