HIV-2 in West Africa. Epidemiological studies
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Conclusions
Introduction

This thesis investigates the epidemiology of HIV-2 infection in The Gambia and Guinea-Bissau. In this last chapter the key findings of the preceding chapters are summarised, put into context and some conclusions will be drawn. The themes are: trends in HIV-2 incidence and prevalence, the cause and maintenance of the HIV-2 epidemic, risk factors for infection, interactions with HIV-1, mortality, the role of plasma viral load, host versus viral factors to explain pathogenesis, HIV-2 infection in children, treatment and HIV-2 vaccines. Finally, four questions that are still open and deserve further research will be identified.

Prevalence and incidence of HIV-2

All studies from West African countries have shown stable or declining prevalences of HIV-2 in diverse populations: female commercial sex workers [1-7], an occupational cohort [8], pregnant women [6, 8, 9, 10], STD patients [11, 12], and the general population [13]. Three cohort studies reported incidence rates over different time periods; among commercial sex workers in Dakar the incidence was stable [4] and in an occupational cohort and in a peri-urban community in Bissau the rates were falling over time in men and stable in women [8, 13].

Chapter 3 compared the HIV-2 prevalence among pregnant women attending antenatal clinics in The Gambia in 2000-1 with the prevalence in a similarly defined population in 1993-5. A non-significant decline of 0.2% (from 1.0% to 0.8%) was observed, in line with the trends seen elsewhere. Chapter 4 estimated the HIV-2 incidence in a rural community in Guinea-Bissau at 4.8 (95% confidence interval (CI) 3.7-6.4) per 1000 person-years of observation (pyo). This is a low incidence in view of the high prevalence of around 8.0% in adults. Although the overall prevalence did not change, the prevalence among young people (< 45 years) had decreased from 5.9% to 4.8% (p = 0.10), and the prevalence among people aged 45 years or above had increased from
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11.8% to 14.8% (p = 0.04) between two rounds of cross-sectional studies (1989-91 and 1996-8), suggesting a cohort effect [unpublished data]. Mathematical modelling is underway to explore this phenomenon in more detail. Because all these studies report stable or declining prevalences in West Africa, and because no new HIV-2 epidemics have been observed outside West Africa, [chapter 2] we can conclude that HIV-2 is not an "emergent epidemic", but an epidemic in decline.

Cause and maintenance of the epidemic

This raises one of the fundamental, still unanswered questions about HIV-2: which events created the epidemic, and what has changed so that the epidemic is no longer sustained? HIV-2 is genetically close to the Simian Immunodeficiency Virus of the sooty mangabey (SIV_{sm}) [14], a monkey. The natural habitat of the sooty mangabey (Cercopithecus torquatus atys) is West Africa. Based on the large degree of genetic homology, the geographic overlap, and the fact that human-monkey contacts are common in West Africa, most researchers maintain that SIV_{sm} is the source of HIV-2 [15]. In a phylogenetic tree SIV_{sm} and HIV-2 are not separate branches; most subtypes of HIV-2 cluster closer to specific strains of SIV_{sm} than to each other [16, 17]. Therefore it is assumed that the 7 different clades of HIV-2 [18, 19] represent at least 7 different zoonotic events. All subtype A strains are thought to be derived from one such zoonotic event.

HIV-1 is genetically related to SIV_{cpz}, a virus of chimpanzees. The habitat of chimpanzees in West-Central Africa overlaps with the area of the greatest diversity of HIV-1, and there appears to be increasing human-primate contact, partly by hunting. In phylogenetic analyses some strains of SIV_{cpz} are closely related to HIV-1 [20]. Because of these reasons it is generally assumed that HIV-1 has originated from SIV_{cpz} [20, 21]. The exact details of this zoonotic event are unknown and are controversial [22, 23]. By using mutation rates of the viral genome as a molecular clock, back-calculations estimated the timing of the original transmission from chimpanzee to human at about 1930 [24, 25].
Recently this has been done for HIV-2 as well. Based on partial sequences of 33 samples the most likely date of the zoonotic event giving rise to the HIV-2 subtype A epidemic was estimated to be 1940 (± 16 years) [26].

Assuming that one person or a few persons became infected with HIV-2 clade A through contact with a sooty mangabey, it is still unclear how this led to an epidemic. It is theoretically possible that the virus used to be more virulent than it is now, but this is unlikely: there is no record of an epidemic of slim disease in West Africa prior to 1985. So, if we assume that the virulence of the virus has not substantially changed over time, there must have been an increase in transmission that amplified a small outbreak into a large epidemic. This could have been due to an increase in unscreened blood transfusions on a large scale, high rates of sexual partner change, many concurrent sexual partnerships or presence of co-factors enhancing sexual transmission like sexually transmitted infections (STI's), or unsterile injections. Several of these factors may have been present at the same time in Guinea-Bissau.

From 1963 to 1974 a bloody war of independence was fought, and a large colonial Portuguese army was present in Guinea-Bissau. During the war many blood transfusions may have been given. Commercial sex may have flourished around the barracks, and STI prevalence was probably high; this is usually seen in wars. In a cross-sectional study among older residents of Bissau it was found that sex with a white man was an independent risk factor for women for HIV-2 infection [27]. As there were very few white men in the country after 1974, this was seen as a proxy for sex with a soldier. Those having served in the army and having had blood transfusions in the 1960s tended to have a higher prevalence of HIV-2 [27]. The authors concluded that the independence war may have been critical for the propagation of HIV-2 through sex work and blood transfusions, and that, once established, sexual relations maintained the epidemic. This could also explain why HIV-2 is only really common in Guinea-Bissau (up to 8% of adults) and nowhere else. In most of West Africa there was peace in the 1960's and 70's, with the notable exception of Nigeria in 1967-70. The hypothesis that the war was responsible for the amplification of the epidemic fits also with the
observations in Caio and Bissau that the highest prevalence is found in people who were young adults in the war years, and that the prevalence in later generations is lower. The transmission of the virus may not be efficient enough to maintain ongoing epidemic spread in the absence of important amplifiers like frequent commercial sex, high levels of STI's, and unscreened blood transfusions.

Marx hypothesised that reuse of unsterilised needles may have been responsible for both the HIV-1 and HIV-2 epidemics [15]. In West Africa various mass vaccination and treatment campaigns against yaws, yellow fever, and small pox were conducted in the final decades of the colonial era [28], and these may have been responsible for mass inoculations with HIV-2. There is no proof for this and it does not explain why HIV-2 became epidemic in Guinea-Bissau and nowhere else.

Risk factors

Chapter 3 examined risk factors associated with prevalent HIV-2 infection among pregnant women in The Gambia. This study was limited by the sentinel surveillance format and could examine very few risk factors. It found recruitment at one particular site in The Gambia (Sibanor) and higher parity to be significantly associated with HIV-2 infection. Parity can be interpreted as a proxy for years of sexual experience, as use of contraceptives is very low in The Gambia [29]. Chapter 4 examined risk factors for incident infection among adults in Caio. Even though the study identified only 51 sero-incident HIV-2 infections, it is the world's largest study of incident HIV-2. It found that blood transfusions after 1989 were not a risk factor, and all persons who became infected had had sexual intercourse. Among women mobility, having been divorced, having had vaginal discharge, having serologically defined active syphilis were significant independent risk factors, confirming earlier cross-sectional studies identifying these as risk factors [1, 12, 30-38]. These risk factors are similar to those identified for HIV-1 infection. Having drunk alcohol on the day of the interview was also significantly associated with HIV-2 infection, as was a history of injections in the 12 months
preceding the interview and sample. The latter may have been a cause or a consequence of HIV-2 infection, so caution is needed in interpreting this association. In men, age below 30 years and serological evidence of active syphilis were significant risk factors for HIV-2. In men injections outside a clinic setting were also significantly associated with HIV-2 infection. The same caution as mentioned earlier for women is needed to interpret this finding.

HIV-1 and HIV-2 interactions

*Dual infection*

After type-specific antibody tests became available, it became clear that both HIV-1 and HIV-2 circulated in West Africa. Samples of some people in West Africa showed dual serological reactivity, and it was not clear whether this was mainly due to antibody cross-reactivity, dual infection, or an infection with a third, unknown virus [39]. Quite early it was demonstrated by PCR that dual infection with both HIV-1 and HIV-2 did occur [40, 41]. Later improvements in PCR techniques showed that a large proportion of people with dually reactive samples (up to 86%) is truly dually infected [42, 43].

*No protection against HIV-1 infection*

In 1995 Travers et al. reported that HIV-2 seemed to offer protection against subsequent HIV-1 infection in a cohort of commercial sex workers in Dakar [44]; this caused excitement and hope [45]. Several research groups in Guinea-Bissau [8, 46], Cote d'Ivoire [47, 48] and our group in The Gambia [49] examined this putative effect in other cohorts. None of the seven analyses so far have been able to reproduce this finding. One of our own studies (Chapter 5) even found that HIV-2 was a significant risk factor for HIV-1 infection. An editorial in *AIDS* concluded that the available epidemiological data do not support a protective effect of HIV-2 infection upon incident HIV-1 infection [50]. The investigators of the cohort in which the original finding was made, have provided no updates of the effect in that cohort since 1999 [51-53], so it is unknown whether the effect in that cohort persisted, or declined over time, or even reversed.
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No protection against disease progression

Gambian clinicians had the impression that HIV-1 and HIV-2 dually (HIV-D) infected patients had a more rapid disease progression than HIV-1 singly infected patients. Others, noting a lower plasma HIV-1 viral load in dually infected patients, [54] hypothesised a partially protective immune response of one virus against the other, presumably leading to a milder disease course. Some studies assessed survival of HIV patients with TB, and found that the mortality rates among HIV-D infected patients were significantly higher than among HIV-2 infected patients and similar to those among HIV-1 patients [55-57]. These studies were restricted to patients with TB, and the follow-up periods were short. In a community-based study in Bissau, no significant difference in mortality between HIV-1, HIV-2 and HIV-D infected subjects was found, but the numbers with HIV-1 and HIV-D in this study were very small (26 and 20, respectively) [58].

Chapter 6 is the first published long-term study analysing the survival and mortality of subjects with dual HIV infection, regardless of a TB diagnosis. Among patients of the genito-urinary (GU) clinic in Fajara, The Gambia, the mortality rate of dually infected patients was similar to that of HIV-1 infected patients, and worse than that of HIV-2 infected patients. This was true overall, and after adjusting for baseline CD4 count. A study among a subset of this cohort found that the plasma viral load of HIV-D infected patients was similar to that in HIV-1 singly infected patients [59]. These data do not support suggestions that HIV-2 infection could mitigate the course of HIV-1 infection.

HIV-1/HIV-2 recombination

If a person is infected with two or more subtypes of HIV-1, these can recombine their genomes to form new strains of HIV-1, and these can be transmitted [60-63]. Some of the recombinant strains are successful in spreading, e.g. CRF01_AE in Thailand and CRF02_AG in West Africa [64]. Recombinations of the genetically rather distant groups O and M have been described [65-67], but so far no recombinations of HIV-1 and HIV-2 have been reported. It is unclear whether this is biologically possible or plausible [68,
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69] and if so, what the epidemic potential of such a recombinant would be. A search for possible HIV-1/HIV-2 recombinant should be done in populations where both viruses circulate in relatively high frequencies, e.g. in the general population of Bissau [8] or Caio [Chapter 4], or among commercial sex workers in Abidjan [48].

Mortality of HIV-2 infected subjects

One of the first epidemiological studies on HIV-2, conducted in Bissau in 1987-1988 [31], showed that the mortality associated with HIV-2 infection was much lower than that usually found in HIV-1 infection. All subsequent studies have confirmed this [70-73]. Chapters 6 and 7 examined adult all-cause mortality in HIV-2 infected people and compared this with that found in HIV-1 infected people. The analysis in the seroprevalent clinical cohort [Chapter 6] demonstrated a lower mortality in HIV-2 patients than in HIV-1 patients, but found that this lower mortality was limited to those with a normal CD4 count (> 500/μl). Among those with a CD4 count < 200/μl the mortality rate was similar between HIV-1 and HIV-2 infected subjects. This could be explained in two ways. The first possibility is that all HIV-2 infected subjects experience a deterioration of their immune system, but this decline is slower than in HIV-1 infection. Once the CD4 count has declined to < 200/μl, patients are at high risk of fatal opportunistic infections and there is no difference in mortality; only the time to reach this low CD4 is longer for HIV-2 infected than for HIV-1 infected subjects. The other possibility is that those with HIV-2 infection fall in either of two categories: those whose immune system is not affected at all by the infection, and those whose immune system is damaged by the infection, at a rate similar to HIV-1.

If the first explanation is right we would expect that old people with HIV-2 would have lower CD4 counts than young people, as on average they will have been infected for longer. There was some indication of lower CD4% in older HIV-2 infected individuals in Caio (r = -.017; p=0.06) [73], but a study from Bissau did not find this (r = -.0038; p>0.05) [74]. This could be examined in other cohorts in West Africa.
If the second explanation is correct, then we would expect a relatively high excess mortality among recent seroconverters, and a limited excess mortality among people who seroconverted long ago. There are too few people with known date of seroconversion to analyse this, but if age is taken as a proxy for time since infection, then this can be examined in a seroprevalent cohort. Two studies so far found that the mortality rate ratio of HIV-2 infected vs. HIV uninfected subjects was higher in the young (<45 years) than in older people and that in older people the rate ratio was not significantly different from one [70, 71]. Due to a higher background mortality in older people the rate ratio is expected to decline even if the rate difference between infected and uninfected subjects is similar to that observed in younger age groups. This question is unresolved, and we are currently investigating this with a survival analysis over a 12-year period in the Caio population.

Role of plasma viral load

Both sexual transmission [75] and mother-to-child transmission (MTCT) of HIV-1 are to a large degree determined by plasma viral load [76]. Transmission rates of HIV-2 are lower than of HIV-1 [Chapter 2]. A large Gambian study showed that the lower transmission from mothers to babies can be explained by the difference in plasma viral load between the two infections [77]. It is likely that the same holds true for heterosexual transmission, but no data have been published so far to support this.

Several studies, both in sero-incident and in seroprevalent cohorts, have shown that baseline plasma viral load is an important independent predictor for survival in HIV-1 [78-80]. Survival with HIV-2 infection is better than with HIV-1 [31, 70-72, 81-84, chapter 6]. Chapter 7 shows that this can be explained by the lower plasma viral load in HIV-2: plasma viral load at baseline was significantly associated with the mortality rate in HIV-2 infected women. In a multivariable model of all HIV infected women (both those with HIV-1 and those with HIV-2) that included plasma viral load, CD4%, HIV-
type and age, virus type per se was not a significant predictor of mortality, but plasma viral load was. This is in agreement with findings of a clinic-based study from Senegal, which found that plasma viral load, regardless of HIV type, predicts the rate of CD4 cell decline [85]. These data indicate that plasma viral load is a more important marker for disease progression than HIV type.

**Host and Virus**

The lower transmission, morbidity, and mortality associated with HIV-2 can thus in part be explained by the lower plasma viral load. HIV-2 infection can occasionally lead to very high plasma viral loads in humans, but this is rare [59, 77]. SIV<sub>sm</sub>, the presumed recent ancestor of HIV-2, grows to very high titres in its natural host without causing a marked CD4 cell depletion or disease [86-88]. Infection with SIV<sub>sm</sub> leads to both humoral and cellular immune responses in sooty mangabeys, but these do not reduce the plasma viral load to low or undetectable levels [87]. This indicates that a high plasma viral load alone is not enough to lead to immunodeficiency; differential host responses to SIV/HIV infection are important as well [87, 89].

It has been hypothesised that the reason for the generally lower plasma viral load is that HIV-2 induces a more vigorous and effective immune response than HIV-1 [90]. Based on this hypothesis our group has conducted detailed studies to map differences in proliferative responses and cytotoxic T lymphocyte (CTL) responses between HIV-1 and HIV-2 infected people at similar, moderate levels of immunodeficiency; so far no obvious differences have been found [unpublished studies, 91].

Integrated viral DNA (provirus) is the source of all plasma virions. HIV-2 infected patients have DNA viral loads similar to those in HIV-1 patients [85, 92-94], but the plasma concentration of virions is lower in HIV-2 infection [95]. This could be explained in several ways. Perhaps a larger proportion of HIV-1 proviruses is actively replicating [85]. Another possibility is that in HIV-1 more DNA is integrated and
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replication-competent compared to HIV-2 [85]. It is also possible that in HIV-1 infection increased proviral DNA levels exist in other compartments than blood [85]. Finally, it may be that HIV-2 virions are cleared more efficiently.

HIV-2 in children

Chapter 8 presents the first long-term observational study of children with perinatally acquired HIV-2 infection. The study reports all-cause mortality but was not able to compare morbidity patterns. The median follow-up time was 6.6 years. Three out of eight HIV-2 infected children died (38%) compared to 12 out of 17 HIV-1 infected children (71%) and 40 out of 448 children of HIV uninfected mothers (9%). The mortality rate of HIV-2 infected children was significantly higher than that of uninfected children (p=0.02), but the difference with HIV-1 infected children did not reach statistical significance (p=0.08). The numbers are small and it is hard to draw firm conclusions. Survival among children with HIV-2 infection may be similar or better to that in HIV-1 infected children. Mortality among children with HIV-2 appears to be higher than in seronegative children. These data suggest that children with HIV-2 infection need the same care as HIV-1 infected children. Unfortunately specific medical care for HIV infected children in Africa, the part of the world with >90% of all cases [96], is almost non-existent.

Treatment

None of the studies in this thesis have examined treatment of patients with HIV-2, and none of the participants in these studies were treated with antiretrovirals. The recent debate and activism about access to treatment for HIV infection has brought this treatment closer to reality for patients in Africa. There are few data on treatment of HIV-2 with antiretrovirals from the developed world [97-102], and some studies from pilot projects of antiretroviral treatment in Africa [103, 104]. From pharmacological
studies it is known that nevirapine and other non-nucleoside reverse transcriptase inhibitors are not effective against HIV-2 [105,106]. HIV-2 may be more sensitive to some protease inhibitors [107]. Resistance to antiretroviral drugs may develop [100, 108, 109], sometimes due to the same mutations that confer resistance to HIV-1 strains [99, 108].

There are no guidelines for treatment of HIV-2. Current guidelines for the treatment of HIV-1 in adults advise to start highly active anti-retroviral therapy (HAART) if the patient is symptomatic or if the CD4 count is ≤ 200 cells/μl [109-111]. Asymptomatic patients with a CD4 count of more than 350 cells/μl, should defer treatment. There is a grey zone for asymptomatic patients with CD4 counts between 200 and 350 cells/μl. In that range treatment decisions depend on the rate of decline of CD4 count, the potential for adherence, and the plasma viral load. If the PVL is higher than 50,000 – 100,000 copies/ml treatment may be considered irrespective of the CD4 count or presence of symptoms [110].

In view of the similar mortality rates of HIV-1 or HIV-2 infected patients with low CD4 counts (<200 cells/μl), [chapter 6] and the predictive power of plasma viral load for CD4 decline [85] and mortality in HIV-2 [chapter 7], it is proposed to use the same criteria for the start of HAART in HIV-2 as in HIV-1. In practice this would mean that only a minority of HIV-2 infected persons in the community would need treatment. Based on the CD4 and PVL data from the perinatal study (chapter 7), and ignoring symptomatology, 5% of HIV-2 infected women would qualify for treatment at recruitment. Based on data of a community-based study in Caio, Guinea-Bissau [73], 7% of HIV-2 infected adults would qualify for treatment. (In a clinic setting, where more subjects with advanced disease are found, these numbers are different. Data from the GU clinic in The Gambia [59, Chapter 6] indicate that 43% of newly registered HIV-2 infected patients meet the CD4 and PVL criteria for treatment). As more trials and projects on HAART are started in Africa, [112] studies should be done comparing the treatment response of HIV-2 infected patients with that of HIV-1 infected patients. This will help formulating rational policies for management of patients with HIV-2, and may
provide valuable insights into the mechanisms of immune reconstitution in HIV-2 infection.

**Vaccines**

Africa needs an AIDS vaccine [113]. In spite of increased investment into vaccine research, including clinical trials in Africa (Uganda and Kenya) an AIDS vaccine is still far away [113, 114]. It is possible that vaccines need to be specific to the clade of the virus, and perhaps even to the HLA type of the host. It is doubtful whether sterilising immunity is feasible at all, so a vaccine preventing disease, not infection, may be the best achievable.

In view of the above, it is unlikely that a vaccine against HIV-1 infection or disease would prove effective against HIV-2. This means that HIV-2 specific vaccines are needed. Large trials are needed to demonstrate the effectiveness of a preventative vaccine [115]. Because the incidence of HIV-2 is low, even in high prevalence areas [Chapter 4], a preventative HIV-2 vaccine trial needs to be quite large. Assuming a high incidence of 5 per 1000 pyo [Chapter 4], a trial that is able to show at least a 75% efficacy against HIV-2 infection needs to follow up over 3000 subjects for three years (see Table 1). If a lower incidence rate is assumed, which is more realistic in view of the observed trends, and a higher power and shorter follow-up period are chosen, the trial size increases to nearly 10,000 subjects. That is a large and very expensive trial.

**Remaining questions and further research**

Soon after HIV-2 was first described it became clear that this virus was less pathogenic and less transmissible than HIV-1, and that its spread and potential spread were more limited. Since then attention for the HIV-2 epidemic has waned. Among the more than 8,000 abstracts of the Barcelona AIDS conference in 2002, less than 1% contained the
Table 1. Sample sizes for HIV-2 preventative vaccine trial

<table>
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<th>Expected vaccine efficacy</th>
<th>Power</th>
<th>HIV-2 incidence rate in control group, per 1000 pyo</th>
<th>HIV-2 incidence in intervention group, per 1000 pyo</th>
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All scenarios are based on 0.05 significance level, 10% loss to follow up per year, and equal numbers of subjects in intervention and control arms. pyo = person-years of observation.

word HIV-2. This does not mean that all relevant research has been done. I conclude with four important questions that are worthwhile to be examined. The first one is of historic public health relevance, two others impinge on retroviral pathogenesis in general, and the fourth concerns the clinical management of HIV-2.

1. Why did a zoonotic event lead to an HIV-2 epidemic in Guinea-Bissau and why is this epidemic in decline now?

In recent decades several animal pathogens jumped the species barrier and caused epidemics in humans (among others: HIV-1, HIV-2, the corona virus causing
SARS, Ebola virus, prions). In the case of HIV-1 and HIV-2 some widely discussed hypotheses have held medical interventions responsible for the epidemics. It seems important to elucidate the origin of these epidemics, whether that means confirming or rejecting these hypotheses. Larger scale phylogenetic analyses than have been done so far, and epidemic modelling studies that try to fit the existing data can contribute to answering this question.

2. Which proportion of people that are HIV-2 infected develop immunodeficiency, or AIDS, and die prematurely?

This proportion needs to be known in order to better understand the pathogenesis of HIV-2 infection, to inform patients about their prognosis, and to help identify factors that may determine non-progression. Long-term follow-up of sero-converters is needed to answer this question. There are few such cohorts and all are small; only collaboration between research groups in West Africa could help to answer this question.

3. Why does HIV-2 infection usually not lead to high plasma viral loads, in spite of proviral loads similar to HIV-1? Is this due to aspects inherent to the virus, or is it due to a more efficient immune response?

This question could be examined by detailed comparative virological and immunological studies in populations where both viruses circulate.

4. Is the virological, immunological, and clinical response of HIV-2 infected people to highly active antiretroviral therapy similar to that in HIV-1 infected people?

In order to establish effective, evidence-based treatment regimens for HIV-2 disease, clinical trials and cohort studies of antiretroviral therapy should be conducted in West Africa, and in Portugal or France.
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