(Molecular) epidemiology of HIV-1, HIV-2 and HTLV-1 in Guinea-Bissau
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Guinea-Bissau

Guinea-Bissau is a small country in West Africa, with a surface area of 36,125 km$^2$, comparable to that of the Netherlands (37,354 km$^2$) (Figure 1) [1]. It has approx. 1,600,000 inhabitants, with 25% of the people living in the capital, Bissau. There is a great ethnic variety and the most frequent ethnicities are the Balante, Fula, Mancanha, Pepel and others, including the Manjago. Guinea-Bissau gained independence from Portugal in 1974 after a long War of Independence (1963 – 74). The most recent war in the country was the civil war in 1998 – 99. Guinea-Bissau is one of the poorest countries in the world [2] and the child mortality is estimated to be 12% and the life expectancy is 48 years [3]. The main employment is in the agricultural sector and the main export product is cashew nuts [3]. Most people live below the poverty line in Guinea-Bissau.

Figure 1 | Map of Africa with magnification of Senegambia and Guinea-Bissau. Illustration by Matt Cotten.
The Caió field station

The setting of this thesis is Caió, a village on the North-western coast of Guinea-Bissau which consists of 10 settlements that are dispersed among cashew and palm tree forests and rice fields. Approximately 10,000 people live in Caió and more than 95% belong to the Manjago tribe. Most people are subsistence farmers. Animism is the main belief system, in which traditions and ceremonies play an important role in everyday life. The Caio population is very migratory and people, often men, frequently travel for work purposes, education, to visit relatives or attend funeral and religious ceremonies. While most people travel within the West African region, there is also emigration to Europe, notably Portugal, France and Spain.

The research project in Caió was initiated in the late 1980s when a physician noticed in a clinic in Ziguinchor (Cassamance, southern Senegal) (Figure 1), that many HIV-2 infected women originated from Caió. This led to the start of the first HIV survey and census of the village by a team from the Medical Research Council (MRC) in Fajara, Gambia. An old building, formerly a shop with wooden benches, was installed as ‘the laboratory’. In 1993, the Bandim Health Project (BHP) intensified ties with the Caió field station and a census system and database very similar to the ones used at the BHP, were implemented in Caió. Strong managerial and scientific collaborations have existed between the MRC field station and the BHP ever since.

Several infectious disease studies have been conducted in Caió by or in collaboration with the field station (Table 1). Most of these studies were either led or supervised by Prof. Hilton Whittle. The main focus of the Caió research has been the natural course of HIV-2 infection. A unique community cohort has been set up; HIV-2 positive individuals were identified during the community surveys and were not selected from a clinic, thereby avoiding a selection bias of ill individuals.

Besides the scientific work, the field station also plays an important role in the community. There is good contact with the village elders, important men and women with leading roles in the community. The project’s vehicle serves as an ambulance when patients from the (government run) primary health care centre in the village’s centre, need to be transported to the hospital in Canchungo, 30 km from Caió. The laboratory facilities are also used for diagnostics for patients from the health care centre.

Three retroviral epidemics in Guinea-Bissau: HIV-1, HIV-2, HTLV-1

Three human retroviruses circulate in the population in urban and rural Guinea-Bissau; Human Immunodeficiency Virus (HIV) type 1 and 2 and Human T cell Lymphotropic Virus type 1 (HTLV-1). These viruses are all zoonoses, infections that at some point have been transmitted from monkey to man (and perhaps vice versa). HTLV-1 was the first retrovirus isolated from humans in 1979 by Robbert Gallo et al. (24) and is thought to have circulated in the human population for at least 20,000 years (25). HIV was isolated for the first time in 1983 and HIV-2 in 1986, the latter from a patient...
Table 1 | Studies conducted in Caió, Guinea-Bissau, 1988 – 2010

<table>
<thead>
<tr>
<th>Study year</th>
<th>Study</th>
<th>Study subjects</th>
<th>Principal investigator(s)</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1989 – 1991</td>
<td>First HIV/HTLV serosurvey</td>
<td>Adults ≥ 15 years of age</td>
<td>A. Wilkins</td>
<td>[5-6]</td>
</tr>
<tr>
<td>1991</td>
<td>First case-control study</td>
<td>HIV+ and HIV- adults</td>
<td>D. Ricard</td>
<td>[7-8]</td>
</tr>
<tr>
<td>1992</td>
<td>Additional small survey</td>
<td>People missed in first serosurvey</td>
<td>P. Aaby</td>
<td>[9]</td>
</tr>
<tr>
<td>1996</td>
<td>Second case-control study</td>
<td>Follow-up of HIV+ subjects and controls</td>
<td>K. Ariyoshi</td>
<td>[10]</td>
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<tr>
<td>1998</td>
<td>Sexual behaviour study</td>
<td>Survey of sexual behaviour and HIV knowledge</td>
<td>E. Lagarde / C. Enel</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>Follow-up sexual behaviour study</td>
<td>In-depth questionnaire selected subjects</td>
<td>C. Enel</td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>Trachoma study – follow-up eyelid surgery</td>
<td>Trachoma patients</td>
<td>R. Bailey</td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>Natural history study</td>
<td>Clinical manifestations in HIV+ and HIV- subjects</td>
<td>M. Schim van der Loeff</td>
<td>[14]</td>
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<tr>
<td>2004</td>
<td>HTLV-1 Study</td>
<td>Neurological manifestations</td>
<td>S. Cooper</td>
<td>[15]</td>
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<td></td>
<td></td>
<td>HTLV-1+ and HTLV-1- adults</td>
<td>S. McConkey</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Strongyloides infection</td>
<td>S. McConkey</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HTLV-1+ and HTLV-1- mothers and children</td>
<td></td>
<td></td>
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<tr>
<td>2006 – 2007</td>
<td>Third HIV/HTLV serosurvey</td>
<td>Adults ≥ 15 years of age</td>
<td>C. van Tienen / A. Zaman</td>
<td>[16-17]</td>
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<tr>
<td>2008</td>
<td>Malaria pilot survey</td>
<td>Children and adults</td>
<td>J. Satoguina / D. Conway</td>
<td>[22]</td>
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<tr>
<td>2009</td>
<td>Neuro AIDS study</td>
<td>HIV+ and HIV- subjects</td>
<td>Y. Choi / D. Clifford / A. Jaye</td>
<td>[23]</td>
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<tr>
<td>2010</td>
<td>HIV-2 elite control studies</td>
<td>HIV+ and HIV- subjects</td>
<td>T. de Silva</td>
<td></td>
</tr>
</tbody>
</table>

Refs, References; HIV, Human Immunodeficiency Virus; HTLV, Human T-cell Lymphotropic Virus

from West Africa [26-27]. Both HIV types have probably entered the human population in the first half of the 20th century [28-29]. All three viruses can be transmitted through vertical transmission, sexual transmission and through contaminated blood (products), although the transmission rates greatly differ between the viruses. HIV-1 and HIV-2 are most frequently transmitted sexually, while HTLV-1 is thought to be mainly transmitted vertically (from mother to child through prolonged breastfeeding).
While HIV-1 has spread worldwide, HIV-2 is mostly confined to West Africa and countries with historical links with Portugal [30]. The relative containment of HIV-2 is probably related to the lower rates of sexual and vertical transmission compared to HIV-1 [31-32]. The lower viral load that is generally seen in HIV-2 infection seems to be the most important factor in the reduced transmission rates [32-33]. Guinea-Bissau is the country where the highest prevalence of HIV-2 has been reported (with a prevalence of more than 20% among elderly people in the 80s) and it is thought that increased risk behavior during the War of Independence and iatrogenic transmission (such as large scale vaccination and treatment campaigns) may have contributed to the initial spread of HIV-2 in Guinea-Bissau [9,13,28,34].

HTLV-1 is an ancient virus and has spread worldwide. A few global areas have a known high prevalence such as Jamaica, southern Japan, Peru and various countries in Sub-Saharan Africa [35]. However, in most countries the prevalence in the general population is unknown [36].

The outcomes of each of these three retroviral infections are remarkably distinct. Approximately 95% of the carriers of HTLV-1 remain asymptomatic and 0.3 – 5% will develop Adult T cell Leukemia (ATL) or Tropical Spastic Paraparesis (TSP) [35]. In untreated HIV-1 infection, more than 95% of the infected individuals will develop AIDS, while this is thought to be approximately 50% in HIV-2 infection [37]. Hence, a very large proportion of HIV-2 infected people are asymptomatic for many years and have undetectable viremia and a normal survival [38]. When HIV-2 infection does lead to AIDS, it is clinically indistinguishable from AIDS caused by HIV-1 [39].

The first study examining HIV in Caió was done in 1988 and showed an HIV-2 prevalence of 8%. HIV-1 was only detected in 14 people, of whom 10 were also infected with HIV-2 [5]. Almost 10 years later, a second study showed that HIV-2 had remained stable and HIV-1 had increased to 3%. HTLV-1 was studied for the first time in 2000 on samples from the 1988 study – the prevalence was 5%, which is high compared to many other endemic areas of the world [6].

In this thesis we wanted to know how the epidemics of these three retroviruses have evolved over time. Is HIV-2 really disappearing? Will HIV-1 take over as the dominant virus (Chapter 2&3) [16,40]? And how has HTLV-1 prevalence changed between 1988 and 2007? Since these viruses can all be transmitted in the same way, can we find associations between HTLV-1 and HIV (Chapter 4) [17]? And how do these viruses, in single and dual infections, affect the survival of infected individuals (Chapter 5)? And, could clinical predictors help us in predicting the outcomes of HIV-2 infection on survival (Chapter 6)? Furthermore, very little is known about the contribution of vertical transmission to the HTLV-1 epidemic, which we explored (Chapter 7). In addition to these epidemiological studies, we have obtained sequences from samples from various studies to improve our understanding of the molecular epidemiology of HIV-2 and HTLV-1 using phylogenetic methods, as described in chapters 8 and 9.
Chapter 1

References


