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Cohort Profile

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Cohort Profile: The Bissau HIV Cohort—a cohort of HIV-1, HIV-2 and co-infected patients

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Abstract

The West African country Guinea-Bissau is home to the world's highest prevalence of HIV-2, and its HIV-1 prevalence is rising. Other chronic viral infections like human T-lymphotropic virus type 1 (HTLV-1) and hepatitis B virus are common as well. The Bissau HIV Cohort was started in 2007 to gain new insights into the overall effect of introducing antiretroviral treatment in a treatment-naïve population with concomitant infection with three retroviruses (HIV-1, HIV-2 and HTLV-1) and tuberculosis. The cohort includes patients from the HIV clinic at Hospital Nacional Simão Mendes, the main hospital in Bissau, the capital of the country. From July 2007 to June 2013, 3762 HIV-infected patients (69% HIV-1, 18% HIV-2, 11% HIV-1/2 and 2% HIV type unknown) were included in the world's largest single-centre HIV-2 cohort. Demographic and clinical data are collected at baseline and every 6 months, together with CD4 cell count and routine biochemistry analyses. Plasma and cells are stored in a biobank in Denmark. The Bissau HIV Cohort is administered by the Bissau HIV Cohort study group. Potential collaborators are invited to contact the chair of the cohort study group, Christian Wejse, e-mail: [wejse@dadlnet.dk].

Why was the cohort set up?

Guinea-Bissau in West Africa is a low-income country with a gross national income per capita of 1240 international dollars in 2013.[1] The country has the highest prevalence of HIV-2 in the world.[2,3] According to the Joint United Nations Programme on HIV/AIDS (UNAIDS), the estimated overall HIV prevalence in Guinea-Bissau is 3.9% (2.9–5.3%).[4] In the most recent (2006) survey from the capital, Bissau, the prevalence of HIV-2 in Guinea-Bissau was 4.4%; this prevalence is higher among older adults,

Key Messages

- The Bissau HIV Cohort consists of the world's largest single-centre cohort of HIV-2 and HIV-1/2 dually infected patients.
- Simple markers of HIV progression are important when viral load measurements are not available and CD4 cell counts are often lacking.
- Loss to follow-up is a major problem and occurs at all stages during the diagnostic and follow-up periods.
- HIV rapid tests overestimate the number of HIV-1/2 dual infections, whereas hepatitis rapid tests underestimate hepatitis prevalence.
- This cohort and corresponding biobank represent a unique opportunity to study co-infections in HIV.

whereas HIV-1 is common primarily among younger adults (HIV-1 adult prevalence 0.1% in 1989, 4.6% in 2006).[5,6] The prevalence of HIV-2 is decreasing in the region but HIV-1 is on the rise.[6,7] Infection with a third retrovirus, human T-lymphotropic virus type 1 (HTLV-1), occurs frequently (7%) as well.[8] A large proportion of retrovirus-infected individuals are also infected with *Mycobacterium tuberculosis*.[9,10] In a prospective community study of tuberculosis (TB) in Bissau from 1996–98, 39.8% of all participants diagnosed with active TB were HIV positive.[11] The TB incidence in Guinea-Bissau is 470/100 000 person-years,[11] among the highest in the world.

The Bissau HIV Cohort was set up in July 2007 by the Bandim Health Project (BHP) and Aarhus University Hospital, Denmark, in collaboration with nurses and physicians from the Hospital Nacional Simão Mendes (HNSM). The BHP is a member of INDEPTH,[12] a network of 36 demographic surveillance systems field sites in 19 countries in Africa and Asia. A demographic surveillance system was established in Bissau by the BHP in 1978; since then, it has generated data at the household level in order to elucidate population and health dynamics in the area. The BHP is a collaboration between the Ministry of Health in Guinea-Bissau and Statens Serum Institut in Denmark.[13] HNSM has 374 beds and is the main hospital in Bissau. The HIV clinic, which is based in the hospital, is the biggest centre for antiretroviral treatment (ART) in the country in terms of patients on follow-up. The HIV clinic has been relocated four times within the hospital as rooms had to be used for other purposes.

The Bissau HIV Cohort is unique in that it consists of the world's largest single-centre cohort of HIV-2 and HIV-1/2 dually infected patients.[14,15] HIV-2 was discovered 2 years after HIV-1[16] and has mainly been restricted to West Africa, where an estimated 1–2 million people are infected.[17] HIV-2 is less transmissible and is associated with slower clinical progression and lower mortality than HIV-1 but, in a proportion of patients, it leads to AIDS with clinical features indistinguishable from the syndrome caused by HIV-1.[18–23] To establish whether the majority of HIV-2-infected individuals survive as long-term non-progressors, an incident HIV-2 cohort must be followed for many years.[24]

HIV-2 is inherently resistant to non-nucleotide reverse transcriptase inhibitors (NNRTIs).[25] The lower global prevalence of HIV-2 relative to HIV-1 and the restricted dissemination of the HIV-2 epidemic have resulted in limited numbers of studies on HIV-2 therapy and immunology. Randomized treatment trials have never been performed, but a protease inhibitor (PI)-based treatment regimen is effective.[26]

The Department of Infectious Diseases at Aarhus University Hospital, Denmark, offers extensive clinical experience with ART in a large HIV in- and outpatient clinic and manages a TB clinical database in Bissau. The Bissau HIV Cohort biobank is located in this department in Denmark. The Bissau HIV Cohort is managed by the Bissau HIV Cohort study group.

Specific aims and objectives

Data are currently lacking on the efficacy of ART in populations infected with multiple agents, especially in terms of the interaction of HIV-1 with HIV-2, HTLV-1 and TB. In particular, clinical experience with HIV-2 infection is limited, and information on therapy for patients infected with both HIV-1 and HIV-2 is scarce.[27–29] This cohort was established to fill this gap by studying clinical, virological and immunological parameters in relation to the efficacy of ART.

Our specific objectives were to generate new knowledge on:

- the influence of immune activation and multiple infections on clinical outcome in HIV-infected individuals with or without ART;
- the identification of simple and inexpensive markers of disease progression in HIV;

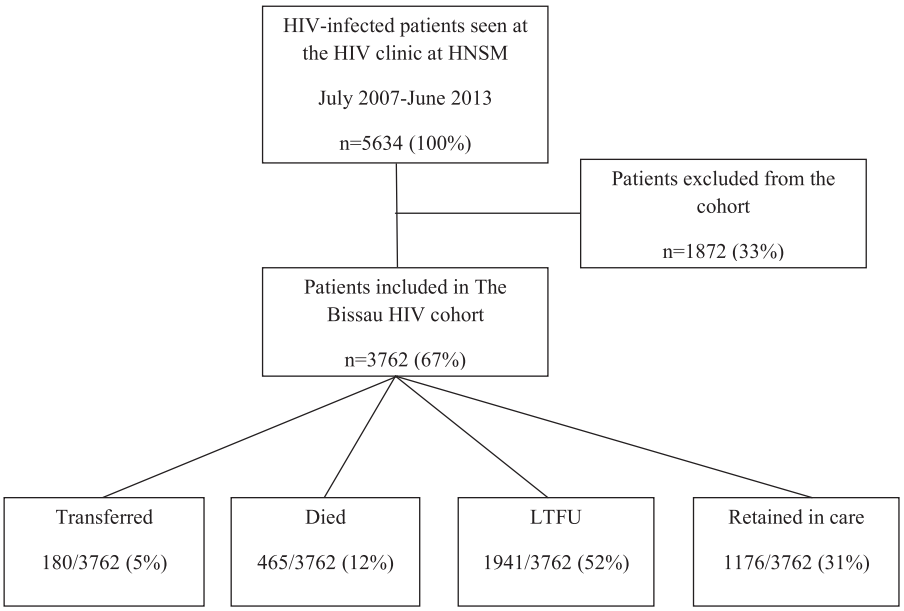

Figure 1. Patient flow at the HIV clinic at HNSM and outcome by December 2013.

- testing to discriminate between HIV-1 and HIV-2 infection, and HIV-1/2 co-infection;
- clinical, immunological and viral effects and mechanisms of infection with various agents such as HIV-1, HIV-2, HTLV-1, TB and hepatitis B, C and D;
- biological evolution of HIV-1 and HIV-2 in terms of phenotype, co-receptor usage, viral fitness and spread of ART-resistant HIV-1 and HIV-2 variants;
- the role of gender in immune-activation markers, viral load and CD4 status as well as sex-based differences in the prevalence of HIV-2 and HIV-1/2 co-infections;
- the description of adverse effects of ART in HIV-1 vs HIV-2 infection;
- the appropriate ART regimens in populations in which HIV-2 is endemic or where multiple infections with different retroviruses are present;
- the implementation, monitoring and evaluation of treatment of retrovirus-infected patients in Guinea-Bissau;
- how protective immunity against HIV infection can be achieved and serve as the basis for later vaccine development;
- how to facilitate clinical trials for efficient ART and HIV vaccine development.

Who is in the cohort?

All HIV-positive patients presenting at the HIV clinic at HNSM are invited to be enrolled in the cohort. Patients are referred to the clinic from the hospital wards, health centres and the hospital's blood bank. Patients may report for HIV testing without prior referral. Most included patients are adults, since the hospital has its own paediatric department, but no age criteria exist for patient inclusion.

Table 1. Enrolment in the Bissau HIV Cohort

Year	Included/all patients at the clinic, n/N (%)
2007	371/419 (89)
2008	602/801 (75)
2009	732/1.056 (69)
2010	798/1.144 (70)
2011	599/894 (67)
2012	392/615 (64)

The main reason for patient exclusion is the lack of reagents for CD4 cell counting or problems with the CD4 cell counting machine. Since inclusion in the cohort takes place immediately after blood sampling for CD4 cell counting, patients are excluded when no CD4 cell counts are available. Specific reasons for exclusion are not registered, but other known reasons for exclusion are patient unwillingness to give blood and private consultation with doctors during the evenings and weekends, when inclusion in the cohort is not possible.

From July 2007 until June 2013, 3762 (67%) patients out of a total of 5634 patients attending the clinic were included in the cohort (Figure 1). At inclusion, 1166 patients (31%) were living within the BHP demographic surveillance study area. Fewer patients were included each year since the cohort was established in 2007 (Table 1). The proportion of all patients included declined from 371 of 419 (89%) in 2007 to 392 of 615 (64%) in 2012 ($P < 0.01$).

Patients included in the cohort were more likely to: be female than male; have data on HIV type; have no education than some education; and have higher CD4 cell counts, compared with patients excluded from the cohort (Table 2). ART was initiated in 2555 patients (68%). The most common first-line regimens are presented in Box 1. By December 2013, the 3762 patients provided 5336 person-years of follow-up. The median follow-up time was 324 days (interquartile range 48–881 days). A total of 1941 (52%) patients were lost to follow-up, 465 (12%) patients died and 180 (5%) patients were transferred to another ART clinic (Figure 1). Patients on ART are considered lost to follow-up (LTFU) when they are more than 3 months late for their last scheduled appointment; patients not on treatment are recorded as LTFU when they do not report to the clinic for 7 months.

How often have they been followed up?

For patients on ART, visits are initially monthly and then every 2–3 months as therapy is stabilized. At each visit, ART is provided and patients are asked about adverse events and HIV-related symptoms. CD4 cell counts are determined and a medical consultation is provided biannually with a follow-up questionnaire on demographic and clinical status. Patients not on ART are seen approximately every 6 months for CD4 cell counts, medical consultation and completion of the follow-up questionnaire.

What has been measured?

At the first visit to the clinic, the patients are examined by a trained assistant who performs a structured interview to gather demographic and clinical information (Box 2). When diagnosed with HIV, patients are given a unique registration number corresponding to a patient file and a personal card that indicates the date of their next clinic visit. ART is initiated according to the latest version of the World Health Organization (WHO) guidelines.[30–32] When a patient does not attend a follow-up visit, active follow-up is carried out by contacting the patient or the contact person by telephone. Patients on ART are contacted when they are more than 1 week late for their appointment, and patients not yet eligible for ART are contacted when they have not visited the clinic in 180 days. Patient contact by telephone is attempted once each week. Patients not LTFU, dead or transferred are defined as retained in care. Information on patient mortality and clinic transfer is collected via patient interviews, telephone conversations with contact persons and healthcare personnel on the hospital wards. Our close collaboration with BHP and their demographic surveillance system enables us to collect near-complete information about deaths of patients living in the BHP study area.

What has it found? Key findings and publications

The clinic faces many problems, including inadequate drug supply, several relocations (which contributed to a high LTFU rate) and limited laboratory capacity. Despite these limitations, several research questions have been answered.

Inadequate drug supply. We published a case report of three cases with Stevens–Johnson syndrome who were switched with high CD4 cell counts from efavirenz to nevirapine during a period of efavirenz drug stock-out.[33]

LTFU. One of the main problems in this cohort, as in many other sub-Saharan African countries, is the large number of patients who are LTFU. Hønge *et al.* found that LTFU occurred at all stages of diagnostic work-up and follow-up.[33] Age younger than 30 years at inclusion, body mass index $<18.5\,kg/m^2$, male gender, HIV-2 infection and CD4 cell count <200 cells/μl were risk factors for LTFU.[34] A qualitative study by Rasmussen *et al.* indicated that HIV-related knowledge was a determining factor for optimal adherence; barriers included perceived stigma, poor infrastructure at the clinic, treatment-related costs and traditional practices.[35]

Limited laboratory capacity. A focus was to identify simple and inexpensive markers of disease progression in HIV, since viral-load measurements are not available in Guinea-Bissau. Oliveira *et al.* showed that irrespective of ART initiation and baseline CD4 count, middle upper arm circumference and measurements of the soluble form of the urokinase plasminogen activator receptor in plasma were independent predictors of early mortality in the cohort.[15]

Our results emphasize the importance of evaluating rapid tests in the context in which they are meant to be used. The HIV confirmatory rapid test SD Bioline HIV 1/2 3.0 (Standard Diagnostics, Kyonggi-do, South Korea) overestimated the number of HIV-1/2 dual infections in the cohort,[36] whereas HBsAg and anti-HCV rapid tests underestimated hepatitis prevalence.[37] Co-infection with hepatitis B, C and D have also been studied.[38,39]

Randomized controlled trials. The Bissau HIV Cohort has been used as a platform for performing a randomized controlled trial of a therapeutic HIV vaccine, demonstrating that therapeutic immunization is feasible and safe.[40,41] We are currently conducting a major randomized controlled treatment trial to compare a PI-based treatment regimen

Table 2. Baseline characteristics of patients included and excluded from the Bissau HIV Cohort

Characteristics	Included, $N = 3762$	Excluded, $N = 1872$	P-value
Sex			
Female	2503 (67)	1168 (62)	<0.01
Male	1259 (33)	704 (38)	
Age at inclusion, median years (IQR)	37 (30–45)	36 (29–46)	0.62
Age group at inclusion			
<15 years	83 (2)	52 (3)	<0.43
15–30 years	1077 (29)	538 (29)	
31–36 years	747 (20)	378 (20)	
37–45 years	988 (26)	452 (24)	
>45 years	867 (23)	232 (23)	
HIV type			
HIV-1	2606 (69)	1187 (63)	<0.01
HIV-2	665 (18)	259 (14)	
HIV-1/2	429 (11)	166 (9)	
Missing	62 (2)	260 (14)	
Ethnic group			
Balanta	781 (21)	No information	–
Manjaco	328 (9)		
Pepel	360 (10)		
Other	2291 (61)		
Missing	2 (1)		
Education			
None	1295 (34)	524 (28)	<0.01
1–4 years	439 (12)	214 (11)	
5–11 years	1682 (45)	945 (51)	
Missing	346 (9)	189 (10)	
Marital status			
Married	1973 (52)	996 (53)	0.05
Divorced	223 (6)	116 (6)	
Widowed	551 (15)	224 (12)	
Single	886 (24)	457 (24)	
Missing	129 (3)	79 (4)	
Baseline CD4 cell count, median cells/μl (IQR)	216 (106–378)	176 (52–307)	0.05
CD4 group	1610 (43)	31 (2)	<0.01
≤200	902 (24)	18 (1)	
200–350	982 (26)	12 (<1)	
>350	268 (7)	1811 (97)	
BMI, median kg/m^2 (IQR)	19.9 (17.6–22.7)	No information	–
BMI group			
≤15	258 (7)		
15.1–18.5	1013 (27)		
18.6–25	1914 (51)		
>25	450 (12)		
Missing	127 (3)		
Received TB treatment before or at inclusion			
Yes	373 (10)	No information	–
No	3387 (90)		
Missing	2 (1)		
ART naïve at inclusion			
Yes	3251 (86)	No information	–
No	511 (14)		

Number of patients (%) are shown unless otherwise stated.

IQR, interquartile range; BMI, body mass index. Numbers may not add up to 100% due to approximations.

Box 1. First-line regimens in the Bissau HIV Cohort

First-line regimens		
HIV-2 infection $N = 382$	HIV-1/2 co-infection $N = 278$	HIV-1 infection $N = 1874$
AZT/3TC/IDVr: 133 (35%) AZT/3TC/ABC: 75 (20%) AZT/3TC/LPVr: 65 (17%) D4T/3TC/IDVr: 31 (8%) Other: 78 (20%)	AZT/3TC/IDVr: 135 (48%) AZT/3TC/ABC: 37 (13%) AZT/3TC/LPVr: 26 (9%) D4T/3TC/IDVr: 25 (9%) Other: 55 (20%)	AZT/3TC/NVP: 809 (43%) AZT/3TC/EFV: 396 (21%) D4T/3TC/NVP: 170 (9%) TDF/FTC/EFV: 107 (6%) Other: 392 (21%)

Number of patients on first-line regimens (%) are shown; information for 21 patients with missing HIV type not shown.

AZT, zidovudine; 3TC, lamivudine; IDVr, indinavir/ritonavir; ABC, abacavir; LPVr, lopinavir/ritonavir; D4T, stavudine; NVP, nevirapine; EFV, efavirenz; TDF, tenofovir; FTC, emtricitabine.

Box 2. Data and variables collected for the Bissau HIV Cohort

Baseline information
- Contact information
- Date of birth
- Gender
- Ethnicity
- Marital status
- Religion
- Level of education
- Height
- Weight
- Middle upper arm circumference
- History of TB treatment or diabetes
- Information about pregnancy
- Presence and size of vaccination scars (classified as due to smallpox vaccination, *Bacillus Calmette-Guérin* vaccination, or unclassified based on the size and characteristics of the scar and on information from the patient about previous vaccinations)
- Past and present smoking status (number of cigarettes per day)
- Alcohol consumption (number of alcohol units per week)

Laboratory data
- HIV screening [Determine HIV-1/2 assay (Abbott Laboratories, Abbott Park, IL)]
- HIV type [SD Bioline HIV 1/2 3.0 rapid test (Standard Diagnostics, Kyonggi-do, South Korea), which was replaced with First Response^{TM} HIV-1/HIV-2 WB (PMC Medical, Mumbai, India) in 2012]
- CD4 cell count
- Haematological parameters (haemoglobin, white blood cell count, platelets)
- Kidney function (creatinine)
- Liver function (alanine and aspartate aminotransferases)
- Blood glucose
- Hepatitis B serology (HBsAg)
- Hepatitis C serology (anti-HCV)
- Syphilis serology (Venereal Disease Research Laboratory test)
- Storage of plasma and cells in the biobank

Follow-up information
- Update of baseline information
- History of ART
- Date of last and next appointment at the clinic
- Date of death, loss to follow-up or transfer

with an NNRTI-based regimen in HIV-1-infected patients (NCT01192035). Demonstrating superiority or non-inferiority of a PI-based regimen for HIV-1 will enable a common first-line regimen for HIV-1 and HIV-2 mono-infected, and co-infected patients.

International collaborations. The cohort actively participates in the International Epidemiologic Databases to Evaluate AIDS (IeDEA)[42] and the West African Platform for HIV Intervention Research (WAPHIR).[43]

Future research plans. Ongoing research involves studies to improve TB diagnosis, studies on co-infection with hepatitis B, C and D, qualitative and quantitative studies of how to reduce LTFU and improve adherence, immunological studies, assessments of gender effects and the evaluation of effects of HIV on vaccines against other infections.

What are the main strengths and weaknesses?

The main strength of the Bissau HIV Cohort is that it comprises the world's largest single-centre cohort of HIV-2 and HIV-1/2 dually infected patients.[14] Other chronic viral infections are prevalent in this study population, including HTLV-1 and hepatitis B. Thus, this cohort represents a unique opportunity to study how co-infections alter immune response, disease progression and response to treatment. Despite difficult working conditions, we have maintained inclusion and follow-up in this large cohort over 7 years. Furthermore, we successfully created a biobank with unique blood samples from a country in which clinical HIV research has been scarce to date.

The main weakness of the current cohort is a high rate of LTFU. The Guinean population is very mobile. Many people are involved in seasonal work and, together with the unstable political situation in the country, people often leave the capital for the rural regions, perhaps receiving

ART at other clinics without our knowledge. LTFU may not be higher than in other African ART cohorts, but comparisons are hindered by heterogeneity in the definition of LTFU and differences in study populations.[44]

Various approached have been established to reduce LTFU in this cohort. Since 2011, all patients who are late for an appointment have been called systematically by a healthcare worker. In 2013, home visits were initiated for patients in the BHP study area. Another weakness of the cohort is that not all patients attending the clinic have been included in the cohort and reasons for exclusion are not registered. Of note, patients excluded from this cohort are offered the same treatment and follow-up as included patients. The only differences between excluded and included patients are the expanded data collection and the storage in the biobank of blood from included patients. Data from all patients at the clinic can be used for epidemiological studies, but studies requiring stored blood samples are only possible on patients included in the cohort. In general, limited laboratory capacity with long periods with unavailable CD4 cell counts has led to many missing counts. In the absence of serum RNA viral load measurements, and limited capacity to diagnose opportunistic infections, it is difficult to fully describe the effect of ART in the cohort.

Can I get hold of the data? Where can I find out more?

The Bissau HIV Cohort is managed by the Bissau HIV Cohort study group. Potential collaborators are invited to contact the chair of the Bissau HIV Cohort study group, Christian Wejse (e-mail: [wejse@dadlnet.dk]). Information about the Bandim Health project can be found at: [www.bandim.org].

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S.J. drafted the manuscript. I.O. is the founder of the cohort. C.M., D. da S. and F.G.C. carried out the clinical assessment of patients. All authors planned and conducted studies within the cohort. C.W. is the chair of the Bissau HIV Cohort study group. All authors read and approved the final manuscript. S.J. is the guarantor for the paper.

The Bissau HIV Cohort study group consists of Amabelia Rodrigues, David da Silva, Zacarias da Silva, Candida Medina, Ines Oliviera, Lars Østergaard, Alex Laursen, Morten Sodemann, Peter Aaby, Anders Fomsgaard, Christian Erikstrup, Jesper Eugen-Olsen and Christian Wejse (chair).

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