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

This thesis describes different aspects of the (molecular) epidemiology of Human Immunodeficiency Virus type 1 (HIV-1), Human Immunodeficiency Virus type 2 (HIV-2) and Human T-Lymphotropic Virus type 1 (HTLV-1) in Caio, a rural area in Northwestern Guinea-Bissau. The unique feature and strength of all the studies presented in this thesis, is that all studies are community-based and study participants were not selected from a medical facility. This enables us to gain valuable insights into the natural progression and epidemiological trends of these infections.

Chapter 1 gives a general, brief introduction to Guinea-Bissau, to the field station operated by the Medical Research Council and the Bandim Health Project and to the studies conducted there. It also gives an overview of the three human retroviruses that circulate in Guinea-Bissau.

Chapter 2 is a review of the current knowledge on HIV-1/HIV-2 dual infection. It describes the epidemiological, immunological and virological aspects of dual infection and discusses the treatment options.

In Chapter 3 the rise of HIV-1 and decrease of HIV-2 in Caio are described, based on data from three large community surveys conducted in the adult population in 1990, 1997 and 2007. The prevalence of HIV-2 decreased in this period from approximately 8.3% to 4.7% while HIV-1 increased from 0.5% to 3.6%. The incidence of HIV-1 remained stable and the incidence of HIV-2 decreased during this period.

Chapter 4 concludes that clinical characteristics cannot replace biological measures to predict HIV-2 related mortality in Caio. In 2003, HIV-2 infected individuals were assessed clinically; they were followed up until 2010. A low Body Mass Index and low Mid Upper Arm Circumference were weakly associated with an increased risk of mortality, but this was not statistically significant. CD4% and plasma viral load are good predictors of mortality and should be used in community settings to guide clinical management and treatment of HIV-2.

Chapter 5 describes the prevalence and incidence of HTLV-1 estimated in the 1990, 1997 and 2007 surveys in Caio. The prevalence of HTLV-1 was approximately 5% in all 3 surveys. The incidence was stable in this period as well. A continued cross-sectional association with HIV suggests that sexual transmission plays an important role in this endemic. A high Odds Ratio was observed for (adult) children of HTLV-1 infected mothers, suggesting vertical transmission is also an important transmission route. Longitudinal analysis indicates that HIV infection increases the risk of subsequent infection with HTLV-1, but not vice versa.

Chapter 6 presents a mortality analysis of all HIV and HTLV-1 infected individuals diagnosed in Caio in any of the studies held between 1990 and 2007. A total of 5376 subjects were included and were followed up until 2009. The adjusted Hazard Ratio (HR) comparing infected individuals to non-infected individuals for HIV-1 infection varied from 4.0 in the oldest age group (≥60 years) to 12.7 in
the youngest (15 – 29 years). The HR for HIV-2 infection varied from 1.2 (oldest) to 9.1 (youngest), and for HTLV-1 infection from 1.2 (oldest) to 3.8 (youngest). This analysis confirms that HTLV-1 infection is associated with significantly increased mortality. There was no indication of interaction of HTLV-1 and HIV-2 infection or of HIV-1 and HIV-2 infection on mortality outcomes. The major limitation of this study is the fact that all subjects had prevalent infections. Its strength is that it is the largest cohort study with the longest follow-up that has been performed on these 3 retroviral infections in the same population.

In Chapter 7 the vertical transmission of HTLV-1 is explored. In a cross-sectional study, children of known HTLV-1 infected and uninfected mothers were tested for HTLV-1 infection. Fourteen out of 55 children (25%) of 31 HTLV-1 infected mothers were infected versus none of 70 children of 30 uninfected mothers. The only factor significantly associated with HTLV-1 infection in the child was the HTLV-1 proviral load of the mother. In an effort to confirm the maternal source of the infection in the child, the Long Terminal Repeat (LTR) region of HTLV-1 was sequenced in 7 mother-child pairs. All sequences within the pairs were identical; sequences differed between the pairs. This study lends support to one of the findings from Chapter 5: mother to child transmission of HTLV-1 contributes to the HTLV-1 endemic in Caio.

Chapter 8 describes the molecular epidemiology of HTLV-1 in Caio. The LTR and/or p24 coding region of HTLV-1 was sequenced in samples of 71 individuals and phylogenetic analyses were performed. Known relatives showed identical sequences, but so did many sequences from unrelated individuals, which is consistent with the low evolutionary rate of HTLV-1. The majority of the viruses belonged to the Cosmopolitan subtype 1a, subgroup D. Two strains were very divergent and belonged to HTLV-1 subtype g and clustered with Simian T-Lymphotropic Virus type 1, Tan90. This gives support to the hypothesis that interspecies transmission contributed to the spread of Primate T-Lymphotropic Virus into the human population in the past. Subtype g was previously only described in monkey hunters from Cameroon. This finding raises the question about the transmission route of this subtype in the Caio community – to what extent does monkey-to-human transmission still take place in Caio or can subtype g spread from human to human?

Chapter 9 presents the analysis of different phylogenetic analyses of HIV-2 gag and env sequences linked to viral load and CD4% measurements and epidemiological data. Despite a decrease in incidence in the past decade, new HIV-2 infections do still occur in Caio (as shown in Chapter 3). In order to answer the question where these infections originate from, sequences were obtained from 103 persons from Caio. Samples were designated ‘incident infection’ if a person had provided at least one HIV-2 negative before the positive sample was obtained and designated ‘pre-1989’ if a person was already HIV-2 infected in the first study in Caio conducted in 1989 – 1990. Sequences from incident infections appeared in clusters as well as in non-clusters, suggesting that no single HIV-2 variant is responsible for all new infections. Nevertheless, incident infections did occur more
often in significant clusters; this suggests that they are associated with onward transmission. Timed phylogenies estimated a surprisingly short median inter-transmission interval of 0.75 years in \textit{gag} and 1.32 years in \textit{env} phylogenies and indicate that onward transmission probably occurs soon after infection. Bayesian skyline plots show a strong increase in the 1990s of the effective virus population size (\( N_e \), i.e. the viruses fit to replicate and transmit) of HIV-1 in the same period that the \( N_e \) of HIV-2 comes into a plateau phase, consistent with the displacement of HIV-2 by HIV-1. A strong increase of HIV-2 in the 1960s and 1970s coincided with the War of Independence against Portugal which may have enabled the spread of HIV-2.

In \textbf{Chapter 10} a general discussion of key findings reported in this thesis is presented. It is argued that HIV-2 and HTLV-1 are neglected tropical infections and the need for more research of these viruses is highlighted. The different possible routes of transmission of HTLV-1 are discussed and suggestions for further studies to look at potential money-to-human transmission are given. Finally, we attempt to draw parallels between the natural decrease of the HIV-2 epidemic and a similar decrease that is very much desired for the HIV-1 epidemic and may perhaps be brought about by large scale anti-retroviral treatment. Modeling of the HIV-2 epidemic with viral load data linked to epidemiological data may provide very useful pointers to curb the HIV-1 epidemic.