Natural simian immunodeficiency virus transmission in mandrills: a family affair?

David Fouchet1,†, Delphine Verrier2,*,†, Barthélémy Ngoubangoye2, Sandrine Souquière2, Maria Makuwa2, Mirdad Kazanji2,3, Jean-Paul Gonzalez2 and Dominique Pontier1

1Laboratoire de Biométrie et Biologie Évolutive UMR5558-CNRS, Université Claude Bernard Lyon 1, Villeurbanne, France
2Centre International de Recherches Médicales de Franceville (CIRMF), B.P 769, Franceville, Gabon, Central Africa
3Réseau International des Instituts Pasteur, Institut Pasteur, Paris, France

Understanding how pathogens spread and persist in the ecosystem is critical for deciphering the epidemiology of diseases of significance for global health and the fundamental mechanisms involved in the evolution of virulence and host resistance. Combining long-term behavioural and epidemiological data collected in a naturally infected mandrill population and a Bayesian framework, the present study investigated unknown aspects of the eco-epidemiology of simian immunodeficiency virus (SIV), the recent ancestor of HIV. Results show that, in contrast to what is expected from aggressive and sexual transmission (i.e. the two commonly accepted transmission modes for SIV), cases of SIVmnd-1 subtype were significantly correlated among related individuals (greater than 30% of the observed cases). Challenging the traditional view of SIV, this finding suggests the inheritance of genetic determinants of susceptibility to SIV and/or a role for behavioural interactions among maternal kin affecting the transmission of the virus, which would highlight the underappreciated role of sociality in the spread of infectious diseases. Outcomes of this study also provide novel insights into the role of host social structure in the evolution of pathogens.

Keywords: aggressive behaviour; emerging infectious diseases; host–parasite interactions; kinship; primate; transmission mode

1. INTRODUCTION

Wildlife pathogens represent a major threat to biodiversity as well as for global economics and public health [1–3]. However, owing to the difficulty in conducting field observations and the complexity of the host–parasite interactions involved, the ecology and population biology of these organisms remain poorly understood. For instance, although animal movements and sociality are considered to be important risk factors for the dissemination of pathogens [4–6], these parameters are rarely explicitly included in epidemiological assessments owing to the lack of relevant data in wildlife populations. Yet, understanding the functioning of pathogen populations and that of their hosts within an ecosystem is crucial for deciphering the epidemiology of diseases of significance for global health (in particular for predicting and preventing the emergence of both animal and human epidemics), as well as the fundamental mechanisms involved in the evolution of virulence and host resistance.

Among recently emerged viral infections now established in humans, the HIV/AIDS pandemic exemplifies the most striking and devastating example of an emerging infectious disease of wildlife origin. It is now well established that HIV results from multiple cross-species transmissions of simian immunodeficiency viruses (SIVs) from non-human primates (NHPs) to humans, with SIVs from chimpanzees and gorillas in West Central Africa and sooty mangabeys in West Africa being the progenitors of HIV type 1 and HIV type 2, respectively [7,8]. However, fundamental questions pertaining to SIV remain obscure, thus precluding a comprehensive understanding of its ecology, and of the evolution and future of HIV in humans. For instance, although SIVs are called immunodeficiency viruses by analogy to HIV, they are generally assumed not to cause AIDS-like symptoms (with the exception of a few anecdotic cases reported in captive African NHPs closely monitored beyond their life expectancy in the wild [9]) but non-progressive chronic infections in their natural hosts, suggesting that they have coevolved with their hosts over an extended period of time [10]. However, this paradigm has been recently challenged by several authors suggesting that SIV may substantially impact immunocompetence, health and survival in chimpanzees [11–13]. In addition, the timing of SIV emergence in NHPs remains a controversial topic, with estimates ranging from time scales of just centuries versus greater than 32 000 years [14,15]. Consequently, the natural history of SIV and the hypothesis of a long-term host–virus co-evolution, as crucial as they are, are still ardently debated.

* Author for correspondence (ddlafoine@free.fr).
† These authors contributed equally to the study.

Another critical parameter that remains poorly understood is how SIV is transmitted and spreads within natural NHP populations. Yet, transmission mode is a key parameter to understanding the population dynamics of a pathogen and the selective pressure imposed by the social and spatial structure of the host population on its persistence [16]. SIV transmission is thought to be predominantly horizontal (i.e. between individuals, through bite wounds and sexual contact) and less frequently vertical (i.e. from the mother, in utero or at birth) [17]. However, these assumptions are based on incomplete, cross-sectional data that do not allow for a comprehensive analysis of infection spread on a population scale. Hence, the natural mode(s) of SIV transmission and their contribution to SIV epidemics remain to be determined.

To date, SIV eco-epidemiology knowledge is limited mostly by the great difficulty in conducting long-term, longitudinal field studies on NHPs. Indeed, these animals very often inhabit inaccessible areas, display cryptic behaviours and prove difficult to follow and repeatedly sample in the wild for both practical and ethical reasons [17–19]. They also live in complex societies with elaborate social structures, which increases the complexity of the mechanisms to be deciphered to comprehend their disease dynamics [5]. The alternative approaches that have been developed so far (e.g. testing of NHPs in zoos and in pets, or using non-invasive sampling methods in the field) not only introduce bias into prevalence estimates [17,20] but also neglect the natural dynamics of disease spread.

In this study, we propose an original approach focused on the role of behaviour in the transmission of infectious diseases to re-examine the transmission of SIV in NHPs. We combined unique epidemiological data derived from 25 years of longitudinal monitoring of a semi-free-ranging population of mandrills (Mandrillus sphinx) in their natural habitat in Gabon (Central Africa) with behavioural observations and a Bayesian approach in order to gain novel insights into the dynamics and transmission routes of SIV within a naturally infected NHP population. In contrast to laboratory experiments that preclude any investigation of natural transmission and the roles of sociality and animal behaviour in this process, semi-free-ranging populations indeed represent a unique opportunity to obtain high-quality data in a situation mimicking natural conditions. Such facilities render possible the study of natural transmission in the light of individual behaviour and how these behaviours might be correlated with pathogen transmission. In addition, capture rates are expected to be high, and data can be reliably and repeatedly collected over long periods of time. The specific aim of the study was to identify a combination of potential transmission modes for SIV and assess their respective contribution to the epidemic spread of the virus.

2. MATERIAL AND METHODS

(a) Study population

Mandrills are NHPs endemic of the dense rain forests of the Congo Basin (southern Cameroon, Gabon, Equatorial Guinea and northern Congo). Mandrills are long-lived (more than 20–25 years life expectancy), and live in hordes of extreme sizes (up to 1000 individuals) that are highly structured both socially and spatially [21]. Females and dependent offspring (representing greater than 95 per cent of the group) are cohesive throughout the year, whereas sub-adult (more than 6 years of age) and adult (more than 9 years of age) males live alone and only join the groups seasonally when females are in oestrus [21]. Therein, they represent a valuable model to investigate both long-term host–parasite interactions and the processes of pathogen transmission and persistence in complex social structures.

Owing to the difficulty in studying this elusive species in the wild [21], most of the current knowledge concerning mandrill biology is derived from the semi-free-ranging population housed at the International Centre for Medical Research of Franceville, Gabon (CIRMF), the largest captive mandrill colony in the world with approximately 200 individuals at present. This colony was initially created in 1983 after the release of 15 unrelated, wild-born individuals (eight females and seven males) into a 6.5 ha rainforest enclosure (E1) [22]. The long-term monitoring programme for this colony [22–27], based on ad libitum observations of individuals and annual captures for veterinary examination, has provided information about individual life history, pedigree, medical history and SIV serological status of each animal. In this colony, sexual maturity is reached at 3–4 years of age in females and at 4–5 years of age in adolescent males. Males begin to develop secondary sexual adornments at 6–7 years of age [24,28] but do not attain social maturity or mate until they reach adulthood at more than 9 years old [23]. Using their especially long canines as weapons [29], adult males compete fiercely with each other, and only a few dominant individuals gain access to fertile females [30].

In 1994, a second semi-free-ranging group was established in another enclosure (E2, 3.5 ha) to maintain a pool of SIV-free mandrills in E1. Four matrilines (a total of 17 mandrills), in which at least one individual was SIV-infected, were transferred from E1 to E2. Since then, individuals testing SIV-positive from E1 during the annual serological screening have been transferred into E2 to keep E1 SIV-free. Following incidents in which adult males crossed the fence out of or into E2 in search of mates in the neighbouring enclosure in 2005, new infections were detected in E1. Four matrilines (a total of 17 mandrills), in which at least one individual was SIV-infected, were transferred from E1 to E2. Since then, individuals testing SIV-positive from E1 during the annual serological screening have been transferred into E2 to keep E1 SIV-free. Following incidents in which adult males crossed the fence out of or into E2 in search of mates in the neighbouring enclosure in 2005, new infections were detected in E1. These voluntary intrusions and transfers of adult males from one enclosure to another are reminiscent of the natural patterns of seasonal male immigration into social groups during breeding periods [21].

Our aim was to decipher the major SIV transmission routes and spread patterns using data collected from colony records between 1983 and 2009. We focused on individuals within enclosure E1 prior to 1994 and on those transferred into enclosure E2 after 1994, as E1 was kept SIV-free from 1994 onwards.

(b) Behavioural data

The occurrence of physical injuries inflicted through bites during aggressive encounters—susceptible to facilitate SIV transmission—were recorded through daily observations of the colony. In order to provide a good approximation of how aggressiveness is affected by age in both genders, biting frequencies were calculated as the total number of bite wounds recorded for a given gender and age divided by the total number of individuals of that gender and age observed in the study population between 1983 and 2009. This parameter, however, probably underestimates the actual occurrence of biting events because it is impossible to detect all bite wounds (e.g. superficial wounds or wounds where animals disappeared following deathly fights).

The pedigree of the colony was determined as previously described [31]. Maternity was routinely allocated from maternal behaviour during the first six months of life and paternity from genetic analyses using human microsatellite loci. Age- and gender-dependent reproductive success was estimated by the mean number of offspring produced per individual for a given age and gender. In males, this rate was used as an approximation of the age and gender-dependent frequency of mating. As for aggressiveness, this rate reflects how sexual behaviour is affected by age in both genders, while it underestimates the real frequency of mating because: (i) each mating event does not necessarily result into the production of an offspring; and (ii) paternity could not be determined for all individuals (in particular, for those born after 2002).

(c) Simian immunodeficiency virus serological status

Wild mandrills are naturally infected with two SIV subtypes, SIVmnd-1 and SIVmnd-2. Mandrill serum samples were initially tested for SIV using either commercial kits detecting anti-HIV antibodies [25,26], or a peptide-based enzyme immunoassay [27,32], which yielded consistent results [32,33]. Knowing that SIVmnd-1 and SIVmnd-2 subtypes existed within the CIRMF mandrill population, genetic analysis to discriminate the subtypes was also performed [27]. After 1999, when SIVmnd-2 was no longer detected, commercial kits (Determine, Abbot, Rungis, France) were routinely used and new cases were confirmed using Western blotting.

(d) Statistical analysis of the maternal kinship effect

Family trees were created based on maternal kinship, and the distribution of SIVmnd-1 cases within matriline was analysed. Relationships between cases were assessed by an index measuring the familial links between all possible pairs of infected and infecting individuals within the study population. Family links between two individuals were considered to equal 0.5, 0.25, 0.125, etc., at the first, second, third, etc., order within maternal kin. For all infected individuals (I), we considered the set of potentially infecting individuals (i.e. individuals who were infectious the year before the observed infection of individual I).

We calculated the statistic $s$ as the sum of the family links between all possible pairs of infected individuals and their potentially infecting counterparts. The distribution of the $s$ statistic under the $H_0$ hypothesis, which contends that maternal kinship does not affect the frequency of SIVmnd-1 transmission, was estimated by randomly permuting the new infections observed each year while keeping the set of already infected individuals non-permutated.

(e) Mathematical modelling and quantifying the contribution of each transmission mode

We designed an age- and gender-structured discrete-time stochastic model to analyse SIVmnd-1 transmission in E2. Different transmission modes were considered. Transmission modes were differentiated by the gender of the infecting and infected animals along with the age distribution of the animals that were able to infect others or were susceptible to infection. The respective effect of each transmission mode was quantified using a Bayesian framework.

We constructed a mathematical model to express how infected individuals affect the probability of infection in susceptible individuals depending on their respective age and sex:

$$ p_\text{a}(t) = \exp\{-\lambda_\text{a}(t - 1)\}. $$

The term $p_\text{a}(t)$ represents the probability that individual $k$ becomes infected between $t - 1$ and $t$ if it is susceptible at $t - 1$, and $\lambda_\text{a}(t - 1)$ represents the infection rate of individual $k$, which depends on both its individual characteristics (gender and age) and the state of the population (number, gender and age of infected individuals at time $t - 1$).

We modelled the three transmission routes by dividing the infection rate into three terms:

$$ \lambda_\text{a} = \lambda_\text{a}^A + \lambda_\text{a}^S + \lambda_\text{a}^P. $$

The term $\lambda_\text{a}^A$ represents the aggressive route and describes SIVmnd-1 transmission through saliva and/or blood during aggressive interactions between individuals of the same gender:

$$ \lambda_\text{a}^S(t) = \beta_{\text{SI},G(k)} B_{G(k)} (a(k,t)) \sum_{l \in \Psi_{(t)}(k)} B_{G(l)} (a(l,t)). $$

The term $G(k)$ represents the gender (M or F) of individual $k$, $a(k,t)$ represents its age at time $t$, $\Omega(t,G)$ represents the set of observed infected individuals of gender $G$ at time $t$, and $\beta_{\text{SI},G}$ represents the SIVmnd-1 infection rate associated with the biting route of transmission in gender $G$. $B_{G} (a)$ is the age- and gender (G)-dependent rate of biting injuries. In the absence of data on ‘who is doing the biting’, we assumed that the age-dependent frequencies of doing the biting and being bitten were the same. Age-dependent biting rates were parametrized using biting data (described in §2B).

We considered a logistic function to model how biting increases with age:

$$ B_M (a) \propto \frac{\exp (\rho_M a + \mu_M)}{1 + \exp (\rho_M a + \mu_M)} $$

and

$$ B_F (a) \propto \frac{\exp (\rho_F a + \mu_F)}{1 + \exp (\rho_F a + \mu_F)}. $$

The term $\lambda_\text{a}^S$ represents the sexual route of transmission and describes the SIVmnd-1 infection of one individual through sexual contact with infected individuals from the other gender. We chose a proportionate mixing law in which females have a constant number of sexual contacts regardless of the number of males in the population. We called $r_G (a)$ the rate at which gender $G$ has sexual contacts, leading to:

$$ \lambda_\text{a}^S(t) = \beta_{\text{SI},G(k)} r_G (a(k,t)) \sum_{l \in \Psi_{(t)}(G)} r_G (a(l,t)) \frac{\gamma_M (a(l,t))}{\sum_{l \in \Psi_{(t)}(G)} \gamma_M (a(l,t))}. $$

The term $G(k)$ is the opposite gender and $\Psi_{(t)}(G)$ is the set of individuals from gender $G$ in the study population at time $t$, regardless of their serological status. We made $r_F = 1$ if $a \geq 3$ years old and $r_F = 0$ if $a < 3$ years old. For $r_M$, we assumed that the frequency of mating in males was a Gaussian function:

$$ r_M (a) \propto \exp \left\{ -\frac{(a - \bar{a}_M)^2}{2\sigma^2} \right\}. $$

$\beta_{\text{SI},G}$ represents the SIVmnd-1 infection rate associated with the aggressive route of transmission in gender $G$. Parameters $a_{\text{min}}$
and $\sigma^2$ were derived from paternity data by estimating how the frequency of reproduction is affected by age.

The term $\beta_G^L$ represents the SIVmnd-1 transmission route and describes the transmission of SIVmnd-1 from one infected female (F) to a related individual of any gender. The rate at which transmission occurs is directly proportional to the familial link (FL) between the two individuals:

$$\lambda_G^L(t) = \beta_{F,G}(\lambda) \sum_{i \in \{I,F,F,G\}} FL(h, l).$$

The term $\beta_{F,G}$ represents the SIVmnd-1 infection rate associated with the familial route of transmission in gender G. Because we had access to quasi-exhaustive data on the SIVmnd-1 status of each individual, the likelihood of each transmission route could be calculated independently for males and females. As a result, parameters associated with males ($\beta_{A,M}$, $\beta_{S,M}$, $\beta_{F,M}$) and females ($\beta_{A,F}$, $\beta_{S,F}$, $\beta_{F,F}$) could be estimated independently.

The most intuitive way to compare the different transmission routes in gender G was to compare their associated rates of transmission ($\beta_{A,G}$, $\beta_{S,G}$, $\beta_{F,G}$). However, direct comparisons were not possible because of the different choices made for the incidence function of the different transmission modes. Interpreting the ratio between the two coefficients made for the incidence function of the different transmission parameters. In practice, the relative weights of transmission routes are estimated based on the consistency between behavioural and epidemic data. The operation was repeated 10,000 times to obtain 10,000 independent realizations of the posterior distribution of $\lambda_{A,G}$, $\lambda_{S,G}$ and $\lambda_{F,G}$. For $\lambda_{A,G}$, $\lambda_{S,G}$ and $\lambda_{F,G}$ priors were chosen as independent truncated (negative values were removed) normal distributions of mean zero and a variance common for the three parameters. In practice, the variance was chosen to be very large so that the priors were non-informative.

Posterior distributions of $\lambda_{F,G}$ were simply derived from the formula

$$\lambda_{F,G} = \frac{\lambda_{A,G} + \lambda_{S,G} + \lambda_{F,G}}{\lambda_{A,G}}.$$

### 3. RESULTS

(a) **Insights into the behavioural risks associated with simian immunodeficiency virus transmission in mandrills**

Over the study period, the mandrill population increased (figure 1a) and 164 births were recorded from 36 females aged greater than or equal to 4 years (figure 1b). Only three males accounted for 85 per cent of the recorded paternity, highlighting the extreme level of competition between males for reproduction. With the exception of one male who started reproducing at 4 years of age in 1983 in the absence of adult rivals among the founder cohort, the overall age distribution of reproduction was consistent with males breeding at greater than or equal to 9 years of age (figure 1c).

Records of biting injuries were used to estimate the occurrence of aggressive interactions between individuals and to measure how these interactions correlated with SIV spread. Seventy-five per cent of the 71 observed biting injuries occurred in males (figure 1d,e). Maximal frequency of aggressive interactions coincided with the onset of social maturity, as individuals of this age group entered into competition for alpha status. Over 50 per cent of biting injuries were observed after 2005 (figure 1f), when adult males from one enclosure began to intrude into the other enclosure, and the rate of injury per adult male doubled after 2005 (adjusted $\chi^2 = 4.73$, $p = 0.03$). Of the 29 injuries reported after 2005, 15 (52%) involved six of the 10 transferred males.

Based on these observations, we proposed hypotheses on the pattern of SIV spread under the two commonly accepted transmission routes (i.e. aggressive and sexual transmission) [17]. We expected an advanced age of infection for males (more than 9 years old) in both
cases, and hypothesized that the increased aggressiveness observed after 2005 should result in an increased number of cases among adult males. We further analysed SIV dynamics in the light of these hypotheses to determine which route of transmission was the most consistent with the observed data.

(b) The SIVmnd-1 epidemic

The two SIV subtypes (SIVmnd-1 and SIVmnd-2) were considered separately because differences were observed in their natural history. One of the female founders was infected with SIVmnd-1 upon arrival at CIRMF. The SIVmnd-1 epidemic that has followed its introduction can be divided into two phases. The first phase (1983–2004) was characterized by an unexpected dispersion pattern of SIVmnd-1 outside the commonly accepted routes (i.e. sexual and aggressive) [17], with a slow accumulation of cases among maternal kin. The second phase (2005–2009) was marked by an acceleration of the epidemic that coincided with a period of increased male–male aggression.

During the first phase, eight individuals that were closely related to the infected female founder acquired SIVmnd-1. In four of these animals (one son, one granddaughter, one daughter and one granddaughter), vertical transmission could not be excluded because they were born to infected mothers and were already seropositive the first time they were captured and tested (within the first 3 years of life). By contrast, the other four animals were infected later (one daughter in 2002 at 16 years of age, one daughter in 1993 at 6 years of age, one son in 2002 at 5 years of age and one grandson in 2003 at 7 years of age), ruling out vertical transmission in these animals. Furthermore, prior to 2003, all infected males were less than or equal to 7 years old, which made transmission through mating or fights for dominance unlikely. Of the 110 individuals for whom both maternity and paternity could be assigned, only three (2.7%) were born from related parents (brother and sister in one case and mother and son in two cases), suggesting that relatedness decreases the likelihood of sexual transmission. Horizontal transmission did occur between closely related individuals on at least four occasions (transmitted from their mother, sister, nephew or niece, aunt or uncle, or cousins) during the first phase of the epidemic.

In 2004, one adult male from E2 (aged 10 years) became infected. This event coincided with a more rapid spread of the virus (figure 2a), particularly among males (figure 2b). Beginning in 2005, new cases in E1 emerged following intrusions of neighbouring males. These infections occurred in older individuals when compared with the local cases in E2 (mean age: 12.9 years and 7.1 years, respectively; permutation test: \( p = 0.024 \); figure 2c,d). Therefore, movements of adult males from one enclosure to another (i.e. voluntary intrusions and transfers; figure 1f) may have played a major role in accelerating the spread of the SIVmnd-1 epidemic after 2005, presumably owing to the aggressive interactions that followed.
Figure 3 displays kin relationships and the associated distribution of SIVmnd-1 cases within the matrilines of the study population as of 2009. A dynamic, year-to-year representation is also available (see the electronic supplementary material, S1). Of the 30 local cases recorded in E2, 25 (83%) occurred within the same matriline. Thirteen (43%) were the offspring of infected mothers and nine (30%) were either the siblings or the grandchildren of an infected individual. The observed maternal kinship effect was statistically significant even after the exclusion of cases where maternal transmission was suspected ($P < 10^{-3}$), which strongly suggests transmission within the matriline. The cases recorded outside the matriline emerged after 2008 and concerned mature individuals (one 11-year old female and three males aged 10, 12 and 20 years, respectively). Together with the advanced age of the individuals transferred from enclosure E1 after seroconversion (figure 2d), these observations suggest that SIVmnd-1 transmission between unrelated individuals mainly occurs after sexual maturity.

(c) Natural transmission modes of SIVmnd-1
Data show that transmission during childhood occurred between related individuals. Hence, in addition to the aggressive and sexual transmission modes, a third route had to be considered to explain the cases of transmission among kin. This route does not directly represent horizontal transmission, but rather an association with the infection status of kin. A Bayesian framework was used to quantify the contribution of the three potential transmission modes: aggressive ($\epsilon_A^F$), sexual ($\epsilon_S^F$) and familial ($\epsilon_F^F$), with G representing the gender ($G = M$ for males and $G = F$ for females).

Results confirmed that one transmission mode alone could not account for the observed prevalence of SIVmnd-1 within the study population (figure 4). However, owing to the large variances in the posterior distributions, only qualitative conclusions pertaining to the respective contribution of each transmission mode could be drawn from this analysis.

In males, the aggressive route was important but could not explain all transmission cases alone (for $\epsilon_A^M$ mode = 0.66, 95% highest posterior density (HPD) interval (0.29–0.89)). Coefficients associated with familial and sexual transmission were smaller (for $\epsilon_F^M$ mode = 0.16, 95% HPD (0–0.49), for $\epsilon_S^M$ mode = 0, 95% HPD (0–0.45)). This suggests that, although familial transmission was observed in the early epidemic, transmission among adult males (observed after 2004) was also efficient.

The low estimated weight of female-to-male sexual transmission is consistent with the fact that, before 2003, all adult males remained non-infected despite frequent mating with infected females (22 individuals were born from infected mothers before 2003). In females, only the coefficient associated with sexual transmission was significantly different from zero (for $\epsilon_S^F$ mode = 0.40, 95% HPD...
However, the uncertainty in the estimation of the model parameters does not allow us to exclude the possibility that the three modes have similar weights (for $A_{F}$: mode = 0.24, 95% HPD (0–0.61), for $B_{F}$: mode = 0.10, 95% HPD (0–0.66)).

Results are qualitatively not sensitive to the choice of weights for the kinship effect (see the electronic supplementary material, S2). Quantitative differences are observed for females. Since cases of familial transmission are often observed between mother and daughter, the weight of familial transmission is slightly larger when transmission occurs mainly between mother and daughter (for $u = 0.10$, mode = 0.12, HPD (0–0.62); and for $u = 0.90$, mode = 0.29, HPD (0–0.56)), while the weight of aggressive transmission is slightly smaller (for $u = 0.10$, mode = 0, HPD (0–0.60); and for $u = 0.90$, mode = 0.19, HPD (0–0.72)).

(d) The SIVmnd-2 epidemic
In contrast with SIVmnd-1, SIVmnd-2 was introduced into the study population by two male founders. New cases emerged from 1987 onwards after the initially infected males reached adulthood. Four other adult males became infected (one in 1987 at 15 years of age, two in 1989 at 8–9 years of age and one in 1992 at 12 years of age) and the virus was naturally extinguished from the population in 1999 upon the death of the last infected animal. SIVmnd-2-infected males were highly successful and sired 81 (73%) offspring. However, no female was infected. Overall, these results suggest that SIVmnd-2 was mainly transmitted by male-to-male aggressive interactions, while male-to-female sexual transmission was rare.

4. DISCUSSION
It is commonly asserted that SIV transmission occurs through sexual and/or aggressive interactions [17]. Challenging this paradigm, the results of the present study report an unexpected correlation between SIVmnd-1 infection and maternal kinship that does not involve vertical transmission. Such an effect has never, to our knowledge, been documented in any NHP species.

This finding was made possible because of the unique animal setting and the high quality of the dataset used, allowing for analysis of the interplay between mandrill behaviour, pedigree and the spread of the SIV epidemic. It raises new hypotheses on the transmission of SIV in natural NHP populations. Specific behavioural interactions among maternal kin may contribute to the observed familial effect. Allogrooming and wound care [34] facilitate saliva and blood exchanges between closely related individuals and represent a potentially significant mode of SIVmnd-1 transmission. Oral interactions through infant play behaviour [35,36] and food testing [37] may be another route of virus entry. Blood-sucking ectoparasites may also be a possible vehicle for horizontal
transmission among maternal kin and should be further investigated. Beyond social behaviour, genetic susceptibility within the infected matriline may also account for the familial effect observed [38–40]. Several mechanisms have already been highlighted to explain differential genetic susceptibility to HIV between individuals [41]. If the observed familial effect is owing to genetic susceptibility to SIVmnd-1, the CIRMF mandrill colony may provide an interesting animal model for further identification of genes and mechanisms associated with natural host resistance against retroviruses, including HIV. The further use of molecular epidemiological tools will allow us to reconstruct the history of SIVmnd-1 transmission within the study population and, hence, to support or refute horizontal transmission among kin versus the inheritance of genetic determinants of susceptibility. Obtaining refined information about aggressive interactions, and social and sexual networks within the study population to improve the power of the statistical approach by including more complex interactions in the model, will also represent the next challenge. Such data will allow us to clarify the different hypotheses generated from the present study and provide more accurate estimates of the weight of the different transmission routes.

Furthermore, through the observed dynamics of SIVmnd-1 and SIVmnd-2, the present study highlighted fundamental differences in the way both viruses spread. Whereas SIVmnd-1-infected individuals of both genders and all ages in the population throughout the study period, SIVmnd-2 was transmitted to adult males only and eventually went extinct. Most of the epidemiological differences observed can be explained by differences in the intrinsic characteristics of the initially infected individuals. Although aggressive male-to-male transmission was efficient, the lack of challengers to the SIVmnd-2 infected males in the early stages of the study population might have precluded the persistence of the virus. The extinction of SIVmnd-2 might also be attributed to the absence of transmission to any female, which might have prevented familial transmission and stabilization of the epidemic within the group. Ultimately, the main difference between the two viruses may be the prevalence of male-to-female sexual transmission. First, although closely related, both variants may present different features resulting in a more efficient male-to-female sexual transmission for SIVmnd-1. Differences in pathogenicity between SIVmnd-1 and SIVmnd-2 have already been suggested [42], and important functional differences between closely related strains are also known in the HIV system (HIV-2 being less easily transmitted, less progressive and more geographically confined than HIV-1) [43–45]. Alternatively, male-to-female transmission may be rare for both SIV variants and transmission from adult males to females may in fact occur through aggressive interactions when choosy females defend their group from unwanted male intrusions [46]. Because cross-territory intrusions happened only after 2005, the latter hypothesis might also explain why SIVmnd-2 was not passed on to females.

Finally, these findings also provide insights into the role of the host’s social structure in the evolution of pathogens.
From an evolutionary point of view, the unique combination of transmission modes described (i.e. familial, aggressive and sexual) is consistent with theoretical models predicting that microparasites should undergo selection to ensure both their local persistence [47] and transmission between patches [16] in hosts living in fragmented populations. Owing to the limited number of resident adult males within groups [21], male-to-male aggressive interactions ensure between-group transmission in mandrills, while familial transmission may represent an important evolutionary complement to ensure the local persistence of the virus. Male-to-female sexual transmission, which cannot be excluded, may contribute to both local persistence and the infection of new populations.

This study complied with animal care regulations and applicable national laws in Gabon.

We thank Jean Wickings and the past and present staff of the CIRMF Primate Centre for keeping detailed records of the population, as well as Joanna Setchell for helpful discussions. We thank John Arnould, Jacques-Olivier Fortrat, Stéphane Bertagnoli, Jean-Michel Gaillard, Jacques Le Pendu and Sabrina Renaud for their constructive comments on the manuscript. We are also grateful to Mike Begon and two anonymous reviewers whose helpful comments greatly improved the present manuscript. The present study was supported by Centre International de Recherches Médicales de Franceville (CIRMF), which is jointly funded by Total Gabon, the Gabonese government and the French Ministry of Foreign and European Affairs (M.A.E.E.). D.V. and J.P.G. are funded by the M.A.E.E. D.F. and D.P. are both members of the ECOFECT LabEx.

REFERENCES


SIV transmission in a primate population

D. Fouchet et al.


33 Onanga, R. et al. 2002 High levels of viral replication contrast with only transient changes in CD4(+) and CD8(+) cell numbers during the early phase of experimental infection with simian immunodeficiency virus SIVmnd-1 in Mandrillus sphinx. J. Virol. 76, 10256–10263. (doi:10.1128/JVI.76.20.10256-10263.2002)


42 Souquière, S. et al. 2009 Simian immunodeficiency virus types 1 and 2 (SIV mnd 1 and 2) have different pathogenic potentials in rhesus macaques upon experimental cross-species transmission. J. Gen. Virol. 90, 488–499. (doi:10.1099/vir.0.005181-0)


