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The ecology of primate retroviruses – An assessment of 12 years of retroviral studies in the Taï national park area, Côte d'Ivoire

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ABSTRACT

The existence and genetic make-up of most primate retroviruses was revealed by studies of bushmeat and fecal samples from unhabituated primate communities. For these, detailed data on intra- and within-species contact rates are generally missing, which makes identification of factors influencing transmission a challenging task. Here we present an assessment of 12 years of research on primate retroviruses in the Taï National Park area, Côte d'Ivoire. We discuss insights gained into the prevalence, within- and cross-species transmission of primate retroviruses (including towards local human populations) and the importance of virus–host interactions in determining cross-species transmission risk. Finally we discuss how retroviruses ecology and evolution may change in a shifting environment and identify avenues for future research.

Introduction

The close evolutionary relationship and similar physiology of non-human primates (hereafter NHP) and humans make NHP a likely source for the zoonotic transmission of viruses (reviewed in: Calvignac-Spencer et al., 2012b; Gessain et al., 2013; Gillespie et al., 2008; Wolfe et al., 1998). NHP retroviruses are arguably the best illustration of this prediction (e.g., simian origins of human immunodeficiency viruses HIV-1 and 2; reviewed in: Sharp and Hahn, 2011) and among the best-characterized NHP viruses. However, despite decades of research, behavioral and ecological factors affecting within- and between-species transmission of retroviruses in NHP remain poorly understood. A full understanding of the ecology of primate retroviruses requires knowledge of the virus itself, the host–virus interface, and the host's ecology. This necessitates multidisciplinary research efforts that are only possible where primatology research projects have been run on a long-term basis in collaboration with veterinarians and molecular biologists.

Taï National Park in the Côte d'Ivoire hosts one of the world's best-studied wild primate populations (Fig. 1). Studies on the chimpanzees and monkeys of Taï National Park were initiated in 1979 and 1989 respectively (Boesch and Achermann, 2000; McGraw et al., 2007). Taï National Park harbors 11 different NHP species, many of which regularly interact (McGraw et al., 2007). For example, many spend much of their time in polyspecific associations (e.g. red colobus – *Piliocolobus badius badius*, sooty mangabeys – *Cercocebus atys*, and Diana monkeys – *Cercopithecus diana*; McGraw and Bshary, 2002; Noë and Bshary, 1997). Hunter–prey relationships also exist in this community as chimpanzees (*Pan troglodytes verus*) regularly hunt other NHP (Fig. 2; Boesch and Boesch, 1989). Local human populations in the area also interact with the primate community, mostly through hunting of

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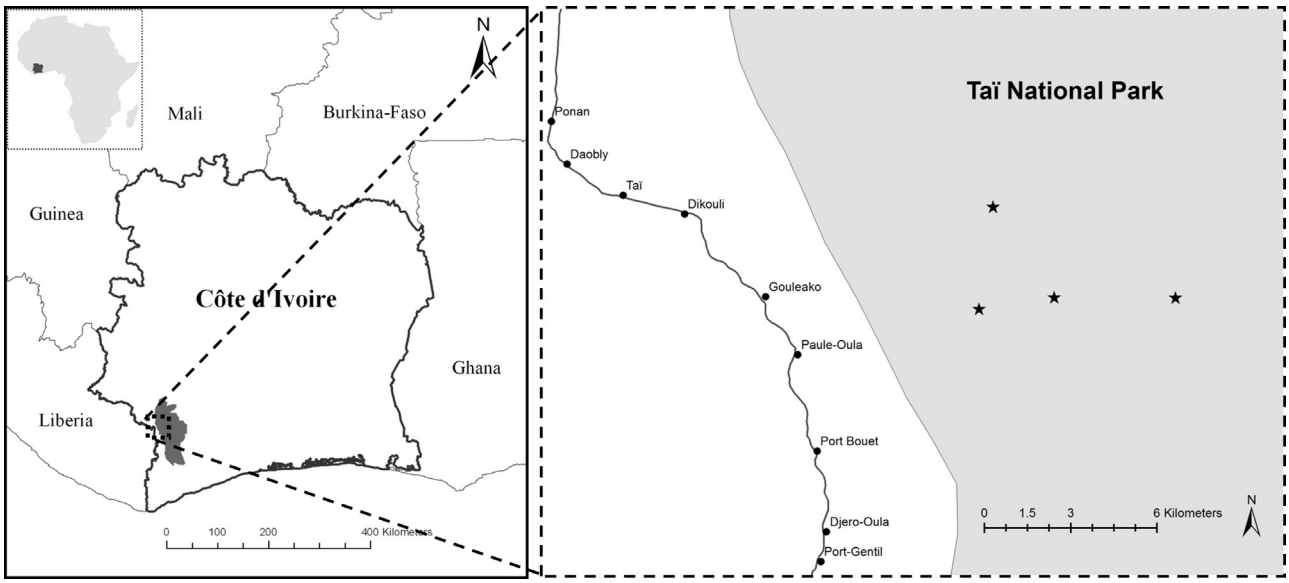

Fig. 1. Location of the main study area. (a) Location of the Taï National Park in Africa and Côte d'Ivoire; (b) close-up of the research area. Stars indicate primatology research camps. This figure was provided by Genevieve Campbell and Hjalmar Kühl and is derived from Campbell et al. (2011).

NHP (Fig. 2; Refisch and Koné, 2005). This complex set of interactions offers ample opportunities for microorganism transmission: through biting, grooming, mating and hunting-related activities such as butchering of carcasses and meat consumption.

In 2002, a perennial veterinary program began its association with the primatology research program. The latter has provided data and access to three groups of well-habituated chimpanzees (Boesch and Achermann, 2000) and well-habituated monkey species (McGraw et al., 2007). This has helped make the primate community in Taï National Park one of the rare instances where thorough data are generated regarding primate ecology and the microorganisms that infect these same individuals (Calvignac-Spencer et al., 2012b). This is particularly true for retroviruses, whose diversity and transmission patterns have been scrutinized since the very beginning of the veterinary studies of this community (although with some bias). These insights are augmented by human health projects that have spawned in the area around Taï National Park (Ayouba et al., 2013; Calvignac-Spencer et al., 2012a) allowing the study of zoonotic retroviral transmission stemming from this primate community. Here we review 12 years of research on primate retroviruses in the Taï National Park area and highlight how the long-term primatology research program (Boesch and Achermann, 2000; McGraw et al., 2007) allowed virological results to be embedded in a relevant ecological context. We focus on results relevant to the ecology of the three retroviruses that have been extensively studied in Taï National Park; namely the simian immunodeficiency viruses (SIV) and their human counterparts (HIV), the simian T-cell leukemia viruses type 1 (STLV-1) and their human counterparts (HTLV-1), and the simian foamy viruses (SFV). We summarize insights gained into their prevalence, virus–host interactions, within- and between-species transmission, within and between NHP species and into the surrounding human population. Finally, we discuss the likely impact of shifting primate community dynamics in the framework of ongoing "natural" and anthropogenic changes.

Prevalence and diversity of retroviruses in Taï National Park NHP

To date in the NHP of Taï National Park, SIV has been detected in sooty mangabeys (SIVsmm), western red colobus (SIVwrc) and olive colobus (SIVolc). The prevalence of SIVsmm in sooty mangabeys is high (apparent prevalence=59% (95% CI=0.35–0.88); Santiago et al., 2005). Similarly, the prevalence of SIVwrc in the red colobus population is reported to be one of the highest observed in wild NHP (apparent prevelance=82% (95% CI=0.66–0.98); Leendertz et al., 2010), whereas SIVolc has so far only been reported in a single olive colobus monkey (Courgnaud et al., 2003). Strict host specificity was observed for the SIV strains found in these NHP (Courgnaud et al., 2003; Leendertz et al., 2010; Liégeois et al., 2009). A collection of fecal samples obtained from the other six monkey species living in the park were screened both serologically and by PCR without any positive results (Locatelli et al., 2011). However, since sampling sizes were very small ($n \leq 10$) except for two species: black and white colobus (*Colobus polykomos*, $n=27$ distinct individuals) and Diana monkeys ($n=23$ distinct individuals), low prevalences cannot be ruled out. Finally, the Taï National Park chimpanzee population, like other *Pan troglodytes verus* populations (Gao et al., 1999; Prince et al., 2002; Santiago et al., 2002), is not infected with SIVcpz ($n=32$, out of a total of 300 chimpanzees living in the park; Leendertz et al., 2011), the chimpanzee specific virus which infects the central and east African chimpanzee subspecies *Pan troglodytes troglodytes* and *Pan troglodytes schweinfurthii* (Keele et al., 2006).

STLV-1 has been detected in sooty mangabeys, red colobus monkeys and chimpanzees. Three of five sooty mangabeys tested in Taï National Park were infected with STLV-1, which does not allow for an accurate estimation of the prevalence in this species (Calvignac-Spencer et al., 2012a; Traina-Dorge et al., 2005). The prevalence of STLV-1 could be estimated in red colobus monkeys (apparent prevalence=50% (95% CI=0.29–0.71); Leendertz et al., 2010). It is markedly higher than at Kibale National Park in Uganda (apparent prevalence=6% (95% CI=0.01–0.20); Goldberg et al., 2009). Behavioral differences between these red colobus populations might play a role in these different prevalences; higher seasonality in Taï National Park seems to lead to a distinct breeding season with higher competition, promiscuity and aggression rates when compared to the Kibale community where births occur year round (Leendertz et al., 2010). Interestingly, all red colobus individuals in Taï (and Kibale) that tested positive for STLV-1 were co-infected with either SIV or SFV or both (Goldberg et al., 2009; Leendertz et al., 2010). In chimpanzees, the prevalence of STLV-1 is also high (apparent prevalence=46% (95% CI=0.28–0.65); Junglen et al., 2010; Leendertz et al., 2004, 2003). The STLV-1 strains circulating in these NHP are not strictly species-specific,

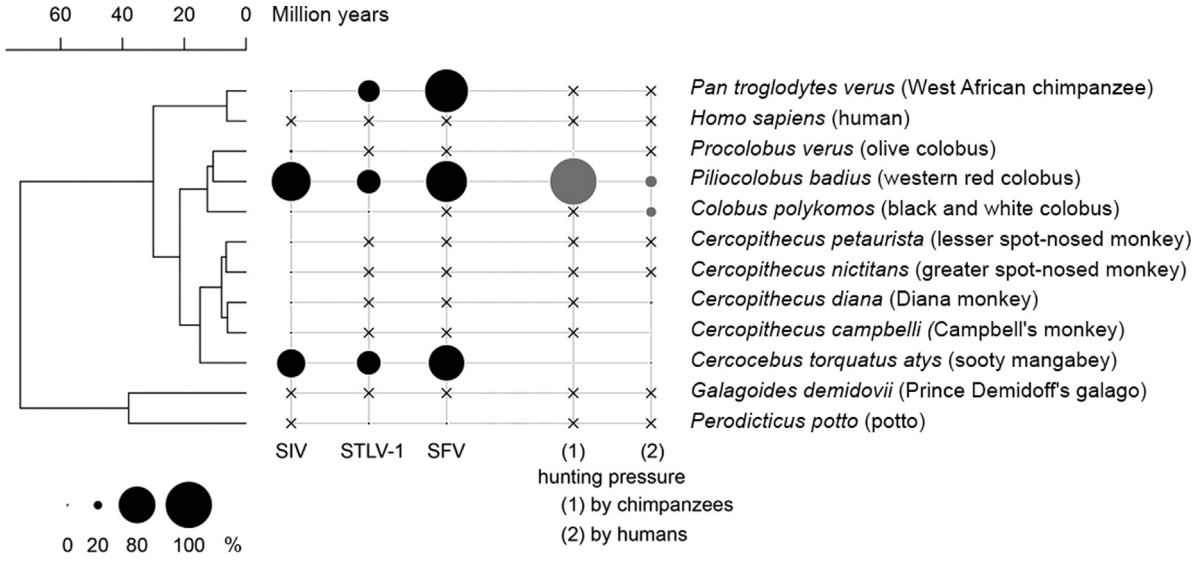

Fig. 2. Phylogenetic relationships, retroviral prevalence and hunting pressure on primates in Taï. This maximum clade credibility tree was identified from a sample of 1000 posterior trees obtained from the 10k project (version 3; based on eleven mitochondrial, six autosomal genes, and two Y-chromosome genes using a Bayesian MCMC performed with MrBayes under a calibrated, relaxed clock model; Arnold et al., 2010). Time axis is in millions of years. All branches are supported by maximal posterior probability values (1.0) but the two supporting the cercopithecine and the spot-nosed monkey clades (0.86 for both). Circle size is proportional to prevalence (black circles) or hunting pressure (gray circles).

yet STLV-1 infecting sooty mangabeys on the one hand and red colobus and chimpanzees on the other, form two relatively homogeneous clades (Calvignac-Spencer et al., 2012a). This suggests that the generally assumed lack of host specificity of STLV-1 may not hold true at this small geographic scale.

SFV has been found in sooty mangabeys, red colobus and chimpanzees. SFV prevalence in sooty mangabeys seems high, but the sample size is still too small to derive a meaningful prevalence estimate (nine positive individuals out of twelve tested; J Gogarten and F Leendertz unpublished data). SFV in red colobus has one of the highest prevalences of all retroviruses so far tested for at Taï National Park (apparent prevalence=86% (95% CI 72–100); Leendertz et al., 2010). This is a similarly high prevalence as found in red colobus in East Africa and non-human primate populations in general (Calattini et al., 2004; Goldberg et al., 2009; Liu et al., 2008). SFV also infects Taï National Park chimpanzees at very high prevalence (apparent prevalence=90% (95% CI=0.80–0.95); Blasse et al., 2013; Liu et al., 2008; Morozov et al., 2009), which is similar to prevalence estimates at other chimpanzee study sites (44–100%; Liu et al., 2008). SFV from Taï National Park NHP conform to the strong pattern of host–parasite co-divergence observed in other vertebrates (Han and Worobey, 2012; Leendertz et al., 2008; Morozov et al., 2009; Murray and Linial, 2006; Switzer et al., 2005).

In summary, sooty mangabeys and red colobus are infected at high prevalence by all three retroviruses while chimpanzees are not infected by SIV but frequently infected with STLV-1 and SFV. For the other primate species found in Taï National Park the occurrence of retroviruses is currently not known, but their genetic relationship to other retrovirus-infected NHP in other parts of Africa suggests they could serve as hosts for these viruses.

Within-species transmission of retroviruses in Taï National Park NHP

Understanding retroviral transmission within a host species is a necessary first step for understanding retroviral ecology. Although within-species transmission dynamics seem an obvious area where retrovirology and primatology could synergistically collaborate, it remains essentially unexplored. This is true at Taï National Park as well, where only a handful of studies have investigated within-species retroviral transmission patterns.

The modalities of transmission have been partially addressed for a number of host–virus combinations. Both SIVsmm and SFVcpz were shown to be regularly transmitted both vertically (mother-to-infant) and horizontally (Blasse et al., 2013; Santiago et al., 2005). STLV-1 in chimpanzees is more rarely transmitted from mother to offspring (only 2/17 infants and juveniles born from STLV-1 positives mothers tested positive thus far; Leendertz et al., 2004). This rate is similar to the vertical transmission rate described for humans that breastfed over 12 months (15.7%; Hino et al., 1996) but it should be noted that here chimpanzee mother status was only determined at the time of this cross-sectional study implying this transmission rate can only be an overestimate (one of the mothers might have been STLV-1 negative throughout their breastfeeding). The importance of STLV-1 horizontal transmission during adulthood is even more equivocal, as many infections appear to arise due to transmission from red colobus, which may occur during frequent hunting of red colobus by chimpanzees (hunting preferences described in detail below); the slow evolutionary rate and lack of depth (in terms of sampling viral diversity) has prevented an understanding of STLV-1 epidemiological processes (Junglen et al., 2010; Leendertz et al., 2004).

As retroviruses reach high prevalences in Taï National Park, an important question is whether individuals accumulate multiple-strains over their lifetime (Goffe et al., 2012). SIVsmm positivity is age-structured, with infections detected more often in adults than juveniles. This could be a function of more frequent aggressive interactions and increased sexual activity associated with adulthood (Santiago et al., 2005). Distinguishable SFVcpz strains, likely the result of multiple independent infections, were shown to accumulate with age in chimpanzees. SFVcpz infection appears to first occur via vertical transmission but is followed in adult life by the acquisition of further infections, possibly stemming from aggressive interactions (Blasse et al., 2013). Interestingly, sex does not seem to influence the accumulation of SFVcpz, which may reflect the involvement of both sexes in aggressive interactions (Blasse et al., 2013). STLV-1 infection in chimpanzees shows a comparable trend, with seropositivity/PCR positivity increasing with age (Junglen et al., 2010; Leendertz et al., 2004), which might be a result of age related hunting activity (see below).

Most NHP live in complex social systems, whose organization likely influences retroviral transmission (Griffin and Nunn, 2012). Santiago et al. (2005) examined the distribution of SIVsmm positivity with respect to dominance rank and demonstrated an excess of high ranking females among SIVsmm positive females. A number of possible explanations for the observed pattern were proposed (e.g., increased mating or grooming behavior associated with higher rank) but the exact mechanism driving this pattern remains unknown (Santiago et al., 2005). While intragroup relationships play a role in the epidemiology of retroviruses, interactions between groups are also expected to play a major role in shaping retroviral transmission patterns. NHP exhibit a huge degree of variation in intergroup dynamics and social structure, and understanding this variation has been a focus of primatologists for several decades (Sterck et al., 1997; Van Schaik and Hooff, 1983; Wrangham, 1980). For example, while female philopatry (i.e., that females stay in their natal group their entire lives while males typically disperse) is common among many NHP species, red colobus exhibit a strong dispersal bias whereby sub-adult females leave their natal groups (Struhsaker, 2010). In these species, the fact that dispersal generally occurs before or concomitantly with sexual maturity and that extra-group copulations are rare, may explain the finding that SIVwrc strains circulating in two red colobus groups were found to segregate according to a particular individual's group membership (Locatelli et al., 2011). Other important grouping behaviors (e.g., fission, fusion, intergroup aggression) are also expected to influence patterns of retroviral genetic diversity, although evidence remains weak and largely circumstantial (Locatelli et al., 2011). The aforementioned studies demonstrate how behavioral observations can aid in the interpretation of retroviral genetic diversity, while highlighting that successful examples of such collaboration are limited to date.

Cross-species transmission of retroviruses among Taï National Park NHP

Many NHP at Taï National Park interact regularly with one another. The position of chimpanzees within this interaction network closely mimics that of humans (Fig. 2). As a result of this likeness and the physiological and genetic similarity of chimpanzees to humans, the chimpanzee/NHP prey system has been used to provide insight into zoonotic transmission risk in human/NHP prey systems (Boesch, 1994; Leendertz et al., 2004, 2008). However, major differences exist between chimpanzee and human hunting behavior: the former species concentrates largely on a single prey, the red colobus, while humans exhibit much less specificity in hunting preference (Fig. 2). Bushmeat market analyses reveal that nearly all NHP species found in Taï National Park are hunted and sold around the park. In markets located on the western edge of Taï National Park, no species accounts for less than 5% of the overall NHP bushmeat biomass, with red colobus and black and white colobus almost equally present (respectively 24.7% and 22.3%; Refisch and Koné, 2005). In contrast, chimpanzees were observed to capture 215 red colobus over a 12 year period, while only successfully capturing six olive colobus and a single sooty mangabey (Boesch and Achermann, 2000). This means that over their lifespan, chimpanzees will be exposed to several hundred kilograms of meat infected with retroviruses, the vast majority of which will be coming from red colobus (Leendertz et al., 2011), while humans will be exposed to retroviruses from a much broader range of species.

Results at Taï National Park have confirmed the importance of red colobus as a source of retroviruses for chimpanzees. Most STLV-1 sequences obtained from chimpanzees belong to clades consisting of one of their prey's STLV-1, with a majority being closely related to STLV-1 identified in red colobus (Leendertz et al., 2004). Two SFVcpz-infected individuals were also found to harbor SFV from their prey, in both cases SFVwrc from red colobus (Leendertz et al., 2008). To date, no evidence of a transmission chain in chimpanzees showing the spread of newly acquired retrovirus has been documented at Taï. SIVcpz, which arose in Central West African chimpanzees after their split from the Western sub-species, consists of a mosaic genome of SIVs from two of its prey species (red-capped mangabeys – *Cercocebus torquatus* – and either mustached guenons – *Cercopithecus cephus*, mona monkeys – *Cercopithecus mona*, greater spot-nosed monkeys – *Cercopithecus nictitans* – or an ancestor of these cercopithecines; Courgnaud et al., 2003; Sharp et al., 2005). The Taï National Park chimpanzees also regularly consume SIV infected monkeys, especially red colobus infected with SIVwrc. This triggered a targeted search for SIVwrc infections in the Taï National Park chimpanzees, but despite extensive efforts (about 10% of the Taï National Park chimpanzee population was tested), no seropositive ($n=23$) or PCR-positive ($n=30$) individual could be detected (Leendertz et al., 2011).

A number of recent studies have provided insights into host mechanisms for SIV/HIV resistance and how these are evaded by different viral genes; these studies have provided evidence for the role of a number host receptors (e.g., CCR5; Samson et al., 1996) and restriction factors (e.g., APOBEC3G, TRIM5a, tetherin, reviewed in; Malim and Bieniasz, 2012), as well as a number of viral genes that antagonize these antiviral host restriction factors (e.g., Vif, Vpr, Vpu, Nef, reviewed in: Kirchhoff, 2010). With respect to the lack of SIVwrc infections in the Taï National Park chimpanzees, a seemingly important interaction is that of host APOBEC3G and lentiviral viral integration factor (Vif). APOBEC3G is an intracellular cytidine deaminase that restrict retroviruses by hypermutating their genomes. Retroviruses counteract APOBEC3G with the activity of Vif, which promotes APOBEC3G degradation by the proteasome. The binding site of Vif onto NHP APOBEC3G was recently shown to be well conserved among cercopithecines, although the sequence itself was under strong positive selection (Compton and Emerman, 2013). By contrast, the site of binding of Vif in the colobine APOBEC3G has shifted, most likely as a way for colobine SIVs to cope with a unique insertion in their host's APOBEC3G sequence that might have concealed the “classical” binding site (Compton and Emerman, 2013). A by-side of this adaptation is that SIVolc (the only colobine SIV tested for sensitivity to APOBEC3G in: Compton and Emerman, 2013) is fully sensitive to the activity of all other NHP APOBEC3G against which it was tested. While further studies are needed to specifically verify that SIVwrc is efficiently restricted by chimpanzee APOBEC3G, it is restricted by human APOBEC3G, which is strictly identical to chimpanzee APOBEC3G at the Vif binding site (Compton and Emerman, 2013). This suggests that SIVwrc is also efficiently restricted by chimpanzee APOBEC3G, preventing infections from propagating, despite extremely high levels of exposure. Conversely, given that SIVsmm efficiently inhibits human APOBEC3G, the lack of SIVsmm transmission into the Taï National Park chimpanzee population (which contrasts with the frequent transmission of SIVsmm to humans; see below) may either be a result of the rarity with which chimpanzees hunt this species or another, as yet undescribed, restriction factor.

Zoonotic transmission of retroviruses in the Taï National Park area

HTLV-1 strains found in West Africa mostly belong to the HTLV-1 subtype A, often referred to as the Cosmopolitan subtype, a clade restricted to humans for which there is no evidence of recent zoonotic transmission events. This makes humans inhabiting the Taï National Park area an ideal test case for local STLV-1 transmission, as zoonotic strains would be immediately identifiable through phylogenetic analyses. Out of ten HTLV-1 strains identified in villages bordering Taï National Park, six belonged to the

subtype A while four were most closely related to local NHP STLV-1 strains (Calvignac-Spencer et al., 2012a). Interestingly, three were likely the results of cross-species transmission from sooty mangabeys while another apparently stemmed from a red colobus monkey, strongly suggesting multiple zoonotic transmission events have occurred in this hunter/prey system.

SIVsmm appears to have crossed the species barrier several times in the Taï National Park area and it is hypothesized that the West African HIV-2 epidemics started here (Santiago et al., 2005). In fact, SIVsmm transfer seems to happen relatively frequently as evidenced by a recent study documenting ongoing transmission of SIVsmm through the identification of a ninth HIV-2 lineage (Ayouba et al., 2013). Mirroring what is observed in the chimpanzee population, SIVwrc and SIVolc have not been detected in the local human population. As discussed above, this might be due in part to the action of human APOBEC3G, which efficiently restricts SIVolc and, maybe, SIVwrc (Compton and Emerman, 2013).

While zoonotic transmission of SFV to humans has been documented in numerous studies, whether secondary transmission occurs remains an open question (Betsem et al., 2011; Mouinga-Ondémé et al., 2012; Switzer et al., 2004, 2008; Wolfe et al., 2004). At the moment these transmission events, thought to occur during bushmeat hunting, appear to remain isolated cases that occur infrequently and SFV has not become established in a human population (reviewed in: Gessain et al., 2013). Around Taï National Park there are no conclusive data on SFV infections in humans; serological evidence suggested that infections may be present (M. Peeters unpublished data; Ali et al., 1996) but no virus genetic material could be amplified from these samples (F Leendertz unpublished data).

Retroviruses in a changing environment

The ongoing massive climate and habitat changes induced by human activities have led many primate communities into non-equibrilium states (Chapman et al., 2010). For example, red colobus are also the most frequently hunted prey of the eastern chimpanzees (*P. t. schweinfurthii*) at Ngogo, in Kibale National Park, Uganda (Mitani and Watts, 1999; Watts et al., 2012), but unsustainable levels of chimpanzee hunting pressure have recently caused this red colobus population to undergo a major decline (Teelen, 2008). This dynamism in the backdrop in which retroviruses circulate creates new evolutionary pressures and epidemiological processes which might result in new patterns of cross-species and zoonotic transmission. At Kyambura Gorge in Queen Elizabeth National Park in Uganda, no red colobus are present and black-and-white colobus (*Colobus guereza*) are the most frequently hunted prey (Krüger et al., 1998). This suggests that chimpanzees shift their prey in the face of changing availability, which will likely have major impacts on zoonotic retroviral transmission patterns; especially if resistance is strain specific as discussed above. For example, if sooty mangabeys become a regular prey item of the chimpanzees in Taï, SIVsmm transmission to chimpanzees could be facilitated (assuming present low exposure is the main explanation for the absence of SIVsmm infection in chimpanzees). Human food preferences and hence exposure may also shift in light of changing prey availability. At Taï National Park, current human hunting levels of all monkeys species have led to their extirpation in many areas within the park (N'Goran et al., 2012). The dramatic changes in monkey population distributions at Taï National Park will likely have major impacts on their retroviruses.

Conclusions

The retroviral studies pursued at Taï National Park highlight the importance of the ongoing integration of primate ecology and behavior findings for the interpretation of viral data. The primatology research programs will be indispensable partners for improving our understanding of retroviral ecology in the coming years. Collaborative efforts at other long-term field sites have already yielded results as striking as the discovery of increased mortality, decreased fitness and AIDS-like disease symptoms caused by SIVcpz in the chimpanzees of Gombe, Tanzania (Keele et al., 2009). Findings such as these would not have been possible without dense longitudinal sampling in combination with detailed primate behavior and life history data. Yet the infection status of many NHP species at Taï National Park remains unknown and even in those species that have been carefully scrutinized, within-species retroviral transmission dynamics are poorly understood. Further, the fitness costs incurred by hosts, genetic counter-strategies deployed in the arms race between viruses and hosts, and the interplay with concurrent co-infections and a host's resident microbiome remain completely unexplored at Tai National Park. Fortunately, the use of non-invasive samples is coming of age, greatly expanding the number of samples and species available for study (Santiago et al., 2002). Ultimately, an increased knowledge about the viral ecology within the park will hopefully help provide a better understanding and predictive framework for the emergence of retroviruses in this area, particularly in the face of a changing environment.

Authors' contributions

JFG, CAK, SCS, SAJL, SW and FHL spearheaded the writing of this manuscript. ECH, AM, IK, MP, RMW, CB and BHH provided essential insights and criticisms. All authors read and approved the final manuscript.

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