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Review

HTLV-3/4 and simian foamy retroviruses in humans: Discovery, epidemiology, cross-species transmission and molecular virology

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ABSTRACT

Non-human primates are considered to be likely sources of viruses that can infect humans and thus pose a significant threat to human population. This is well illustrated by some retroviruses, as the simian immunodeficiency viruses and the simian *T* lymphotropic viruses, which have the ability to cross-species, adapt to a new host and sometimes spread. This leads to a pandemic situation for HIV-1 or an endemic one for HTLV-1. Here, we present the available data on the discovery, epidemiology, cross-species transmission and molecular virology of the recently discovered HTLV-3 and HTLV-4 deltaretroviruses, as well as the simian foamy retroviruses present in different human populations at risk, especially in central African hunters. We discuss also the natural history in humans of these retroviruses of zoonotic origin (magnitude and geographical distribution, possible inter-human transmission). In Central Africa, the increase of the bushmeat trade during the last decades has opened new possibilities for retroviral emergence in humans, especially in immuno-compromised persons.

Contents

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Introduction

A large proportion of viral pathogens that have emerged during the last decades in humans are considered to have originated from various animal species (Weber and Rutala, 1999; Wolfe et al., 2007). This is well exemplified by several recent epidemics such as those of Nipah, Severe Acute Respiratory Syndrome, avian flu, Ebola, monkey pox, and Hanta viruses (Flanagan et al., 2012).

When considering the huge diversity of animal reservoirs and the variety of factors leading to animal/human contacts followed by viral cross-species transmission, one can hypothesize that the emergence of new viruses of zoonotic origin is very probable, if not ineluctable. However, anticipating the species jumps, identifying high-risk viruses before they emerge in humans, and predicting when, how and with which magnitude such events can occur remains extremely difficult (Flanagan et al., 2012).

Indeed, emergence of a viral disease in Humans results from the succession of various events, often complex, implying several factors. Each of these steps, and of the associated factors, (of viral, host, environmental or socio-cultural origin) is crucial for the emergence success. Fortunately, the absolute necessity for a perfect connection between these different items may explain the relative rarity of viral emergence in Humans.

After the initial interspecies transmission *per se*, viruses disseminated into the human population through various and distinct mechanisms. Some of them are well characterized and understood, thus allowing a certain level of risk control and prevention. Surprisingly and in contrast, the initial steps that lead to the emergence of several viruses, and of their associated diseases, remain still poorly understood. Epidemiological field studies conducted in certain specific high-risk populations are thus necessary to obtain new insights into the early events of this emergence process (Parrish et al., 2008).

Human infections by simian viruses represent increasing public health concerns. Indeed, by virtue of their genetic and physiological similarities, non-human primates (NHPs) are considered to be likely the sources of viruses that can infect humans and thus may pose a significant threat to human population. This is well illustrated by retroviruses, which have the ability to cross species, adapt to a new host and sometimes spread within this new species (Locatelli and Peeters, 2012). Sequence comparison and phylogenetic studies have thus clearly showed that the emergence of human immunodeficiency virus type 1 (HIV-1) and HIV-2 in humans have resulted from several independent interspecies transmissions of different SIV types from Chimpanzees and African monkeys (including sooty mangabeys), respectively, probably during the first part of the last century (Aghokeng et al., 2006; Hahn et al., 2000; Plantier et al., 2009; Van Heuverswyn et al., 2006; Van Heuverswyn and Peeters, 2007). The situation for Human T cell Lymphotropic virus type 1 (HTLV-1) is, for certain aspects, quite comparable. Indeed, the origin of most HTLV-1 subtypes appears to be linked to interspecies transmission between STLV-1-infected monkeys and humans, followed by variable periods of evolution in the human host. Gessain and Mahieux (2000), Nerrienet et al. (2001), Sintasath et al. (2009a), Wolfe et al. (2005).

In this review, we will present the current available data on the discovery, cross-species transmission from monkeys and apes to humans, and molecular virology of the recently discovered HTLV-3 and HTLV-4 retroviruses, as well as on simian foamy retroviruses present in different human populations at risk, especially in central African hunters.

HTLV-3/HTLV-4 and related simian retroviruses

Human T Lymphotropic Viruses (HTLV-1, HTLV-2 and HTLV-3) as well as their related simian counterparts (STLV-1, STLV-2 and STLV-3) constitute the Primate T-cell Lymphotropic viruses (PTLV) group (Lairmore and Franchini, 2007). These different deltaretroviruses share several epidemiological and molecular characteristics. While PTLV-1 and PTLV-2 strains have been extensively studied since the 80's, studies on PTLV-3 are more recent but their number increased after the discovery of HTLV-3 in 2005 (Calattini et al., 2005; Wolfe et al., 2005). HTLV-4, the fourth HTLV retrovirus was also discovered in 2005, but a simian counterpart of this virus has not been identified to date (Sintasath et al., 2009a; Wolfe et al., 2005).

STLV-3/HTLV-3 discovery and epidemiological characteristics

The first STLV-3 strain (STLV-L/PH-969) was isolated in 1994, after co-culture of human cord blood lymphocytes with peripheral blood mononuclear cells (PBMCs) obtained from an Eritrean sacred baboon (*Papio hamadryas*) kept in captivity in a research laboratory in Leuven (Belgium) (Goubau et al., 1994). Sequencing of this virus, considered as the third lineage of the PTLV group and labeled thus as STLV-3, revealed a significant nucleotide divergence when compared to HTLV-1 and HTLV-2 prototypical sequences (40% and 38%, respectively). From December 2001, a series of other STLV-3 strains were then described. Those strains were Polymerase Chain Reaction (PCR)-amplified from the PBMCs of different monkey species, originating from West, Central and East Africa. Some of these STLV-3 viruses were present in wild-caught and/or wild-born animals living in Cameroon, Nigeria or Ethiopia, while other monkeys had been kept in captivity either in France in an ethological center, or in US zoos (Courgnaud et al., 2004; Meertens and Gessain, 2003; Meertens et al., 2002, 2003; Takemura et al., 2002; Van Dooren et al., 2001, 2004). Most STLV-3 serologies resembled an HTLV-2 pattern (gag-p24 > gag-p19 and env-gp21 GD21, +/− env-gp46 K55) when determined with an HTLV-1/2 commercial western-blot assay (HTLV2-4 WB GenLabs) and/or with other assays (INNOLIA) (Courgnaud et al., 2004; Meertens and Gessain, 2003; Meertens et al., 2002; Van Dooren et al., 2004). Very few data are available on the epidemiological determinants (i.e., age, sex, modes of transmissions) of STLV-3 infection within infected non-human primates (NHP) as to date, most studies were performed in wild-caught monkeys (Courgnaud et al., 2004; Liegeois et al., 2008; Sintasath et al., 2009a; 2009b; Takemura et al., 2002). STLV-3 prevalence varies greatly according to the NHP species, the geographical location and the methodologies used for animals sampling (living monkeys kept as pets in villages, dead animals with bushmeat samples collection of blood or of dried blood spots), but STLV-3 infection has not been linked to any pathology so far. STLV-1 and STLV-3 can be found in the same primate species and even in the same animal (Courgnaud et al., 2004; Liegeois et al., 2008; Sintasath et al., 2009a). Based on partial

or complete sequence analysis, STLV-3 lineage is now considered to be composed of four main subtypes (A–D) that roughly correspond to the geographical source of the strains. Subtype A comprises strains from East Africa (Ethiopia and Eritrea), subtype B corresponds to strains from West and Central Africa, while the subtypes C and D comprise strains from Central Africa. Therefore, and although STLV-3 genome can be edited by double-stranded RNA adenosine deaminase (Ko et al., 2012), its variability remains low as it is the case for other PTLVs.

In 2005, we and others reported the discovery of HTLV-3, a third HTLV type, in two asymptomatic individuals living in the rain forest area of South Cameroon (Calattini et al., 2005; Wolfe et al., 2005). Sera from those individuals exhibited HTLV indeterminate serologies when tested with commercial western-blot assays. These two viruses could not be isolated in culture, but the proviruses were PCR-amplified using a series of primers designed to amplify all known HTLVs and STLVs. More recently, the same teams reported the discovery of two additional HTLV-3 strains in other individuals (Lobak18 and Cam 2013AB) from Cameroon (Calattini et al., 2009; Zheng et al., 2010).

HTLV-4, another retrovirus found in humans

The fourth HTLV type (HTLV-4) consists so far of a unique human strain (1863LE), whose provirus was also found in the PBMCs obtained from a hunter living in Cameroon (Wolfe et al., 2005). The WB profile was also classified as HTLV-indeterminate. Phylogenetic studies indicated that HTLV-4 constituted clearly a monophyletic viral group and is considered as the oldest PTLV known-lineage (Switzer et al., 2009). Its sequence is equidistant from HTLV-1, HTLV-2 and HTLV-3, sharing only 62–71% nucleotide identity with them, respectively. Given previous epidemiological data on PTLV-1 and PTLV-3, it is likely that a monkey species is infected or has been infected with the simian counterpart of HTLV-4. However, despite screening of a large number of monkey species from Cameroon, Gabon and Democratic Republic of Congo, the search for such a virus has been unsuccessful up to now (Ahuka-Mundeke et al., 2012; Liegeois et al., 2012, 2008; Sintasath et al., 2009a, 2009b).

Molecular virology

HTLV-3 and HTLV-4 genomic organization

The prototype HTLV-4 proviral sequence (1863LE) is 8791-bp long (Switzer et al., 2009; Wolfe et al., 2005), while that of HTLV-3 (Pyl43) is 8553-bp long but contains a 366-bp deletion (Calattini et al., 2006a). Other HTLV-3 sequences are larger (8922-bp long for Lobak18, 8917-bp for 2026ND and 8913-bp for Cam2013AB) (Calattini et al., 2009; Switzer et al., 2006; Zheng et al., 2010). The overall HTLV-3 and HTLV-4 genomic organization is similar to that of other retroviruses with the presence of *gag*, *pro*, *pol* and *env* Open Reading Frames (ORF) encoding for structural and enzymatic proteins from non-spliced or singly-spliced mRNAs. As other HTLVs which belong to the complex retroviruses family, the provirus also contains additional ORFs: *tax* and *rex* on the sense strand and the Antisense Protein of HTLV-3 (APH-3) or of HTLV-4 (APH-4) ORFs on the antisense strand (Larocque et al., 2011) (Fig. 1). The presence of additional ORFs that would encode for auxiliary proteins is the subject of current investigations (see below). HTLV-3/-4 proviral DNA sequence is flanked by two complete Long Terminal Repeat (LTR) sequences. Contrary to HTLV-1 and HTLV-2 5′LTR that contains three 21-bp repeats sequences (also name Tax Responsive Elements), HTLV-3/-4 5′LTRs contain two of those motifs (Calattini et al., 2006a; Switzer et al., 2006, 2009). They correspond to transcription factor binding sites, where the RNA $Polymerase_{II}$ complex will be recruited through Tax interaction. A c-Myb binding site is also present in HTLV-4 5′LTR (Switzer et al., 2009). HTLV-3/-4 3′LTRs also contain a promoter whose regulation is currently unknown and that allows transcription of *aph-3/4* mRNAs (Larocque et al., 2011).

Due to the lack of HTLV-3 or HTLV-4 transformed cell lines, most results described below have been obtained either *in vitro*, after transfection of plasmids encoding different isolated proteins, or thanks to the use of HTLV-3 or HTLV-4 infectious molecular clones (Chevalier et al., 2008, 2007; Larocque et al., 2011).

HTLV-3/-4 cell entry

HTLV-3/-4 tropism *in vivo* is currently unknown, yet it is clear that the virus infects at least cells that belong to PBMCs. As HTLV-1/-2, which, in addition to dendritic cells, infect activated CD4+ and CD8+ T cells, respectively *in vivo*, we have shown that HTLV-3 surface envelope glycoprotein (gp46 or SU) binds to both activated CD4+ and CD8+ T, but also to naïve CD4+ T cells (Jones et al., 2009). The latter do not bind HTLV-1 or HTLV-2 SU and do not express detectable levels of heparan sulfate proteoglycans (HSPGs), neuropilin-1 (NRP-1) and Glucose transporter 1 (GLUT-1). A series of experiments also demonstrated that GLUT-1 serves at a post-binding step factor for HTLV-3. These results indicate that the complex of molecules used by HTLV-3 to bind and enter into CD4+ and CD8+ T lymphocytes *in vitro* differs from that of HTLV-1 and HTLV-2 (Fig. 2). Ongoing experiments are currently being performed using blood samples from STLV-3 infected animals and should allow the determination of PTLV-3 tropism *in vivo* in non-human primate cells.

Characterization of Tax-3/-4 proteins

Since Tax is both a viral transactivator and a viral oncogene, most experiments were aimed at characterizing the function of this protein. As in a subset of HTLV-1 carriers, HTLV-3 Tax (Tax-3) protein is expressed *in vivo* and allows an antibody response (Chevalier et al., 2006), while data are not available for Tax-4. Tax-3 sequence shares a number of key similarities with Tax-1, including the presence of a putative Nuclear Localization Signal (NLS), a functional CBP/p300 binding domain, a Nuclear Export Signal, a CR2 binding domain and a PDZ binding motif (PBM) (Chevalier et al., 2006). Importantly, this latter sequence is critical for the ability of the Tax-1 protein to transform cells *in vitro*. *In vitro* analyses showed that, as Tax-2, HTLV-4 Tax protein lacks a PBM but contains the other domains (Switzer et al., 2009).

When ectopically expressed, Tax-3 displays a strong nuclear localization with some cytoplasmic speckles. In addition to its ability to transactivate the 5′LTR, Tax-3 also activates the NF-kB pathway (Chevalier et al., 2008). A series of experiments was recently performed to compare the global gene expression profile of cells expressing Tax-1, Tax-2 and Tax-3. This led to the confirmation that Tax-3 was functionally analogue to Tax-1 (Chevalier et al., 2012). Functional data are not available for Tax-4.

HTLV-3 and HTLV-4 putative auxiliary proteins

HTLV-1 encodes 4 different auxiliary proteins: p13, p30, p12 and p8 which results from a proteolytic cleavage of p12 (for a recent review, see (Edwards et al., 2011). Those proteins play important roles in HTLV-1 infected cells: p30, notably promotes viral latency by decreasing expression of the viral transcription transactivator Tax, and in turn, favors viral persistence and escape from the immune system (Nicot et al., 2004). p12 mediates cell proliferation and differentiation by activating STAT-5 signaling (Collins et al.,

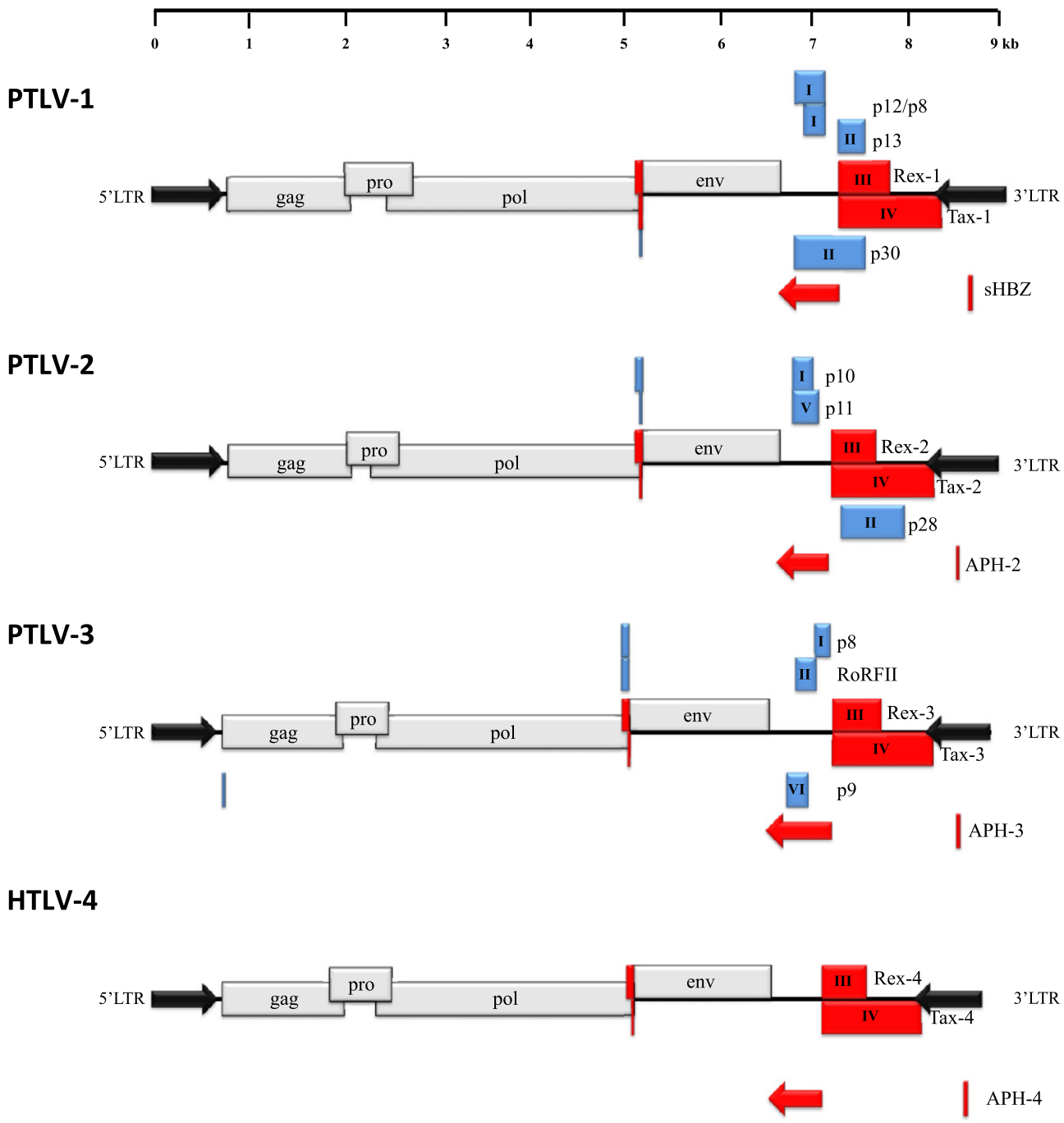

Fig. 1. Schematic representation of PTLV-1, -2, -3 and -4 genomic organization and coding potential. PTLVs are complex retroviruses displaying a conserved genomic arrangement. Grey: colored boxes indicating Open Reading Frame (ORF) encoding structural and enzymatic proteins (gag, pro, pol and env); Red: ORF encoding regulatory proteins (Tax, Rex, sHBZ (HTLV-1), APH-2, -3 and -4 (HTLV-2, -3 and -4, respectively)). Blue: ORF encoding auxiliary proteins: p8/p12, p13, p30 for HTLV-1; p10, p11, p28 for HTLV-2 and p8, p9, RoRFII for PTLV-3. The presence of ORFs encoding auxiliary proteins in HTLV-4 sequence was reported from in *silico* analyses only.

1999). p12 also promotes escape from immune surveillance by reducing the activation of CTLs and NK cells (Banerjee et al., 2007). p8, promotes conjugate formation and favors HTLV-1 transmission (Van Prooyen et al., 2010). Finally, p13 increases mitochondrial ROS (Reactive Oxygen Species) production, thus altering cell fate and thus favoring bypass of the immune surveillance (Silic-Benussi et al., 2010). p13 may also promote viral latency and favors viral persistence (Andresen et al., 2011).

As HTLV-1/-2 genomes, the sequence located downstream the HTLV-3/–STLV-3 or HTLV-4 *env* gene (named pX) contains several ORFs (open reading frames) encoding putative auxiliary proteins. Those proteins would be translated after complex splicing of their respective mRNAs. The presence of a doubly spliced mRNA that would encode a 85 amino acid highly hydrophobic and leucine rich protein named RorfII was reported several years ago in STLV-3 infected cells (Van Brussel et al., 1996). More recently, two other mRNAs that would encode a 63 and a 79 amino acid long proteins named p8 and p9, respectively were also amplified from STLV-3 infected cells (Turpin et al., 2011). Their function is currently under characterization.

Regarding HTLV-3, the presence of additional mRNAs has only been predicted for some strains after *in silico* analyses. A first

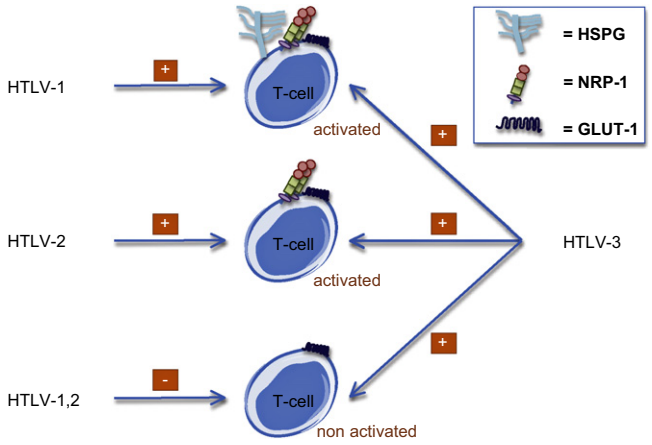

Fig. 2. Schematic representation of HTLV-1, -2 and -3, receptor complexes on T cells. HTLV-1 binding and entry require the presence of heparan sulphate proteoglycans (HSPGs), Neuropilin 1 (NRP-1) and glucose transporter type 1 (GLUT-1) on the surface of activated $CD4^+$ cells. On the other hand HTLV-2 preferentially targets CD8+ cells and is more dependent on the level of GLUT-1 and does not require HSPGs. Unlike HTLV-1 and HTLV-2, HTLV-3 binds to primary resting cells that do not express detectable levels of HSPGs, NRP-1 or GLUT-1. GLUT-1 may participate in the final fusion step of entry (Jones et al., 2011). −: cells cannot be infected, +: cells can be infected. Figure was made using Servier Medical Art.

report suggested the presence of four ORFs encoding putative 96, 122, 72 and 118 amino acid long proteins in 2026ND proviral sequence (Switzer et al., 2006). Surprisingly, only one ORF encoding a putative 131 amino acid long protein named ORF-I and previously reported for a STLV-3 sequence (Sintasath et al., 2009b) is present in Cam2013AB (both viruses belonging to subtype D) pX sequence (Zheng et al., 2010), while the presence of additional ORFs was not reported for Lobak18 or Pyl43.

In silico analyses conducted on HTLV-4_{1863LE} genome provirus revealed the presence of five putative ORFs that might encode proteins of 101, 161, 99, 133 and 115 amino-acids (Switzer et al., 2009). However, none of those ORFs starts with a methionine codon. Thanks to the construction of an HTLV-4 molecular clone, investigating whether those mRNAs are truly present in infected cells should be tested.

Antisense protein of HTLV-3 and HTLV-4

As described above, and as it is the case for all HTLVs, HTLV-3 and HTLV-4 proviruses encode antisense proteins (APH-3 and APH-4, respectively). Transcription of their respective mRNAs starts at different initiation sites. Both proteins were recently characterized from cells transfected with molecular clones (Larocque et al., 2011). APH-3 and APH-4 are 221 (28 kDa) and 158 (18 kDa) amino acid long, respectively and are translated from spliced mRNAs. Contrary to HBZ (Gaudray et al., 2002) and as their APH-2 HTLV-2 homologue (Halin et al., 2009), their sequence is devoid of a classical basic leucine zipper. It contains however LXXLL and LXXLL-like motifs that could allow binding to CBP/p300. *In silico* analyses suggest that APH-3 and APH-4 are more closely related to APH-2 than to HBZ (Larocque et al., 2011). However, in transfected cells, both proteins are localized into the cell nucleus and nucleolus, APH-3 being also partially detected in the cytoplasm (Larocque et al., 2011). Surprisingly, this localization is more similar to that of HBZ than to APH-2. As their HTLV-1 and HTLV-2 counterparts, both APH-3 and APH-4 repress transcription from the HTLV-1 5′LTR (Larocque et al., 2011). Whether APH-3 and APH-4 are widely expressed *in vivo*, such as their HTLV-1 and HTLV-2 counterparts (Douceron et al., 2012; Satou et al., 2006) remains to be determined.

Simian foamy viruses in humans

History

The first foamy virus was described in rhesus monkey kidney cells in 1954 (Enders and Peebles, 1954). Since then, foamy viruses have been isolated from many different animal species, including bovines, felines and equines and several non-human primate species (Meiering and Linial, 2001; Murray and Linial, 2006; Saib, 2003; Winkler et al., 1999). The prevalence of FVs in naturally infected animals is generally high, but can vary widely according to species and environmental conditions. Several epidemiological studies indicated that, among captive NHP populations (Blewett et al., 2000; Calattini et al., 2004; Hussain et al., 2003; Schweizer et al., 1999, 1995), but also in free-range colonies (Calattini et al., 2006c; Mouinga-Ondeme et al., 2010) and in the wild (Jones-Engel et al., 2005; Leendertz et al., 2010; Liu et al., 2008), SFV seroprevalence can reach up to 75–100% in adults, but is generally much lower in infants and juveniles (Liu et al., 2008). SFV virions are present at a high concentration in the saliva of infected NHPs (from 10^4 to 10^9 FV RNA copies/10^4 cells equivalent). In African green monkey and macaques NHPs, oral mucosa tissue is indeed an important site for viral replication (Falcone et al., 1999; Murray et al., 2008, 2006). These results, as well as epidemiological studies and long-term behavioral observations, strongly suggest a saliva-based means of transmission such as bites, licking, and mucosal splashes (Calattini et al., 2006c; Leendertz et al., 2010). The infection by SFV does not seem to cause any disease in infected NHPs, but specific studies have not been conducted to adress this question.

Foamy viruses in humans

The first foamy virus to be isolated in humans was reported by Achong et al., in 1971 from the cell culture of a Kenyan patient suffering of nasopharyngeal carcinoma (Achong et al., 1971). Recent phylogenetic studies demonstrated that this virus originated from the East African chimpanzee subspecies (*Pan t. Schweinfurtii*). This virus has now been renamed as the "prototype foamy virus", PFV. However, it remains unclear whether this first "human" foamy isolate arose from an *in vivo* cross-species transmission from a chimpanzee to the African carrier, or if it originated from a cell culture contamination.

During the 70's/80's, several laboratories tried to demonstrate the existence of other sporadic cases of FV infected persons but also to search for human populations where such virus could be endemic. Results were contrasted. Whereas several serological studies provided evidence for FV in different populations, other groups mainly found negative results. (reviewed in (Meiering and Linial, 2001)). Such discrepancies reflected the high percentage of non-specific serological reactivities and the lack of specific confirmatory test at that time. Indeed, when SFV-specific serological (western blot (WB), radio-immunoprecipitation (RIPA), specific IF) and molecular assays (PCR) were available, most of the positive results obtained previously in different human populations, as well as in several series of patients (neurological disorders, cancers, thyroiditis, inflammatory diseases), were not confirmed (Meiering and Linial, 2001).

Those studies also lead to the discovery that some persons working directly with NHPs were truly infected by SFVs. The first clear evidence of SFV in Humans was shown in 1995 among 3 laboratory and monkey house personnels at risk for acquiring simian viruses (Schweizer et al., 1995) (Table 1). After these initial studies, a Center for Diseases Control (CDC) team demonstrated that, some workers occupationally exposed to NHPs were SFV infected (Heneine et al., 1998). Another study demonstrated the presence of SFV infection in workers from a primate facility in

Table 1
Epidemiological data of SFV-infected persons being occupationally exposed to NHP.

Country	Number of cases	Sex M/F	Risk factors	Reported injuries	Viral strain	References
Germany	3/41	NA	Animal caretaker	Bites	AGM	Schweizer et al. (1997, 1995)
North America (USA and Canada)	4/231	4/0	Animal caretaker Research scientist Animal care supervisor Veterinarian	Bites (3)	AGM (1) Baboon (3)	Heneine et al. (1998)
North America	4/133[a]	NA	Zoo keepers	NA	NA	Sandstrom et al. (2000)
Canada	2/46[b]	NA	Primate facility workers	Bites	Macaques (1)	Brooks et al. (2002)
North America	10/187[c]	8/2	Animal caretaker (4) Veterinarian (3) Animal care supervisor (1) Technician (2)	Bites (4) Scratches (2) None (2) Others (2)	Chimps (8) Baboon (1)	Switzer et al., 2004
Gabon	2/20	2/0	Veterinarian (1) Technician (1)	Bites (2)	Mandrill (1) Macaque(1)	Mouinga-Ondeme et al. (2010)
China (Yunnan)	2/12	NA	Zookeepers	Bite, Spit (2)	Macaques (2)	Huang et al. (2012)

NA Not available.

[a] Presence of SFV infection was based only on specific seropositivity.
[b] PCR was found positive in the PBMCs of 1/2 seropositive individuals.
[c] PCR was found positive in the PBMCs of 9/10 seropositive individuals.

Table 2
Epidemiological data of SFV-infected persons being exposed to NHP in natural settings.

Country	Number of cases	Sex M/F	Risk factors	Reported injuries	Viral strain	References
Cameroon	3/1099	2/1	Individuals reporting direct contact with NHP blood and/or body fluids	Hunting Butchering Pets	Mandrill (1) Cercopithecus (1) Gorilla (1)	Wolfe et al. (2004)
Indonesia	1/82	1/0	Monkey temple workers	Bites Scratches	Macaques	Jones-Engel et al. (2005)
Cameroon	4/1164	3/1	General adult population from villages located close to NHP habitats	Bites (3) None (1)	Gorilla (3) Chimp (1)	Calattini et al. (2007)
	9/85	9/0	Individuals reporting direct contact with NHPs (bites, scratches, wounds, etc.)	Bites (9)	Gorilla (5) Chimps (2) Mandrill (1) Cercopithecus (1)	
South and Southeast Asia countries (Thailand, Indonesia, Nepal, Bangladesh)	3/305	1/2	Monkey temple workers Villagers Pet owners	Bites (3)	Macaques : *Macaca fascicularis* (2) *Macaca mulatta* (1)	Jones-Engel et al. (2008)
Cameroon	1/35	1/0	Pygmies (Hunters, Butchers)	Bite (1)	Chimpanzee	Calattini et al. (2011)
Cameroon	2/1321	1/1	General adult population from villages located close to NHP habitats	None (2)	Gorilla (1) Cercopithecus (1)	Betsem et al. (2011)
	37/98	37/0	Individuals reporting direct contact with NHPs (bites, scratches, wounds, etc.)	Bites (37)	Gorilla (31) Chimps (3) Cercopithecus (3)	
Gabon	15/78	15/0	Villagers with bites or scratches (Hunting/ Pet)	Bites (15)	Gorilla Chimps Cercopithecus	Mouinga-Ondeme et al. (2012)
DRC	3/3334	0/3	Villagers	Butchers preparing monkey to eat (2) None (1)	Angolan Colobus Red Tail monkey	Switzer (in press)

Only persons with SFV infection demonstrated by both serology and molecular findings were listed here.

Canada (Brooks et al., 2002). Interestingly, among 187 persons occupationally exposed to NHPs from the large CDC cohort, SFV infection was found to be much more frequent (3.4%) than infection by other simian retroviruses such as SIV (0.06%), STLV (0%) or simian type D retrovirus (0.5%) (Switzer et al., 2004). Such transmission in personnel from zoos or primate centers was also recently demonstrated in Gabon and in China (Huang et al., 2012; Mouinga-Ondeme et al., 2010) (Table 1).

After demonstrating that SFV could infect some laboratory and zoo workers, the next step was to search for such zoonotic retroviral infection in a more natural setting. Wolfe et al. pioneered that work by investigating the presence of SFVs in individuals, living in central African forests. They focused their study on villagers from Cameroon, who reported direct contacts with blood and/or body fluids from wild non-human primates. While 10 out of 1099 (1%) individuals from Cameroon, had antibodies to SFVs, only 3 out of these 10 seropositive persons had detectable SFV sequences in the DNA extracted from their PBMCs (Table 2). This study indicated that contacts with NHPs, which may happen during hunting and butchering can play a role in the emergence of human retrovirus (Wolfe et al., 2004).

We also developed and extended such studies in different areas and populations of South Cameroon. After initial studies demonstrating both a high prevalence and genetic diversity of

SFVs in monkeys and apes from Gabon and Cameroon (Calattini et al., 2004, 2006b), we investigated the presence of SFV infection in humans living in these regions. We demonstrated the presence of SFV infection in more than 50 persons (Bantus or Pygmies), the great majority of them being hunters having been bitten by an ape (mostly gorilla but also chimpanzee) or a small monkey (mostly *C. nictitans*) during hunting activities (Betsem et al., 2011; Calattini et al., 2007). A recent report from Gabon confirmed such frequent cross-species transmission in hunters after severe bites from mostly gorillas (Mouinga-Ondeme et al., 2012) (Table 2).

The situation in Asia is less known. However, recent reports have already indicated SFV transmission from different macaques species to temple workers, villagers and pet owners in different countries form South and Southeast Asia mostly through bites (Jones-Engel et al., 2005, 2008) (Table 2). Human and macaques sympatry in Southeast Asia dates back as far as 25.000 years and human-macaque commensalism is frequent in many monkey temples of these regions with, each year, a very large number of persons, including tourists, at risk for macaques bites (Jones-Engel et al., 2006). Indeed, a model has predicted that in Bali, for every 1000 visitors to monkey temple, approximately 6 persons will be infected with SFV (Engel et al., 2006).

Molecular virology

FV genomic organization

FV are complex retroviruses with genome length ranging from 10 479 bp (Feline FV (Bodem et al., 1998)) to 13249 bp (Simian FV, chimpanzee strain (Herchenroder et al., 1994)). FV genome comprises the canonical retroviral *gag*, *pol* and *env* genes, as well as two additional genes *tas* and *bet* that encode proteins having regulatory functions. It is flanked by two LTRs which contain elements crucial for FV transcription (Fig. 3).

FV life cycle

FVs have an internal promoter located in the *Env* gene that allows basal transcription of the Tas and Bet regulatory proteins (Campbell et al., 1994). Once produced, the Tas transactivator activates the internal promoter (IP), giving rise to a positive feedback loop (Kang et al., 1998). When sufficient amount of Tas is produced, it can also bind to specific elements in the LTR promoter, with a lower affinity than for the IP. Activation of the LTR, which remains otherwise silent, induces the expression of the Gag, Pol and Env structural proteins, ultimately leading to the formation of viral progeny (reviewed in (Rethwilm, 2010)). Tas was also shown to be a suppressor of RNA silencing (Lecellier et al., 2005).

Unlike Gag proteins from orthoretroviruses which are cleaved and processed into capsid, matrix and nucleoprotein, FV Gag proteins are only partially cleaved at the C-terminus generating two species: a long and a shorter proteins that only differ by 4 kDa, both being incorporated in the virion (Enssle et al., 1997). They contain three Glycine and arginine-rich regions (the GR boxes) important for the correct FV assembly and the nuclear localization of Gag (Lee and Linial, 2008; Yu et al., 1996b), the role of which is still not elucidated.

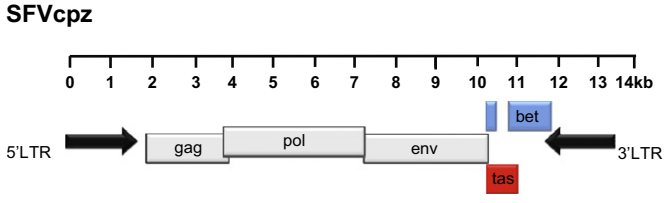

Fig. 3. SFV open reading frames and transcription map. A scheme of SFV genome (chimpanzee strain) and proteins encoded by each *mRNA* are shown. ORFs are indicated by boxes. The SFV genome includes the canonical retroviral *gag*, *pol* and *env* genes and is flanked by two large LTRs which contain elements crucial for FV transcription. Two additional genes *tas* and *bet* encode proteins having regulatory functions. Indeed, the transactivator Tas binds to the 5'LTR and is responsible for the transcription of the structural genes *gag*, *pol* and *env*.

Unlike other retroviral Pol proteins, Pol precursor protein is synthesized independently of Gag, from a distinct mRNA (Yu et al., 1996a). This questions the mechanism ensuring Pol packaging together with Gag. One possible mechanism is that FV genomic RNA makes the bridge between Gag and Pol (Peters et al., 2005). Unlike Pol from orthoretroviruses which is cleaved in three molecules, FV Pol is then auto-catalytically cleaved into one molecule containing the protease and the reverse transcriptase domains, and another one containing the integrase domain (Pfrepper et al., 1998).

Env protein is cleaved into leader peptide, the surface (SU) and transmembrane (TM) glycoproteins, but contains an endoplasmic retention signal which contributes to its site of budding. Indeed, particles bud from cells primarily through the endoplasmic reticulum. Moreover, since Gag alone cannot form VLPs (Virus-like particles), interactions between Env and Gag are essential for virion budding (reviewed in (Lindemann and Goepfert, 2003)).

The role of the Bet regulatory protein is not well understood. However, it was shown that Bet can neutralize the cytosine deaminase APOBEC3G (ApolipoproteinB mRNA-editing enzyme catalytic polypeptide 3 G) protein (Lochelt et al., 2005), although it is controversial (Delebecque et al., 2006).

Finally, FVs can also go through a late reverse transcription step, before the release of FV particles. Thus, unlike orthoretroviruses, FV particles can contain FV RNA and FV DNA genomes, and interestingly, FV DNA genomes produced in the infected cells can undergo intra-cellular retrotransposition, with efficiency depending upon FV strain and cell type considered (reviewed in (Rethwilm, 2010)).

Of note, unlike HTLVs, no antisense protein is coded by FV genome.

FV tropism

FV can infect most cell types *in vitro*. Heparan sulfates were found to represent attachment factors. However, FV receptor has not yet been discovered and is probably ubiquitous. Once productively infected, cells usually form syncitia with a "foam-like" cytopathic effect, before cell death occurs (Fig. 4A to D). However, some cell lines as well as primary cells of the myeloid or lymphoid lineage can also remain chronically infected (Mikovits et al., 1996; Yu et al., 1996c). The cellular and viral factors involved in persistence *versus* lytic infection are not well understood, but might involve the regulatory proteins Tas and Bet, with a switch from Tas expression driving virus particle formation to *Tas* deletion with a maintained Bet expression (Saib et al., 1995). *In vivo*, FV tropism was not intensively investigated so far, but 2 studies indicate that FV DNA was found in CD4+ lymphocytes (1/3 AGM and 3/4 chimpanzees), CD8+ lymphocytes (2/4 humans, 9/9 AGM and 4/4 chimpanzees), monocytes (1/4 human and 2/7 AGM and 1/4 chimpanzee) and B cells (1/4 human) (Falcone et al., 1999; von Laer et al., 1996). Moreover, in NHPs, FV site of replication has been found to be the superficial epithelial layer of the oral mucosa (Falcone et al., 1999; Murray et al., 2008, 2006), which explains the mode of transmission of FV by saliva through bites (Betsem et al., 2011).

FV genetic stability

FV genomes display a high evolutionary conservation among all the species infected and FV genetic variability within one infected animal is very low over time ($<1\%$ variation) (Schweizer et al., 1999). This genetic stability might be explained by the long co-evolution with their host (more than 30 million years) (Switzer

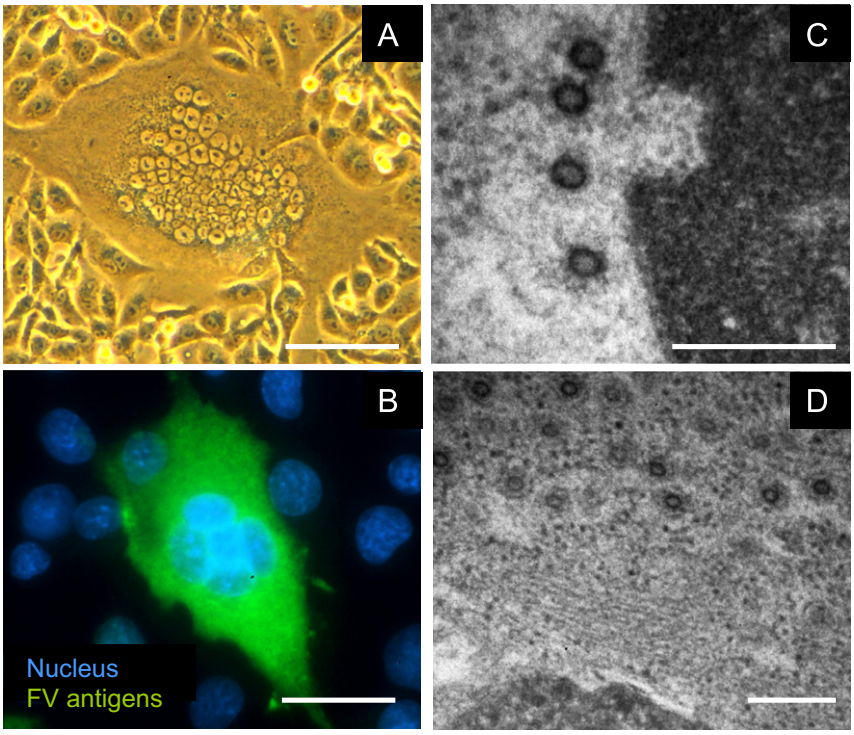

Fig. 4. Observation of foamy virus and foamy viral infected cells. BHK cells were infected with a primary chimpanzee SFV strain (isolated from an SFV-infected hunter, Betsem et al., 2011) (A) and (B) or by the prototypic strain of SFV (C) and (D) at a multiplicity of infection of 10 and fixed 4 days post-infection. (A) Observation of the SFV-infected cells was performed under light microscopy and shows a large FV-induced syncytium with a "foamy" aspect. (B) An immunofluorescent staining was performed as previously described (Calattini et al., 2007). FV antigens are revealed in the green channel and nuclei are stained with DAPI. (C) and (D) Results of the electron microscopy performed on the FV-infected BHK cells. Sections represent FV viral particles at the proximity of the nucleus (C) or near the microtubule network (D). Scale bars represent 10 μm (A), 3 μm (B) or 300 nm (C) and (D).

et al., 2005) and their subsequent efficient adaptation. Endogenous Foamy viruses have even been found in the genomes of sloth (Katzourakis et al., 2009), coelacanth (Han and Worobey, 2012b) and Aye Aye (Han and Worobey, 2012a).

Despite this global genetic stability, recombination events between several circulating FV strains as well as deletions and mutations have been reported in wild-living chimpanzees (Liu et al., 2008).

FV restriction in humans

Several groups also reported genetic modifications including deleterious mutations in the Bet accessory gene in one SFV-infected human (Callahan et al., 1999). Some other features were also reported in humans infected with FVs, although they are probably not specific to human infection. This includes deletion in the U3 sequence of the LTR, which might improve FV replication at least *in vitro* (Schmidt et al., 1997). This also includes deletion in the Tas sequence, which might be linked with the chronicity of the infection as previously suggested (see above).

However, when looking at FV polymorphism in viruses present in human PBMCs (5 individuals), we did not find striking differences between those viruses and that present in NHPs, suggesting that, even decades after primary infection, FV genomes are still fully replicative (Rua et al., 2012a). This raises the question of their apparent restriction in humans which might thus be linked to their immune control. *In vitro,* FVs are sensed by human hematopoietic cells and induce the production of the antiviral cytokines IFN-I (Rua et al., 2012b). In culture systems, the addition of type I IFN (Regad et al., 2001; Rhodes-Feuillette et al., 1990; Sabile et al., 1996), or the expression of various IFN-stimulated genes, including APOBEC3 and tetherin, impair FV replication (Delebecque et al., 2006; Dietrich et al., 2011; Lochelt et al., 2005; Perkovic et al., 2009; Russell et al., 2005; Xu et al., 2011). It is tempting to speculate that the type I IFN response is in large part responsible for the control of viral replication in infected individuals. In line with these *in vitro* studies, it was reported once that FV genomes found in humans displayed few *G* to *A* mutations, as if they were partially sensitive to the action of the APOBEC3G restriction factors, which are induced by IFN-I (Delebecque et al., 2006). In addition, neutralizing antibodies are known to inhibit SFV transmission and infection in rhesus macaques (Williams and Khan, 2010), indicating that the adaptive immune response may control further the virus *in vivo*. Studies are thus needed to understand the role of the adaptative immune system in FV restriction in humans.

Discussion

The recent discovery of HTLV-3/4 and foamy retroviruses in humans raises important questions, still unanswered, concerning different aspects of the natural history of these retroviruses (Fig. 5).

1) The first question concerns the magnitude and the distribution of these viruses in humans living in areas that are highly endemic for infected non-human primates.
   Concerning foamy viruses, around 100 persons have already been convincingly reported as infected by SFV (Tables 1 and 2). Most of them are living in central Africa, especially in villages or settlements located in the forest area of Cameroon and Gabon. In most cases, infected persons are men who reported a close contact, especially a bite from a NHP during hunting activities (Fig. 6). However, in few cases including some women, the exact origin of the infecting contact remains yet unknown (Betsem et al., 2011; Calattini et al., 2007; Wolfe et al., 2004). This suggests the possibility of viral transmission during handling,

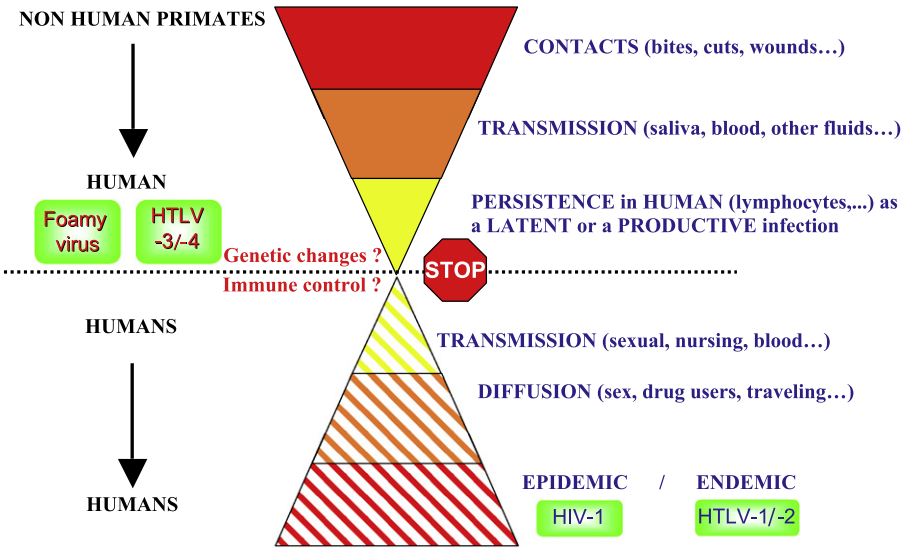

Fig. 5. Schematic representation of the different steps leading to possible retroviral emergence from non-human primates to Humans. Such viral emergence is a multi-step process involving mostly viral transmission *per se* to Humans by different possible contacts with infected body fluids (initial spill-over) and then spread in the human population. For HTLV-3/4 and simian foamy viruses, the inter-human population diffusion has not been yet demonstrated and the zoonotic strains seems to be mainly restricted in the few persons having been directly in contact with infected NHPs. This is totally different to the situation with the other human retroviruses of zoonotic origin as HIV-1 and HTLV-1, which have became largely epidemic and endemic, respectively.

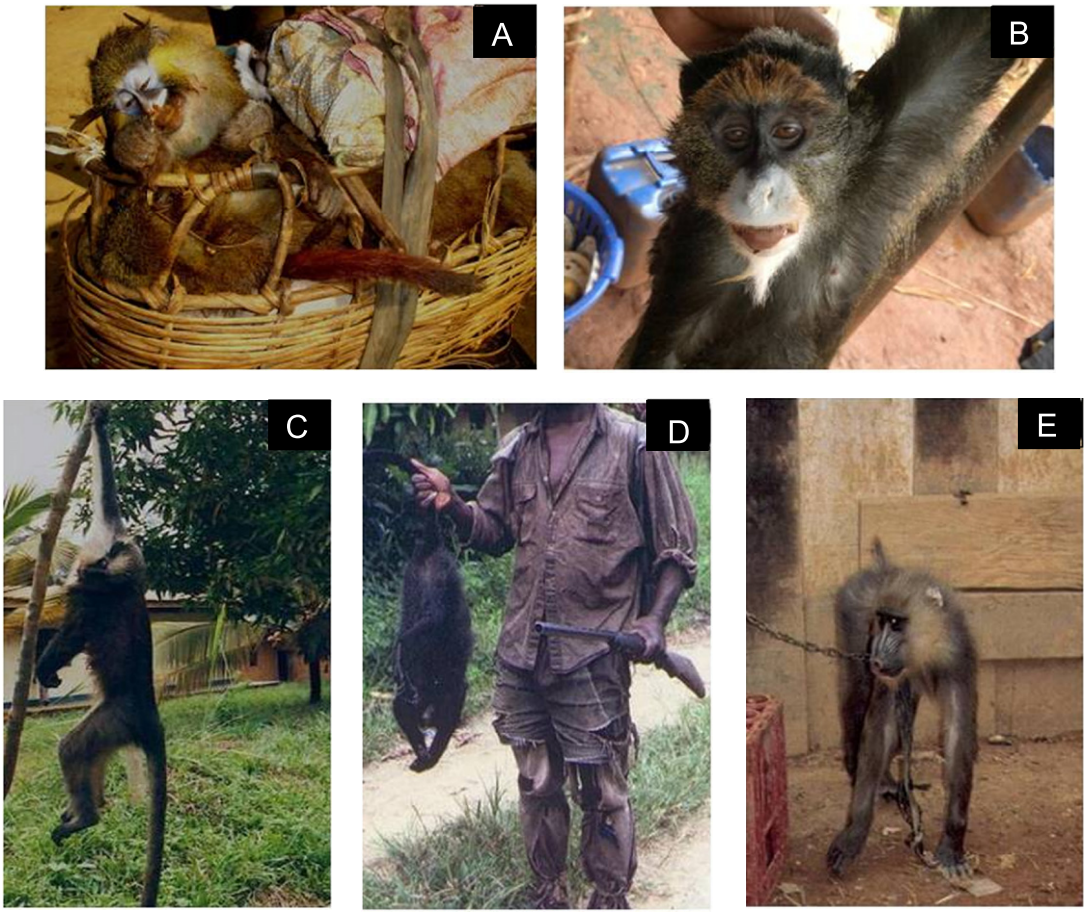

Fig. 6. Common scenes in villages of rural areas of South and East Cameroon showing possible human exposure to simian retroviruses. (A) Full basket of wild-monkey game for sale. (B) Hunted monkey (*C. neglectus*) for consumption. (C) Hunted monkey (*C. cephus*) for sale. (D) Hunter and a monkey (*C. nictitans*) he just killed. (E) Captive mandrill (*M. leucophaeus*) used as a pet.

processing, or food preparation tasks, of possibly infected NHP game. These tasks are frequently performed by women. Future studies are also necessary to define SFV prevalence in humans living in other areas of Africa. In Asia, even if the situation is less known, presence of SFV have already been clearly reported in some persons (Huang et al., 2012; Jones-Engel et al., 2005,

2008). Furthermore, contacts between persons and NHPs are in Asia common (Jones-Engel et al., 2006). Thus, SFV infections in humans are likely to be very prevalent among persons who live or work near NHPs.

Concerning HTLV-3 and HTLV-4, the only data available so far were obtained from a series of a few thousand individuals mostly living in south Cameroon (Calattini et al., 2009, 2011, 2005; Wolfe et al., 2005; Zheng et al., 2010), an area where STLV-3 strains are endemic in several monkey species. One could however hypothesize that HTLV-3/4 viruses are also present (probably at a low prevalence) in other populations living in other countries of West, Central and East Africa. Indeed, in such regions; (i) HTLV indeterminate Western blot serologies are frequent, including some patterns that are quite similar to those found in HTLV-3 infected persons and (ii) STLV-3 strains have been reported to be endemic in several monkey species from West (Meertens and Gessain, 2003), Central (Liegeois et al., 2008; Meertens et al., 2003), and East Africa (Takemura et al., 2002; Van Dooren et al., 2004). However, studies specifically aimed at detecting HTLV-3 and HTLV-4 in such countries have not been published. We should also keep in mind the very peculiar epidemiology of HTLV-1 and HTLV-2, with the presence of high endemic foci, often located nearby large regions with a low prevalence. This has been well exemplified recently in South Cameroon for HTLV-2. Indeed, in this large area, HTLV-2 is nearly absent, except in the Bakola's Pygmy population (Mauclere et al., 2011). Such situation which is very probably linked to a founder effect followed by favorable viral transmission in a given community, may also happen for HTLV-3 or -4 infections.

2) The second question concerns the possibility of inter-human transmission of those retroviruses.

Based on available data, SFV transmission among humans has not been yet demonstrated. Indeed, only around 40 family members (mostly spouses) of men infected by SFV have been studied and scored negative (Betsem et al., 2011; Callahan et al., 1999; Heneine et al., 1998; Switzer et al., 2004; Boneva et al., 2007) suggesting that SFV transmission does not occur frequently through sexual contacts or saliva exposure. The persistence of infectious virus in PBMCs, and the identification of infected blood donor (CDC study conducted in North America (Boneva et al., 2002)) had raised safety concerns regarding a potential viral transmission through blood transfusion. These concerns are supported by recent studies demonstrating that SFV can be transmitted in macaques through blood transfusion of an infected donor animal ((Khan and Kumar, 2006) and reviewed in (Khan, 2009)). Studies are ongoing to search for SFV replication sites in infected humans (Rua et al., unpublished data).

The HTLV-3/4 situation is probably different. Even if these viruses originally arose through interspecies transmission from STLV-3/4 infected monkeys to humans, it is difficult to speculate on the relative part of the direct acquisition from infected monkeys *versus* the acquisition from other infected humans through sexual activity or breast-feeding. Most HTLV-1/2 infected individuals living in central Africa were very probably infected through human contacts and not through NHPs interspecies transmission. Familial studies on larger series of HTLV-3/4 infected studies are thus required to determine whether those viruses can be transmitted from humans to humans.

3) The third question concerns their possible associated morbidity and mortality in humans.

Concerning SFVs, their apparent lack of pathogenicity in humans is based on studies conducted on a very limited number of cases with a short follow-up (Boneva et al., 2007), and contrasts with the massive *in vitro* lytic properties of these viruses both in monkeys and in human cells. The selection bias inherent to the enrolment of mostly healthy persons, in the few published series limits greatly the ability to identify any potential acute and/or severe associated diseases. Ongoing case-control study, based on a larger number of SFV-infected persons is therefore necessary to shed light on any possible chronic diseases and/or biological abnormalities associated to SFV infection in humans. However, we have to keep in mind that, as for all the diseases associated with HTLV-1, incidence of disease in an SFV infected person might be very low and may follow very long latency periods. Thus, more data are absolutely needed before SFV can be classified as a non-pathogenic virus in humans.

Regarding HTLV-3/4, the situation is even more complex, since only 5 cases (4 HTLV-3 and one HTLV-4) have only been reported (Calattini et al., 2009, 2011, 2005; Wolfe et al., 2005; Zheng et al., 2010).

Questions regarding any possible chronic/acute disease and/or biological abnormality in humans are similar to SFVs with the necessity of a case-control study based on larger numbers of HTLV-3/4 positive individuals, with a long term follow-up. Regarding viral tropism and pathogenicity of STLV-3, colonies of infected STLV-3 NHP are already available and might allow to answer to these questions. Alternatively, the use of other animal models such as humanized-mice might also allow us to determine the pathogenicity of those viruses.

Finally, another way for determining whether diseases are associated with these retroviral infections in humans would be to conduct a specific study among hospitalized patients, in Africa (for both SFVs and HTLV-3/4) or in Asia for SFV infection.

Conclusion

Hunting wild game, including several non-human primate species has been performed for millennia, in several areas of the African continent by different populations. Some of them were even quite specialized in such hunting activities as all the Hunter-gatherer groups, including several Pygmies tribes living in Central Africa. In most cases, bushmeat hunting and related-activities (butcher, smoked meat, selling, consumption, pets,..) were quite restricted to remote areas with mostly local meat consumption. The situation has greatly changed during the last decades due to several factors. As an example, there has been a tremendous increase of hunting activities, resulting from a combination of urban demand for bushmeat, greater access to NHP habitats provided in part by logging roads, easier accessibility to fire arms, and an increase in populations living in forest areas, as well as the associated increase in local food needs. Growing urban populations, expansion of logging industries and oil and mining companies and even in some cases, armed conflicts have also contributed at different levels to the increase of bushmeat trade. Interestingly, in a study conducted in South Cameroon, most SFV-infected persons were relatively young and have acquired the virus during the last 20 years indicating that such cross-species transmission is still ongoing (Betsem et al., 2011). Today, between 3 and 5 million tons of bushmeat are eaten each year (with around 15% originating from NHPs) in Central Africa. There is an evident lack of economic options of affordable substitutes. Indeed, bushmeat is around 75% cheaper than domestic meat (Coad et al., 2010; Karesh and Noble, 2009; Macdonald et al., 2011; Wolfe, 2005).

Several studies have well demonstrated that many if all NHP species killed in central Africa are endemic for several retroviral infections including different SIV, STLV and SFV ((Betsem et al., 2011) and reviewed in (Locatelli and Peeters, 2012; Peeters and Delaporte, 2012). Thus, in Central Africa, the number of contacts at risk for retroviral infection between humans and infected

NHPs has greatly increased during the last decades opening thus new possibilities for retroviral emergence in the local human population.

Finally, it is important to envision the consequence of such retroviral infection in an immuno-compromised person. Indeed, HIV is now endemic in many African countries at a relatively high level in rural and urban adult populations that are now at risk for retroviral (STLV, SFV, SIV) cross-species transmissions. Such co-infections are very likely to occur in Central African populations where HIV-1 is endemic and were in fact already reported (Switzer et al., 2008). The outcome of an HTLV-3/4 or SFV infection in an immunosuppressed person is unknown. However, one may expect that such co-infection may modify (pro)viral load and/or tissue distribution (as shown for macaques co-infected with SIV and SFV for instance (Murray et al., 2006)) and thus possibly viral transmission and pathogenicity in the infected person.

Efforts to reduce the risk of cross-species transmission are thus necessary to try to better control the potential threat of such simian retroviruses in humans. Therefore, development of alternatives to hunting is necessary locally with all the different partners living in these areas where interaction with NHPs, and other games, mostly through hunting is part of the culture and tradition, as well as related to important economic needs.

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