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Foamy Viruses Affecting Animals and Humans and their Public Health Concerns: A Review

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ABSTRACT

Foamy viruses (FVs) are complex retroviruses under the genus *Spumavirus* of family Retroviridae. They cause induction of multinucleated giant cell formation which presents numerous vacuoles, giving the monolayer culture a foamy appearance. FVs can infect animals as well as humans. In case of the *Human foamy virus* (HFV), a defective variant (named ΔHFV or HFVΔTas) negatively interferes with replication of parental counterpart. Some species, such as rhesus macaques, African green monkeys, chimpanzees and cats harbor closely related yet serologically distinct FV subtypes. Unanticipated FV pathogenicity may warrant appropriate attention to biosafety practices to prevent occupational infections and the importance of additional studies to better define clinical outcome of these zoonotic infections. During cross-species infection and subsequent passages a rapid and fatal disease can occur, with changes from nonpathogenic to pathogenic potentials. In persons occupationally exposed to non-human primates, *Simian foamy virus* (SFV) infection occurs persistently showing that simian retroviruses cross into humans more frequently. Simian Immunodeficiency Viruses (SIV), mostly are nonpathogenic in their natural hosts but during cross-species infection a rapid and fatal disease can occur. Enzyme Immuno Assay (EIA), Western blot analysis and Polymerase Chain Reaction (PCR) amplification are the important diagnostic tests for FVs. FVs are also being exploited as potential vectors that can be used for gene therapy which is gaining much attention of the researchers worldwide. Strengthening sero-epidemiological as well as molecular investigations and public health surveillance programme along with extra precautions while transferring xenograft are some of the approaches to prevent these viral infections.

Key words: *Foamy virus*, *Retrovirus*, *Spumavirus*, animals, simian, equine, humans, epidemiology, diagnosis, prevention, control, vectors, gene therapy, cross species transmission, zoonosis

INTRODUCTION

Foamy viruses (FVs) are complex retroviruses with unique features among the retroviral family (Linial, 1999; Lecellier and Saib, 2000). As evident by their name, they induce the formation of multinucleated giant cells which present numerous vacuoles, giving the monolayer culture a foamy aspect and appearance. The virus is endemic in wild as well as captive animal populations and is responsible for causing super infection frequently. There is also report of viral recombination. A 5.3-23 per cent of the population has been found positive in a number of research centers as well as zoos for the presence of the genome of the virus. In chronic virus infection, as seropositivity is a likely indicator, the issue of transfusion transmissibility in humans is raised potentially. In developed countries, people who are exposed to non-human primates such as those associated with handling of animals; zookeepers; or exotic pet enthusiasts; hunters of bush meat and handlers (in the developing world) are at the risk of exposure. This makes the public health importance of the virus significant due to its zoonotic implication (Heneine *et al*., 2003; Brooks *et al*., 2007; Gautret *et al*., 2007). In African apes as well as monkeys the virus is present endemically. In the year 2004, a team jointly led by the United States and Cameroon has proven the ability of the virus to cross over to humans. This team has found the presence of the virus in gorillas along with mandrills and guenons (Wolfe *et al*., 2004; Switzer *et al*., 2005). In case of FV infection, a defining characteristic is persistence in the absence of disease but with the presence of antibodies. In case of patients suffering from several neoplastic as well as degenerative diseases (like myasthenia gravis and multiple sclerosis; thyroiditis and Grave's disease) *Foamy virus* has been isolated but the etiological role of the virus is still unclear. Indication is however been provided by recent studies that in case of humans as well as animals that are experimentally infected the virus is not pathogenic (Liu *et al*., 2007).

The *Foamy virus* (FV) infection mechanism and potential to cause disease has been studied in various animal models viz., rabbit and mice and recovery of the virus has been done from several different organs in such animals. In animals infected with FV, pathology has not been noted. In humans, FV infection is associated with various diseases including thyroiditis de Quervain and Grave's disease; multiple sclerosis and myasthenia gravis. Use of multiple assays including western blot, Imunofluorescence assay (IFA) and Polymerase Chain Reaction (PCR) have failed to confirm the association of such diseases with FVs. As in man and animals this virus has no definite pathogenesis it has been dubbed as 'a virus in search of a disease' (Weiss, 1988; Schmidt *et al*., 1997). Transmission of *Simian foamy virus* (SFV) results in a stable as well as persistent infection that seems to be latent. Infection due to SFV is therefore, far non-pathogenic with no evidence of clinical outcome that may have any adverse effect in the natural primate hosts (non-human) or by injection experimentally. Since there is well documentation of the emergence of pathogenic viruses from the non-pathogenic ones upon cross-species infection it is essential to take necessary precautions for deterring infection due to SFV in human. Such steps will ultimately help in preventing the emergence of a novel pathogen thereby reducing the transmission risk due to another human retrovirus that is potentially pathogenic (Khan, 2009). The present review discusses the salient features of the foamy viruses, their epidemiology and the disease these cause along with advances in diagnosis, prevention and control measures to be adapted to tackle these viruses.

Etiology: Foamy Viruses (FV) are RNA viruses under the genus *Spumavirus* of the family *Retroviridae*. FVs have distinct morphology. These viruses bud primarily from the endoplasmic

reticulum rather than the plasma membrane (Meiering and Linial, 2001). All FVs characterized to date have very large genomes (between 12 to 13 kb) with the classical structural genes (*gag*, *pol*, *env*) and regulatory Open Reading Frames (ORFs) located at the 3' end of the *env* gene, which are under the control of both the 5' Long terminal repeat (LTR) and an Internal Promoter (IP) (Lochelt *et al*., 1993). *Equine foamy virus* (EFV) is an 80-100 nm ss-RNA virus which belongs to the nonpathogenic widely spread complex unconventional retroviruses that have been isolated from nonhuman primates, cattle, cats and more recently from the blood of horses (Tobaly-Tapiero *et al*., 2000; Lecellier *et al*., 2002). The polymerase (*pol*) precursor protein is processed by the viral protease particularly at one site that causes release of a protease reverse transcriptase along with an integrase protein. It is necessary to generate several mutations around the cleavage site for examining whether it is necessary to cleave the *pol* precursor protein for enzymatic activities as well as viral replication efficiently. It has also been found that *pol* encapsidation is reduced significantly in certain mutants (Roy and Linial, 2007).

In *Human foamy virus* (HFV), the prototype *Foamy virus*, two accessory proteins have been described *viz*., Tas (originally called Bel1)-the potent DNA binding transactivator of viral gene expression of both the LTR and the IP and Bet-which plays an important function in the establishment and control of viral persistence *in vitro* (Saib *et al*., 1995a; Bock *et al*., 1998). The mechanisms of viral persistence are not recognized, genetic variability most likely does not form the basis of this equilibrium as seen with lentiviruses (Schweizer *et al*., 1999). The major cell types wherein SFV replicates is the epithelial cells (differential) of oral mucosa. For explaining the innocuous nature of infection due to SFV the limited replication of SFV in short-lived differential superficial cells that shed into saliva are taken into consideration. Such finding explains the FV transmission among Non-human Primates (NHPs) at higher efficiency (Murray *et al*., 2008).

FV replication differs from that of conventional retroviruses like type C oncoviruses and lentiviruses and more closely resembles that of the other family of reverse transcriptase-encoding viruses, the Hepadnaviridae (Linial, 1999). The glycoprotein of the Prototype FV (PFV) has only got the capability of fusion activity significantly at neutral pH which suggests that the uptake mechanism may deviate from other Fvs (Stirnnagel *et al*., 2013). In the case of the *Human foamy virus* (HFV), it has been suggested that a defective variant (named ΔHFV or HFVΔTas) negatively interferes with the replication of the parental counterpart (Saib *et al*., 1993; Saib *et al*., 1995a; Linial, 2000). HFVΔTas is generated by alternative splicing of the wild-type pregenomic RNA and contains a 301-bp deletion in the gene of the viral transactivator, which lead to the creation of an intronless auxiliary *bet* gene. FVs synthesize specific subgenomic mRNA for the expression of viral enzymatic products. In retroviruses, *pol* is usually synthesized as a *gag-pol* fusion protein derived either from a frameshift event or through stop codon suppression but in FVs the *pol* is expressed from a spliced mRNA by translational initiation at the first AUG in the *pol* gene independently of Gag expression (Yu *et al*., 1996). This particularity, together with the late-occurring reverse transcription which leads to incorporation of infectious viral DNA into virions, resembles more to hepadnaviruses than to retroviruses (Yu *et al*., 1996; Lecellier and Saib, 2000). The Long Terminal Repeat (LTR) of *Foamy virus* is unique with respect to the Major Splice Donor (MSD) location which is located upstream of the signal of polyadenylation (Schrom *et al*., 2013). Based on nucleotide sequence analysis it has been shown that EFV is phylogenetically the most distant FV compared to the HFV prototype. However, EFV contains the classical FV genomic organization, its envelope (Env) glycoprotein does not harbor the characteristic Endoplasmic Reticulum (ER) retrieval motif located in the C terminus of Primate FV Env

(Netzer *et al.*, 1990; Goepfert *et al.*, 1997). Since this dilysine motif has been shown to be responsible for the budding of HFV from the membranes of the ER (Goepfert *et al.*, 1999), its absence in EFV Env should lead to a change in the viral budding site. Further characterization of EFV was done by Lecellier *et al.* (2002), demonstrating the existence of the FVs' specific sub genomic *pol* mRNA, a replication-defective EFV genome during persistent infection similar to that described for the HFV. At the protein level, they detected localization of EFV gag in both the cytoplasm and the nucleus and EFV env mainly in the Golgi complex, unlike the HFV Env, which is sequestered in the endoplasmic reticulum. EFV Tas was detected both in the nucleus and the cytoplasm of Tas-transfected cells, while Tas of other FVs is localized strictly in nuclear components. In addition, electron microscopy analysis revealed that EFV budding occurs at the plasma membrane and not intracellularly, as is the case for primate FVs (Tobaly-Tapiero *et al.*, 2000; Lecellier *et al.*, 2002). In the recent past, FVs were considered interesting tools for gene therapy due to their wide cellular tropism and large genomes (Liu *et al.*, 2007). The ability of EFV to bud at the cell surface rather than intracellularly could make this virus an attractive backbone for the design of a new generation of FV-based vectors, escaping artificial distraction of internal cellular membranes to gain higher viral titers (Tobaly-Tapiero *et al.*, 2000; Rethwilm, 2010).

Epidemiology: The prevalence of FV infection in naturally infected animals is generally high and varies widely depending on the species and environmental conditions. Some species, such as rhesus macaques (Johnston, 1971), African green monkeys (Schweizer *et al.*, 1999), chimpanzees (Hooks *et al.*, 1972) and cats (Winkler *et al.*, 1998), harbor closely related yet serologically distinct FV subtypes. Seroprevalence rates are usually high in animals housed in captivity, reaching 100% compared to animals studied in the wild. FVs are highly lytic *in vitro* in contrast to being innocuous *in vivo* and produce a persistent infection in their natural hosts (Saib *et al.*, 1995b; Linial, 2000).

The mechanisms of FV transmission are not well understood. The available data suggests the probability of a saliva-based means of transmission, such as licking or biting. The earliest controlled study of FV transmission was conducted in cattle where *Bovine foamy virus* (BFV) infection is endemic (Johnson *et al.*, 1988). It showed that newborn calves had passive immunity but which diminished by age of 3 to 5 months. Calves negative for BFV at birth when kept with infected adults show infectivity rate of approximately 35% within 10 weeks and 85% by 3 years. In a similar study performed with captive baboons (Broussard *et al.*, 1997), infants were initially FV negative and had passive maternal antibody, as in cattle, however by age of 15 months, 1 of 10 juveniles became FV infected. Adults were tested 100% positive. In case of wild chimpanzees, vertical transmission of SFVs has been demonstrated and it has been hypothesized that it accounts for a number of primary infections. It has also been demonstrated that in case of adult chimpanzees super infection i.e., infections with various SFV strains that are chimpanzee-specific is common. This proves that even in single community scale the dynamics of SFV in wild chimpanzee is complex (Blasse *et al.*, 2013). In China, there has been high prevalence of SFV in *Macaca mulatta* thereby suggesting the zoonotic spread of *Simian foamy virus* in human (Huang *et al.*, 2012). During the years 1995 and 1996 two comprehensive studies have been performed suggesting the presence of FV in certain populations of human. Initial screening by ELISA showed that 17% of Pacific Islanders and 34% of samples from central Africa have been found to be positive for FVs. These well-controlled studies taken together indicate that in human population FV infections are not much prevalent (Meiering and Linial, 2001). Researchers in Canada have conducted a surveillance work regarding the prevalence of SFV in workers who come in contact with

non-human primates. By this study it is well proven that in humans there is no definite proof of pathogenesis of SFV nor is there any evidence of transmission of SFV by blood. It is however inferred that the lack of data is responsible for not excluding the risk of transmission of SFV via transfusion completely (Schweizer *et al*., 1997; Heneine *et al*., 1998). In multiple occupational as well as non-occupational contexts contact between persons as well as non-human primates is widespread in Asia which is responsible for the likely occurrence of SFV infection among persons in this continent (Jones-Engel *et al*., 2008).

Determination of the *Simian foamy virus* serotype-2 (SFVmcy-2) full length sequence has been done from a macaque in Taiwan. It has been found that SFVmyc-2 is having high degree of relationship with SFV serotype 1 (SFVmcy-1) which is an isolate from the same species with the exception of a putative receptor binding domain (RBD) present in the envelop (Galvin *et al*., 2013).

Han and Worobey (2012) have reported the discovery as well as analysis of an endogenous *Foamy virus* (PSFVaye) within the aye-aye (*Daubentonia madagascariensis*), a strepsirrhine primate found in Madagascar, genome. The divergence of PSFVaye from all simian foamy viruses has been indicated on the basis of phylogenetic analysis. This suggests *Foamy virus* association with primates since the haplorrhine-strepsirrhine split.

Disease: Till date, except for the FV, all retroviruses have been shown to cause disease in some host, infected either naturally or accidentally. Simple retroviruses such as *Murine leukemia virus* (MLV) and *Avian leukosis virus* (ALV) induce tumors and/or immunodeficiencies with long latency periods. *Bovine leukemia virus* (BLV), *Human T cell lymphotropic virus* (HTLV) type 1 and *Human immunodeficiency virus* (HIV) (the complex retroviruses) can also be highly pathogenic. Simian Immunodeficiency Viruses (SIV), mostly are non-pathogenic in their natural hosts but during cross-species infection a rapid and fatal disease can occur. There is compelling evidence that both HIV-1 and HIV-2 have been introduced into the human population via zoonotic transmission on multiple occasions (Gao *et al*., 1992,1999; Myers *et al*., 1992). Human FV has been described as "a virus in search of a disease" (Weiss, 1988). Many viruses persist in their natural hosts in the absence of disease only to reveal their true pathogenic potential when they cross species barriers. *Persistent simian foamy viral* (SFV) infections occur in persons occupationally exposed to non-human primates, which shows that simian retroviruses cross into humans more frequently (Switzer *et al*., 2004). FVs are considered as apathogenic but still feline FVs are found to be associated with health abnormalities that are transient in nature in animal models (Maternlak *et al*., 2013).

Studies have been conducted for examining whether SFV shares the transmissibility traits through the supply of blood. Regarding this issue, blood from monkey infected with SFV has been transfused into a monkey which is SFV-uninfected within a controlled environment. Following establishment of a viral 'set-point' the highest level of detectable virus is concomitant with seroconversion that has been demonstrated by a quantitative analysis. Changes have been noticed during early infection by analysis of lymphocytes that are circulating. By demonstrating the transmissibility of SFV through transfusion of whole blood in Non-Human Primate (NHP) model, understanding of potential risk in association with donation of blood by humans infected with SFV is also increased (Brooks *et al*., 2007). Not withstanding evidences for FVs' true non-pathogenicity, caution should be taken when purposefully introducing viruses or vectors into new host species, including in performing xenotransplantations using organs from foreign species, which are known to harbor endogenous or naturally occurring viruses. Necessary precautions are also warranted

with use of primate material for production of biologicals which could also unintentionally introduce FV into the human population. Unanticipated FV pathogenicity may warrant appropriate attention to biosafety practices to prevent occupational infections and the importance of additional studies to better define the clinical outcome of these zoonotic infections. This occurs when sufficient passages and enough opportunities are provided to the virus for crossing species barriers (Sandstrom *et al*., 2000; Meiering and Linial, 2001; Brooks *et al*., 2002).

A permanent threat to health of human is the occurrence of transmissions of animal viruses to humans zoonotically; which is further increased by changes in the lifestyle of human. Various SFVs are capable of causing zoonotic infection for which special attention must be given in this aspect (Bastone *et al*., 2003). Even though infection due to FV is apparently benign there is common chance of trans-species zoonosis. This has led to the isolation of the *Prototypic foamy virus* (PFV) from human sources, which has got the potential for transmission from germ-line (Mullers *et al*., 2011; Goldstone *et al*., 2013). The potential for SFV infection to cause human disease is not yet fully understood. Apathogenicity apparently in natural hosts as well as humans who are infected zoonotically is considered as unique feature of FVs (Goepfert *et al*., 1996; Lindemann and Rethwilm, 2011). All the primate species (non-human) investigated so far that include prosimians as well as New World and Old World monkeys and apes virtually harbor distinct and species-specific clades of SFV. There is however no evidence that supports the existence of a *Foamy virus* which is specific to human. Widespread infection of healthy as well as sick humans with FV had not been confirmed in earlier reports.

All FV infections in contrast in humans are zoonotic in nature and have been identified in persons who are exposed to non-human primates occupationally. Several public health questions have been raised by the introduction of SFV into humans regarding the outcome of disease as well as the potential for transmissibility from human-to-human. The data which is available from a very limited number of humans who are SFV infected suggest the non-pathogenic nature of these infections which are not easily transmissible (Heneine *et al*., 2003). There has been report of SFV infection in persons who are occupationally exposed to NHPs. It is interesting to note that there is no record of secondary transmission to spouses which suggests that humans may act as dead-end hosts (Callahan *et al*., 1999; Lerche, 2010). In monkey as well as human cells the apparent lack of pathogenicity in infected persons on the basis of a very limited number of cases is strongly contrasting with the massive lytic properties of such FVs. The incidence of a disease in a person who is chronically infected by a retrovirus may be very low and a very long latency may also be followed. Due to the pandemic of *Human immunodeficiency virus* (HIV) there has been great underestimation regarding co-infections in areas where persons infected with SFVs live. In a macaque model there is enhancement of cellular tropism of SFV due to enhancement of immunosuppression induced by *Simian immunodefficiency virus* (SIV) (Mergia *et al*., 1996; Vandamme *et al*., 1998). Studies have shown that several specific foamy viruses infect chimpanzees in certain areas of Central Africa raising the potential risk of retroviral infection in humans which is linked to contact with chimpanzees (Calattini *et al*., 2006). For characterization of SFVs in NHPs that are wild-born and for investigation of cross-species transmission to humans, Polymerase Chain Reaction (PCR) based studies have been carried out on blood as well as tissue samples. Such study has confirmed the presence of novel strain of SFV in Gabon and the chances of cross-species transmission at a higher rate from bites of gorillas (Mouinga-Ondeme *et al*., 2012). Especially during the hunting activities humans may get infected from bites of gorillas (Betsem *et al*., 2011).

Diagnosis: Evidence of SFV infection includes seropositivity as well as detection of proviral deoxyribonucleic acid (DNA) along with *Foamy virus* isolation (Heneine *et al*., 1998). Plasma can be screened for the presence of FV by using Enzyme Immuno Assay (EIA) as well as Western blot specific for FV. For measuring the proviral loads, DNA extracted from buffy coats can be used for Polymerase Chain Reaction (PCR) amplification (Switzer *et al*., 2012). Seperate Western Blot (WB) testing by the use of two different SFV antigens is used currently for serological detection of SFV. For facilitating serological testing for the detection of SFV, western blot assay by the use of combined antigens has been developed (Hussain *et al*., 2003). EFV has been recently isolated from blood samples of naturally infected healthy horses after co-culture of phytohemagglutinin (PHA)-activated lymphocytes derived from seropositive horses with permissive human U373-MG cells (Tobaly-Tapiero *et al*., 2000, 2005) have described the successive steps leading to the isolation of the EFV from peripheral blood lymphocytes of infected horses.

SFV-1 infections have been monitored from time to time by Polymerase Chain Reaction (PCR) and Reverse Transcriptase (RT), cytopathology as well as immunofluorescent assay and it has been found that all cells are permissive for SFV-1. This demonstrates that SFV-1 has a broad host range with respect to species as well as types of cells. Fibroblasts as well as epithelial cells along with neural cells have all shown cytopathology extensively which is characteristic of infection due to *Foamy virus*. The reverse transcriptase values in the lymphoid as well as macrophage cell lines that are infected with SFV-1 are lower by several fold than that of the fibroblasts as well as epithelial cells. It is therefore evident by such diagnostic approach that SFV-1 appears to establish persistent infection of low level in lymphoid as well as macrophage cell lines (Mergia *et al*., 1996).

For detection of SFV in Non Human Primate (NHP) species in Asia three assays have been developed that include: Enzyme Linked Immunosorbent Assay (ELISA), Western blot assays by the use of *gag* protein of the virus (recombinant) along with an indicator cell line for the detection of macaque FV. The correlation of the recombinant ELISA with the presence of FV sequences can be detected by PCR (Hahn *et al*., 1994; Jones-Engel *et al*., 2007). For determination of the prevalence of SFV in macaques, PCR amplification of the 5' Long Terminal Sequence (LTR) has been found to be useful as it is largely invariant, thereby providing high probability of detection of the virus. Specific anti-SFV antibodies can be detected by the use of ELISA (Hood *et al*., 2013). On the basis of the sequencing of the envelop gene on the viral external surface, grouping of the *Feline foamy virus* (FFV) can be done. For placing FFV in several neutralization groups, serum neutralization assays using autologous virus is done.

Subsequent use of group-specific PCR using primer sets specific for each group of the virus helps to detect super infection (Winkler *et al*., 1998). Use of reverse transcriptase polymerase chain reaction (RT-PCR) has helped in the detection of FV in faecal sample (Liu *et al*., 2008). As in case of SFV infection most tissue harbors solely the proviruses that are latent in nature, quantitative RT-PCR (qRT-PCR) is used for the expression of group specific antigen (*gag*) RNA. The *gag* gene is selected as this region is highly conserved in nature among all the primary isolates. The lower limit for detection by qPCR is 10 copies per 10^5 cell equivalents. This assay can be used for examination of blood as well as buccal swabs, necropsy tissues as well as tissues from animals infected with SFV. Such study reveals that blood is a site of persistence of the virus but not of replication (Murray *et al*., 2006). By the use of *Feline foamy virus* (FFV) modular ELISA has been established which is suitable for determination of immunoglobulin (Ig) G as well as IgM antibody responses against structural as well as non-structural proteins of FFV. The validation of ELISA has been done with standard reference sera. Antibodies against group specific antigen (*gag*) have been

found to be 36% whereas against the non-structural protein the presence of antigen has been found to be 19-25%. In this small epidemiological study there has been no significant association of FFV antibodies with clinical disease (Cummins *et al.*, 2005; Romen *et al.*, 2006). The nucleotide sequence of the New World SFV has been determined completely in spider monkey (SFVspm). Cloning of the genome up to the 5' end of the LTR into plasmid vectors has been done starting from the conserved region present in the integrase (IN) domain. Molecular probes have also been developed allowing the serological investigation of trans-species transmission of SFVspm to humans (Thumer *et al.*, 2007). Using *Feline foamy virus* (FFV) as model system, establishment of modular ELISA has been done which is suitable for determination of feline IgG as well as IgM antibody responses against structural as well as non-structural FFV proteins (Phung *et al.*, 2005; Romen *et al.*, 2006). As far as the diagnosis of *Bovine foamy virus* (BFV) is concerned baby hamster kidney-21 (BHK-21) cell line has been used as an indicator cell line (Ma *et al.*, 2007; Guo *et al.*, 2011). ELISA specific for *gag* protein has also been used for the detection of seropositivity to BFV in milk of cattle (Romen *et al.*, 2007). Enhanced Green Fluorescent Protein (EGFP) expression assay can be used successfully for examination of the host range of BFV *in vitro* simply as well as rapidly. Moreover, this assay also proves the ability of BFV to infect several cell lines of bovine and human, rat and monkey origin productively (Ma *et al.*, 2008). For improving the accuracy of detection of *Human foamy virus* (HFV) there has been establishment of an indicator cell line by co-transfection of BHK-21 cells with two plasmids: one that contains a G418 antibiotic resistance marker and the other that includes the luc gene. *Foamy virus* activated luciferase (FAL) assay has been conducted and it has been proven that this assay is a useful technique for diagnosing as well as quantitating HFV infection rapidly (Tai *et al.*, 2001).

Prevention and control: For emerging infections like the foamy viral infection, strengthening of the public health surveillance system is warranted in order to provide early warnings, which forms the basis for the primary recommendations. Integrating the efforts along with coordination of budgetary resources for prevention as well as control is a challenge faced by governments both locally as well as nationally. Building of capacity for sustaining these efforts may form the greatest challenge of all. Persons working with NHP or with NHP material are at the risk for exposure occupationally to infectious materials like SFV which are potentially hazardous causing zoonotic infection. Strategies for prevention are required for reducing the risk for needle sticks along with mucocutaneous exposure. Emphasis for the safety guidelines must be given so that the laboratory workers along with the animal handlers carry out the invasive tasks taking extra precaution (Sotir *et al.*, 1997). There is need to identify the population with prevalence of SFV substantially which is proven to be helpful in assessment of the consequences of SFV infection in human and for quantifying the risks associated with exposure to primates. The significance of the disease in humans caused by SFV clinically as well as its transmissibility from person to person is still unclear. There is therefore need of structured interviews annually and wide spread laboratory studies must be conducted on this basis on the whole blood along with oral as well as urogenital specimens (Neumann-Haefelin *et al.*, 1993; Boneva *et al.*, 2007). The studies conducted recently on the endogenous retroviruses have revealed their role in threatening the safety of xenotransplantation both for the recipient of a transplant and for people who are in contact with the patient possibly. The risk of such complication is low but there is urgent need of invoking the precautionary principles on the basis of the history of the disease (Michie, 2001). For several of the retroviruses since the emergence of pathogenic from non-pathogenic viruses upon cross-species infection is well

documented it is essential to undertake precautions necessarily to deter in human SFV infections. Such steps will help in prevention of the emergence of a novel pathogen, thereby reducing the risk of transmission of another pathogenic human retrovirus potentially (Khan, 2009). Serological as well as molecular approaches need to be used in combination for identification of human infection with SFV. Identification of the endemic foci of infection due to SFV helps in facilitating longitudinal studies (Switzer *et al*., 2012). The hunting of NHPs including mandrills is required to be prevented in order to help preventing these endangered species and most importantly for preventing the FV from getting transmitted to humans (Calattini *et al*., 2007; Switzer *et al*., 2008).

During the present One Health concept, rapid, confirmatory and advanced diagnostic tools equipped with early warning and screening/monitoring systems must be fully utilized for detection of viruses like the *Foamy viruses* infecting animals and humans (Hussain *et al*., 2003; Schmitt and Henderson, 2005; Belak, 2007; Gautret *et al*., 2007; Jones-Engel *et al*., 2007; Deb and Chakraborty, 2012; Deb *et al*., 2013; Dhama *et al*., 2012, 2013a, b, 2014). Along with this, recent developments in vaccines as well as therapeutic regimens need to be explored to their full potential to combat Fvs besides adapting appropriate prevention and control strategies to lessen the cross-species transmissions and related zoonotic concerns (Heneine *et al*., 2003; Switzer *et al*., 2004; Wolfe *et al*., 2004; Calattini *et al*., 2007; Meeusen *et al*., 2007; Khan, 2009; Dhama *et al*., 2008, 2013c, d, e, f; Mahima *et al*., 2012; Switzer *et al*., 2012; Tiwari *et al*., 2014).

USE OF FOAMY VIRUSES IN GENE THERAPY

Gene therapy aims at modification of genetic material of living cells in order to achieve therapeutic benefit and involves the insertion of a gene that is functional into a cell for replacement of a gene that is absent or defective. Somatic tissues have been explored widely for introducing foreign genes for treatment of several diseases. In this regard the expression of therapeutic gene in a sustained fashion without causing any adverse effect to the recipient is of prime concern. A vector therefore which is associated with little or no reaction immunologically is preferred and in this regard *Foamy virus* (FV) vector is found to be beneficial and significant (Pandya *et al*., 2001; Lindemann and Rethwilm, 2011). For treating genetic immunodeficiencies, therapeutic potential of stem cell gene therapy has been demonstrated. It has been found that proliferation of lymphocytes as well as neutrophil adhesion defects can be corrected without any genotoxic complications (Bauer *et al*., 2008). FV acts as an efficient system of virus integration which can be used for studying regeneration of limb and tail in salamanders. It has been shown that FV vectors that are replication deficient causes transduction of cells efficiently in two different models of regeneration in cell culture as well as *in vivo*. Expression of tissue specific transgene has been achieved by using FV vectors during regeneration of limbs. FV vectors are also considered as efficient means of transferring genes into axolotl limb or tail and it has been proven to be a non-toxic method of gene delivery into axoltols either *in vivo* or *in vitro* (Khattak *et al*., 2013). There has been establishment of hybrid vectors (FAD) for combining features of the transduction of adenovirus vectors efficiently with the advantage of integration into the genome of host cell in a stable fashion. For direct gene delivery to joints FAD vectors have been done. Recombinant FAD that encodes Enhanced Green Fluorescent Protein (EGFP) or human interleukin 1 receptor antagonist protein (IL1RA) complementary deoxyribonucleic acid (cDNA) has been generated. It has been indicated by the results that FAD vectors are able to transfer gene efficiently to synovium and by such means arthritides can be treated (Weber *et al*., 2013). It is however controversial regarding the application of FV vectors to the Central Nervous System (CNS) but researchers have

proved that these novel vectors can be used for transduction of neural along with other non-dividing cells (Zhang *et al.*, 2010). There is chance of leukemia development following gammaretroviral vector mediated gene therapy for which much emphasis has been given in recent time indicating the requirement of long-term follow up following hematopoietic stem cell gene therapy. Studies have also been conducted indicating the use of FV vectors for treatment of children with leukocyte adhesion deficiency type 1 (LAD-1) (Bauer *et al.*, 2013). FV vector can correct a rare immunodeficiency which is X-linked known as the Wiskott-Aldrich Syndrome (WAS). Transplantation of Haematopietic Stem Cells (HSC) that are transduced with FV vector has been done in WAS knockout mice. It has been confirmed by secondary transplantation that successful transduction of bona fide HSCs can be done by FV vectors that express WAS protein (Uchiyama *et al.*, 2012).

CONCLUSION

The biggest challenges lie in the matter of understanding the interactions of *Foamy virus* and the hosts. There is need to work more for defining the target cells which are infected *in vivo* along with the immune response of the host to FV infection. Small animal models like rabbits and mice must be made available to conduct more studies on this particular virus. For several of the retroviruses the emergence of viruses that are pathogenic from the non-pathogenic viruses upon cross-species infection is well documented. It is therefore prudent to take necessary precautions to detect SFV infections in humans. These steps will thereby help in preventing the novel pathogen emergence thus reducing the transmission risk of another pathogenic human retrovirus potentially. Advances in the serological as well as molecular diagnosis of FV infection further would help in undertaking better strategy for the prevention as well as control of such viral infections by early detection and timely curbing of the disease. Much study is required to be carried out on the natural history as well as species origin of the infections by supporting attentions appropriately to follow biosafety practices for preventing occupational infections. This highlights the importance of additional studies to define in a better way the clinical outcome of such zoonotic infections. In biomedical research, frequent use of macaques that helps in identification of persistent retroviral infection from macaques to human beings will have implications to formulate public health policy along with occupational health and safety. At the same time, studies must be conducted on endemic foci of infection due to SFV thereby facilitating determination of these zoonotic retroviral infections. The inherent characteristics of FV vectors set them apart from orthoretroviral vectors favorably and further necessitates the need of conducting basic research on this particular virus for applying them in gene therapy.

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