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Review Article

Some Retroviral Diseases of Humans and Animals: A Prospectus

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ABSTRACT

This prospectus, gives an account on five, highly epidemiologically significant, virus members of the family *Retroviridae* and the ailments they cause. These are the human (HIV-1 and HIV-2) and three animal retroviral diseases of veterinary importance *viz.* the Enzootic Bovine Leucosis Virus (EBLV); the Caprine Arthritis-Encephalitis Virus (CAEV) and the Equine Infectious Anemia Virus (EIAV). This is expected to give a dimension that can aid field veterinarians, especially in developing countries, to help in differential clinical diagnosis, between diseases that may have similar clinical picture to retrovirus infections in animals.

This article also gives enlightenment on the history, classification, properties, ecology and the interesting peculiarities of the family *Retroviridae*.

Keywords: *Retroviridae*; HIV; AIDS; Infections

INTRODUCTION

The family *retroviridae*

The historic discovery of retroviruses was made in 1908, when scientists showed that the chicken leucosis, a form of leucosis and lymphoma was caused by a virus. This was followed by a number of discoveries of retroviruses in chickens and other mammals [1-3]. Retrovirus virions are sensitive to heat, detergents and formaldehyde. They are relatively resistant to UV light. The surface glycoproteins may be partially removed by proteolytic enzymes. Retrovirus virion buoyant density is 1.16-1.18 gcm^{-3} in sucrose and the virion sedimentation co-efficient (S20,W) is approximately 600S in sucrose [1].

According to up-dated published information, previously the family *Retroviridae* was divided into three subfamilies (*Oncovirinae*, *Lentivirinae*, and *Spumavirinae*), but are now divided into *Orthoretrovirinae* and *Spumaretrovirinae* [3]. The term oncovirus is now commonly used to describe a cancer-causing virus [3].

Like most viruses, retrovirus particles are composed of a protein capsid, a nucleic acid (Ribonucleic Acid-RNA) and an envelope. The capsid is generally spherical enveloped with an average diameter ranging between 100 to 200 nm^3. The Envelope is composed of lipids (obtained from the host plasma membrane during the budding process) as well as glycoprotein encoded by the envelope (Env) gene. The retroviral envelope serves three distinct functions: Protection from the extracellular environment *via* the lipid bilayer, enabling the retrovirus to enter/exit host cells through endosomal membrane trafficking, and the ability to directly enter cells by fusing with their membranes.

The RNA

The RNA constitutes about 2% of the virion dry weight. The retrovirus virion contains two identical positive-sense, linear, single-stranded RNA molecules 7-13 kilobases in length. The two molecules are present as a dimer, formed by base pairing between complementary sequences [1,3].

A peculiar property of members of the family *retroviridae* is that they insert a copy of their Ribonucleic Acid (RNA) genome into the DNA of a host cell that they invade, thus changing the genome of that cell [3]. Once inside the host cell's cytoplasm, the virus uses its own reverse transcriptase enzyme to produce DNA from its RNA genome, the reverse of the usual pattern, thus retro (backwards). The new DNA is then incorporated into the host cell genome by an integrase enzyme, at which point the retroviral DNA is referred to as a provirus. The host cell then treats the viral DNA as part of its own genome, transcribing and translating the viral genes along with the cell's own genes, producing the proteins required to assemble new copies of the virus. This process is indeed, the first natural genetic engineering known in animal virology. It also occurs in bacteriophages.

Viral proteins and functions

Proteins of the retrovirus particle constitute about 60% of the virion dry weight. They consist of capsid proteins, predominated

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by the group specific antigen proteins (GAG); proteases (PR); Poly proteins (Pol) and envelope proteins. Group-specific antigen (gag) proteins are major components of the viral capsid, which are about 2000-4000 copies per virion. Gag possesses two nucleic acid binding domains, including matrix (MA) and nucleocapsid (NC). Specifically recognizing, binding, and packaging the retroviral genomic RNA into assembling virions is one of the important functions of Gag protein. Gag interactions with cellular RNAs also regulate aspects of assembly [1,3]. The expression of gag alone gives rise to assembly of immature virus-like particles that bud from the plasma membrane. In all retroviruses the Gag protein is the precursor to the internal structural protein [3].

Protease (pro) is a proteolytic enzyme which functions in the proteolytic cleavage during virion maturation to make mature GAG and Pol proteins.

Pol proteins are responsible for synthesis of viral DNA and integration into host DNA after infection.

The Env proteins are responsible for major functions in the initial process of infection of susceptible cells by retroviruses. Thus they enable the retrovirus to be infectious. They play a role in association and entry of virions into the host cell. Utilizing the Surface Component (SU) of the Env protein the retrovirus particle gains ability to bind its target host cell using specific cell-surface receptors; while the ability of the retrovirus to enter the cell *via* membrane fusion is imparted by the membrane-anchored trans-membrane component [1,3].

Other viral proteins

Beside the major viral proteins, mentioned above, there are other minor proteins [1,3]. These are two main types; the nucleocapsid protein (NC) and the viral enzymes. The NC protein is the most abundant and it coats the viral RNA; while the enzyme proteins are present in much smaller amounts. Enzymes present in the retrovirus virion are the RNA-dependent DNA polymerase (Reverse Transcriptase; RT), DNA-dependent DNA polymerase, Ribonuclease H (Rnase H) Integrase and Protease. The retroviral Rnases H have been demonstrated to show three different modes of cleavage: internal, DNA 3′ end-directed, and RNA 5′ end-directed. All three modes of cleavage constitute roles in reverse transcription. Therefore, The Rnase H activity is essential in several aspects of reverse transcription. The use of an Rnase H activity during retroviral replication displays a unique strategy to copy a single-stranded RNA genome into a double-stranded DNA, since the minus-strand DNA are complementary and make base pairing to retrovirus genome in the first cycle of DNA synthesis. The Rnase H ribonuclease activity is also required in the retroviral life cycle, since it generates and removes primers essential by the Reverse Transcriptase (RT) for the initiation of DNA synthesis [3].

Viral lipids and carbohydrates

Both viral lipids and carbohydrates are found in the envelope [3]. Lipids constitute about 35% of the virion dry weight. They are derived from the plasma membrane of the host cell. Carbohydrates constitute 3%, by weight, of the virion.

HUMAN IMMUNODEFICIENCY VIRUSES (HIV-1 AND HIV-2)

A dearth of information has thus far been gathered regarding knowledge on the Human Immunodeficiency Viruses (HIV-1 and HIV-2). It is well documented that these viruses damage cells of the immune system and weaken their ability to fight everyday infections and disease, causing the disease known as, Acquired Immune-deficiency Syndrome, (AIDS) [4].

AIDS is the name used to describe a number of potentially life-threatening infections and illnesses that happen when the immune system has been severely damaged by the HIV virus.

Historically, both HIV-1 and HIV-2 are believed to have originated in non-human primates in West-central Africa, and are believed to have transferred to humans in the early 20th century [1].

HIV-1 appears to have originated in southern Cameroon through the evolution of SIVcpz, a Simian Immunodeficiency Virus (SIV) that infects wild chimpanzees subspecies Pan *Troglodytes troglodytes* [1,4,5]. The closest relative of HIV-2 is SIVsmm, a virus of the sooty mangabey (*Cercocebus atys atys*), an Old World monkey living in littoral West Africa (from southern Senegal to western Côte d'Ivoire) [1,4,5].

HIV-1 is the most common type of HIV and occurs all over the world. Around 95 percent of people living with HIV have HIV-1 [1,6,7].

Though HIV-2 is mainly present in West Africa, but it has slowly smouldering through the world, including other parts of Africa, Asia, Europe and the Americas [8].

HIV-1 and HIV-2 are both retroviruses that can have similar effects on the human body, however, they are genetically distinct. Published molecular virological data revealed that the genomes of the two viruses only had a 55 percent sequence identity [1-4,6].

Co-infection of HIV-1 and HIV-2

Although each virus can be contracted individually, still they can also be contracted together a situation referred to as co-infection [6,9-13]. This phenomenon is predominantly seen in West Africa [9]. However, a great concern is felt towards its existence worldwide. HIV-2 seems to have lower mortality rates, less severe symptoms and slower progression to AIDS than HIV-1 alone or the co-infection [13]. In co-infection, however, this is largely dependent on which virus was contracted first. HIV-1 tends to dominate HIV-2 in progress of the clinical disease [13].

In spite of the fact that both types of HIV cause long-term conditions, and that there is no cure for HIV, the presence of Anti-Retrovirus Treatment (ART) enable most people with the virus to live a long and healthy life [10].

The HIV-1

HIV-1 is related to viruses found in chimpanzees and gorillas living in western Africa [1,4].

Scientists divide HIV-1 into a major group (Group M) and two or more minor groups, namely Group N, O and possibly a group P [1,7]. Each group is believed to represent an independent transmission of SIV into humans (but subtypes within a group are not).

Group M

With 'M' for "major", this is by far the most common type of HIV, with more than 90% of HIV/AIDS cases deriving from infection with HIV-1 group M. The M group is subdivided further into clades, called subtypes, that are also given a letter (A, B,C, D, E, F, G, H, I, J, K, L) [1,7]. Table 1 illustrates the global distribution of the different subtypes.

Table 1: Global distribution of the subtypes (clades) of the major group (M) of HIV-1.

Subtypes (clades) of the HIV-1 'M' Group	Global geographical distribution
A	Eastern Africa.
B	Is dominant in Europe, the Americas, Japan, and Australia is the most common form in the Middle East and North Africa and Haiti [6,7].
C	Is the dominant form in Southern Africa, Eastern Africa, India, Nepal, and parts of China [6].
D	Is generally only seen in Eastern and central Africa [6].
E	Is found in Southeast Asia which is the dominant form for heterosexuals as transmission rate is much higher than most other subtypes.
F	Has been found in central Africa, South America and Eastern Europe [8].
G	Has been found in Africa and central Europe [8].
H	Is limited to central Africa [8].
I	Was originally used to describe a strain that is now accounted for as CRF04_cpx, with the cpx for a "complex" recombination of several subtypes.
J	Is primarily found in North, Central and West Africa, and the Caribbean [9].
K	Is limited to the Democratic Republic of Congo (DRC) and Cameroon [8].
L	Is limited to the Democratic Republic of Congo (DRC) [10].

Some of the subtypes are known to be more virulent or are resistant to different medications [1,3,4].

Historic emergence of the HIV-1

Before the discovery of the HIV-1 in 1983, as the causative agent of AIDS, several observations were recorded by different virologists and medical practitioners at different parts of the world [1-4].

In this context, the flow of events that led to the discovery of the HIV-1, as the causative agent of AIDS, has been extracted from the literature as stated below.

In 1981: Cases of a rare lung infection called Pneumocystis Carinii Pneumonia (PCP) were found in five young, previously healthy gay men in Los Angeles. At the same time, there were reports of a group of men in New York and California with an unusually aggressive cancer named Kaposi's Sarcoma. In the same year, the first cases of PCP were reported in people who inject drugs. By the end of 1981, 270 cases of severe immune deficiency among gay men; of whom 44.8% had died.

In June 1982: A group of cases among gay men in Southern California suggested that the cause of the immune deficiency was sexual and the syndrome was initially called Gay-Related Immune Deficiency (or GRID).

In late June 1982: The disease was reported in haemophiliacs. In January 1983, AIDS was reported among the female partners of men who had the disease suggesting it could be passed on *via* heterosexual sex.

In September 1982: The term Acquired Immune Deficiency Syndrome (AIDS) was given for the first time by CDC to describe the disease. They described it as "A disease at least moderately predictive of a defect in cell mediated immunity, occurring in a person with no known case for diminished resistance to that disease."

Following that, the AIDS was described in different parts of the world.

In 1983: A turning point in the AIDS research became apparent when researchers at the Pasteur Institute, in May 1983, in France, reported the discovery of a new retrovirus called Lymphadenopathy-Associated Virus (or LAV) that could be the cause of AIDS.

In April 1984: The National Cancer Institute announced they had found the cause of AIDS, the retrovirus HTLV-III. In a joint conference with the Pasteur Institute they announced that LAV and HTLV-III are identical and the likely cause of AIDS.

In May 1986: The International Committee on the Taxonomy of Viruses (ICTV) said that the virus that causes AIDS will officially be called HIV (Human Immunodeficiency Virus) instead of HTLV-III/LAV.

Using modern molecular biological techniques, the origin of the HIV-1 and HIV-2 was identified as zoonotic coming from the chimpanzees [1,4].

How to get infected with HIV

From a virological point of view, the HIV is a fragile virus and does not survive outside the body for long. It is found in the body fluids of an infected person. This includes semen, vaginal and anal fluids, and blood and breast milk. HIV cannot be transmitted through sweat, urine or saliva. The most common way of getting HIV is through having anal or vaginal sex without a condom.

Other means of getting HIV include sharing needles, syringes or other injecting equipment. Vertical transmission from mother to baby during pregnancy, birth or breast feeding can occur [8,9]. The chance of getting HIV through oral sex is very low.

Symptoms of the AIDS infection

Two to six weeks following exposure to the HIV, symptoms start as a short flu-like illness, which lasts for 7-15 days [1,4,8]. After disappearance of these symptoms, HIV may not cause any symptoms for many years, although the virus continues to damage the immune system. This means that many people with HIV do not know they're infected. So, people who are at high risk are advised to have regular testing. Anyone who thinks he could have HIV should get tested. Some people are advised to have regular tests as they're at particularly high risk [1,8].

Diagnosis of HIV-1

Diagnosis of AIDS infection depends on clinical examination of the suspected person and by laboratory testing [8,10,11]. Early diagnosis of AIDS will enable the start of early treatment (within 24-72 hours). This indeed is expected to help in controlling the virus. Exposed persons to HIV infection should be retested within 1-3 months (the window period).

Treatment for HIV-1

The general strategy of AIDS treatment aims at reducing the viral load in the patient to undetectable levels [1]. A group of medicines called the Antiretroviral Treatment (ART) are currently utilized worldwide in treatment of the HIV [1,4,8]. The mode of action of these drugs is bidirectional; i.e. they help the immune system to repair the affections brought about by the HIV infection and to prevent further damage and to stop virus replication [1,4,8].

A salient recommendation in the strategy of HIV treatment is to start as soon as possible following exposure; and that ART is to be initiated in all patients living with HIV, regardless of CD4 count [14-16]. Although ART has long-term adverse effects, these are minimal compared with complications of untreated HIV infection. The ART that are generally used are Nucleoside Reverse Transcriptase Inhibitors (NRTIs), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), Protease Inhibitors (PIs), Integrase Strand Transfer Inhibitors (INSTIs), and pharmacokinetic enhancers or boosters (improve pharmacokinetic profiles of some ART and increase their effectiveness, resulting in lower doses of the antiretroviral being needed). NRTIs, NNRTIs, and PIs are the antiretrovirals most commonly used [14-17].

Although guide-lines and protocols for ART may differ in most countries, a first-line ART regimen will generally consist of 2 NRTIs in combination with a third agent (either an INSTI, NNRTI, or boosted PI) [14,18].

Different forms of medicines are available such as fixed-dose combination tablets that combine a number of drugs in 1 tablet [16-18]. Tenofovir is available as tenofovir disoproxil fumarate or the oral prodrug tenofovir alafenamide. Tenofovir alafenamide is available only in fixed-dose combination formulations with other antiretroviral agents.

HIV is able to develop resistance to a single HIV medicine very easily, but taking a combination of different medicines makes this much less likely [16-18]. Most people with HIV take a combination of medicines. It's vital these are taken every day as recommended by the treating doctor.

Living with HIV

In order to ensure reduction of the viral load to significantly undetectable and untransmittable (U=U) situation, people living with the HIV should receive effective treatment, advised to take regular exercise, eat a healthy diet and to stop smoking [19]. This indeed, will reduce the risk of passing HIV on to others. Without treatment, the immune system will become severely damaged and life-threatening illnesses such as cancer and severe infections can supervene. It's rare for a pregnant woman, living with HIV, and receiving timely and effective HIV treatment and medical care, may not transmit the disease to their babies.

HIV-2

The first identification of HIV-2 occurred in Senegal in 1986 [8,12]. It is closely related to Simian Immunodeficiency Virus endemic in sooty mangabeys (*Cercocebus atys*) (SIVsmm), a monkey species inhabiting the forests of Littoral West Africa. Phylogenetic analyses show that the virus most closely related to the two strains of HIV-2 which spread considerably in humans (HIV-2 groups A and B) is the SIVsmm found in the sooty mangabeys of the Tai forest, in western Ivory Coast [8]. Since 2010, eight HIV-2 groups were identified (A to H). Of these, only groups A and B are pandemic. The other six groups, humans are dead ends for them [10].

Epidemiologically, HIV-2 has not been widely recognized outside of Africa. Group A is found mainly in West Africa, but has also spread globally to Angola, Mozambique, Brazil, India, Europe, and the US. Despite the presence of HIV-2 globally, Group B is mainly confined to West Africa [8-10,13]. Despite its relative confinement, HIV-2 should be considered in all patients exhibiting symptoms of HIV that not only come from West Africa, but also anyone who has had any body fluid transfer with a person from West Africa (i.e. needle sharing, sexual contact, etc.) [20-24].

Transmission of HIV-2

Both types of HIV can be transmitted by similar methods. However, the transmission rate is much lower in HIV-2 than HIV-1. The most risk factors for HIV-1 and HIV-2 transmission include sex without a condom and sharing needles or syringes, through direct contact with bodily fluids that contain the virus, including: Blood; sexual fluids; breast milk [16,22,23]. It has been observed that, the most common mode of HIV-2 transmission is heterosexual sex. However, heterosexual transmission rates of HIV-2 are five to 10 times lower than those of HIV-1. It is worth mentioning that, transmission rates of HIV-2 between mothers and babies are 20-30 times lower than those of HIV-1. It is important to note that, there is little risk of transmitting HIV through sex if a person takes HIV medications correctly and is able to maintain an undetectable viral load. This can also significantly reduce the risk of mother-to-child transmission [22-25].

Clinical signs of HIV-2

The clinical manifestations of HIV-2 AIDS are similar to those for HIV-1. However, some minor differences have been reported. HIV-2 has been found to be less pathogenic than HIV-1 [14,26,27]. People with HIV-2 tend to have a lower viral load, in their blood, than people with HIV-1 [14,15]. HIV-2 tends to develop more slowly than HIV-1 [17,18]. People with HIV-2 may have a longer period without symptoms than people with HIV-1, and the rate of progression to stage 3 HIV is slower [8,22,23]. HIV-2 also has a lower mortality rate than HIV-1; HIV-2-infected individuals usually have a long clinically latent period of 10 years or more, resulting in a mortality rate estimated to be two-thirds lower than that for HIV-1 [17]. Indeed, many HIV-2-infected individuals appear not to progress to AIDS at all [22].

Minor differences in pathology resulting from HIV-2, compared to HIV-1, infection have been observed [17]. For example, in the Ivory Coast, encephalitis was shown at autopsy to be almost restricted to individuals with HIV-2-related causes of death (18%; nfl40), compared to HIV-1 (!1%; nfl170). Whether this is because people infected with HIV-2 generally survive longer than those infected with HIV-1 or if HIV-2 is more neurotropic, neuropathogenic than HIV-1 is unknown [18]. Additionally, AIDS-associated Kaposi's sarcoma occurs in around 10% of HIV-1-infected individuals, although it is less frequent in HIV-1-infected Gambians and approximately 12 fold less frequent still in HIV-2-infected Gambians [19,20].

HIV-2 diagnosis

Like diagnosis of AIDS infection in HIV-1, diagnosis of HIV-2 depends on clinical examination of the suspected person and by laboratory testing [8,11,26]. Also like the situation in HIV-1, HIV-2 diagnosis can also be made when a patient has no symptoms but positive blood work indicating the individual has the virus. The Multispot HIV-1/HIV-2 rapid test is currently the test of choice that can differentiate between the two viruses [11]. Recommendations for the screening and diagnosis of HIV have always been to use enzyme immunoassays that detect HIV-1, HIV-1 group O, and HIV-2. Differential diagnosis of HIV-2 should be considered when a person is of West African descent or has had sexual contact or shared needles with such a person. West Africa is at the highest risk as it is the origin of the virus [8,26].

Treatment of HIV-2

Disease monitoring in patients with HIV-2 includes clinical evaluation and CD4 cell counts, while treatment includes Anti-Retroviral Therapy (ART), Nucleoside Reverse Transcriptase Inhibitors (NRTIs), Protease Inhibitors (PI), and Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) with the addition of CCR5 co-receptor antagonists and fusion inhibitors [14,18,28].

HIV-2 appears to be resistant to NNRTIs intrinsically, but may be sensitive to NRTIs [27]. Protease inhibitors have shown variable effect, while integrase inhibitors are also being evaluated. Combination regimens of the above listed therapies are being looked into as well, also showing variable effect depending on the types of therapies combined [22,23,28].

If a pregnant mother is exposed, screening is performed as normal. If HIV-2 is present, a number of perinatal ART drugs may be given as a prophylactic to lower the risk of mother-to-child transmission. After the child is born, a standard six-week regimen of these prophylactics should be initiated. Breast milk may also contain particles of HIV-2; therefore, breast feeding is strictly non-advisable.

Preventing HIV-1

Since the discovery of HIV in 19831, and the present situation that it became a global scourge through time, HIV prevention has become a vital issue in reducing the spread of infection among people, anywhere in the world [1-3]. There are many effective ways to prevent or reduce the risk of HIV infection [14,15] including using a condom for sex Post-Exposure Prophylaxis (PEP) Pre-Exposure Prophylaxis (PrEP) treatment for HIV to reduce the viral load to undetectable level, if a person is using drugs, not to share needles or other injecting equipment, including syringes, spoons and swabs. For people with HIV, who have been taking HIV treatment and their viral load has been undetectable for 6 months or more, this indicates that they cannot pass the virus on through sex. This is referred to as the Undetectable=Untransmittable (U=U) situation [20,21].

ANIMAL RETROVIRUS DISEASES

In this mini overview three animal virus diseases are discussed as the Enzootic Bovine Leukosis (EBL), Equine Infectious Anemia (EIA) and Caprine Arthritis Encephalomyelitis (CAE). These diseases predominantly exist in the developed world [1]. However, they can be introduced into the developing countries through importation of foreign breeds for up-grading of productivity in their livestock.

We chose these diseases, in this study, because of their grave prognosis; especially the EBL and the EIA that necessitates humane destruction of the sick animals [29,30].

Enzootic bovine leukosis

EBL was first reported in Lithuania, Eastern Europe [31]. Since that date the disease was reported in various European countries, the USA, Australia and worldwide. Through animal trade and animal by-products, the disease has spread all over the world [31].

Naturally, EBL is a neoplastic disease of cattle, buffalo and capybaras. It causes severe economic losses to the dairy and meat industry worldwide [29,30]. Cattle may be infected at any age, even in utero. EBLV infection is mostly subclinical, but about 30% of cattle over 3 years of age develop persistent lymphocytosis, and a smaller proportion develop lymphosarcoma in various internal organs [1].

Symptoms of superficial lymph node hypertrophy and splenomegaly in Lithuania, Eastern Europe [31]. Since that date the disease was reported in various European countries, the USA, Australia and worldwide. Through animal trade and animal by-products, the disease has spread all over the world [31].

Clinical signs and symptoms

According to published data animals infected with EBLV, develop lymphosarcoma, become emaciated, show loss of appetite, decrease in production, but there is no evidence of fever [30-32]. In 75%-90% cases, peripheral lymph node increase in size. Other signs include arrythmia, murmur in heart, blindness, paresis, paralysis, indigestion, ulcers, peritonitis, hematuria, hydronephrosis and intra-abdominal hemorrhage. Cattle with lymphosarcomas may die suddenly, due to rupture of the spleen [4].

EBLV transmission

It is reported that transmission of EBLV occurs mainly during the process of dehorning, injections, tattooing and rectal examination [30-32]. Animals can also acquire infection from bronchial secretion especially when they are housed in a crowded place [33,34]. Sexual transmission of EBLV has not been reported. In utero transmission of the virus from mother to calf occurs when the dam is in the condition of lymphocytosis. The virus has also been known to be transmitted by contaminated equipment, biting of insects, milk from infected cow, but not colostrum as it contains anti EBLV antibodies [35]. Body fluids such as saliva, nasal and bronchial fluids are also rich in virus load. Natural dissemination of virus occurs through transfer of cells infected with virus [30,31]. Blood contaminated needles, surgical equipment; gloves used for rectal examinations etc. are responsible for artificial transmission of EBLV. Virus is also transmitted mechanically by blood sucking insects especially tabanids [30,33].

On experimental infection, young sheep are very susceptible to the BLV and develop tumours. Deer, rabbits, rats, guinea-pigs, cats, dogs, sheep, rhesus monkeys, chimpanzees, antelopes, pigs and goats can also be experimentally infected [33-40].

EBL is non-zoonotic [13,41].

Diagnosis

Published data, indicated that diagnosis of the EBL infection can be made on the basis of clinical signs such as lymphosarcoma, enlarged lymph node and serological tests [1,4]. Conventional serological techniques [30,33,36] such as Agar Gel Immuno Diffusion (AGID), Passive Hemagglutination Assay (PHA), Enzyme-Linked Immunosorbent Assay (ELISA) and Radio Immunoassay (RIA), have been implemented around the world. A number of PCR methods such as nested PCR, real time PCR, direct blood-based PCR have been applied for the detection of infection [37]. Other methods that can be used for detection are the western blotting for the detection of viral proteins, syncytium formation assay and indirect immunofluorescent assay for the detection of BLV antigen [30,32].

Differential diagnosis

The EBL can be differentiated clinically, from diseases that cause internal or external body masses. Such diseases as neoplasia carcinoma, melanoma, abscess, and fat necrosis and with the diseases that develop external masses that is *Corynebacterium pseudotuberculosis* and tuberculosis [30-33].

Treatment

As there is no drug of choice for EBL infection is thus far available, only symptomatic treatment is done using prednisone [30,38]. However, in most cases slaughter and culling of infected animals is practiced [30,31,38].

Prevention and control

No vaccines are available for control of EBL infection [30,39]. Stringent measures are usually taken to control and prevent EBL [31,33]. Such measures include separation of the seropositive cows from the non-infected ones. To use colostrum from seronegative cows only and always feed calves pasteurized milk and replacer milk [35]. Calving pens of seropositive cows should be separate. Use only EBLV negative bulls for service and artificial insemination [39]. Insect repellents are also used. Hygeinic measures should always be followed when using surgical interference, dehorning or injections [31,42].

Economic impact of EBL

EBL is a constraint in animal production. On the other hand, it causes immunosuppression which predisposes the animal to secondary infection and ultimately leads to its death. Decreased productivity of the infected animal leads to its culling. Subclinical infection can result in great economic losses [40]. It was also found that 3% reduction in milk production was associated with the seropositive cows. Loss on the potential of cow's production and death of the animal due to lymphosarcoma are the common economic losses caused by EBL [40]. Restrictions are also imposed on the trade of infected animals and their products. The cost of replacing an animal in production, the diagnostic and veterinary care, and the loss of a calf and milk production over about 10 months are indirect economic losses caused by EBL [40].

EQUINE INFECTIOUS ANEMIA (SWAMP FEVER)

Equine Infectious Anemia (EIA), is a worldwide disease of Equids (horses ponies, donkeys, mules and zebras) [43-45]. It is also called Swamp Fever [43,46]. EIA, as a disease, was first identified in 1843 [34,44]. In 1904, the infectious organism that caused EIA was identified as a filterable agent [47,48]. In the 1970s EIAV was characterized as a retrovirus and assigned to the genus lentivirus [43]. With the discovery of HIV-1 in 1983 and its classification as a lentivirus, (based largely on similar morphology and serological cross reactivity with EIAV), there was a rapid serial discovery of related animal lentiviruses, including simian, bovine, and feline immunodeficiency viruses [43,45]. The virus is non-zoonotic, though many nations in the world eat horse meat. Also it does not pose risk to non-equid animals [49-51].

Clinical signs

The clinical signs of EIA have been well covered by Anderso and McGuire, et al. [49,52,53]. In brief, with the on-set of EIA infection, the clinical signs are usually the most severe; subsequent episodes of the disease gradually become less severe, even though the horse remains infected and a potential source of infection for other horses [43]. These episodes of overt disease, which may occur weeks to months apart, are the result of mutations that occur in the virus over time, thus creating a novel "strain" that causes clinical signs in the same horse, until its immune system responds and is once again able to suppress the virus [51]. Other clinical signs of EIA may be presented by edema of the limbs and abdomen, rapid weight loss, swollen lymph nodes, and bleeding tendencies. Infection may also lead to neurological signs (ataxia) [52], abortion, or rarely sudden death. In some cases the infection can pass unnoticed manifested by low grade fever and anemia. Like the Human Immunodeficiency Virus (HIV) and other immunodeficiency viruses, the EIA virus causes persistent, lifelong infection in the infected hosts by insertion of generating DNA sequence that is based on its RNA, into the DNA of white blood cells. So, after recovery of infection, most horses become asymptomatic carriers of the virus [53]. If the horse is exposed to stress, then infection will appear again [54].

Transmission

Many reports have elaborately addressed the mode of transmission of the EIA virus. The virus is mechanically, by hematophagous biting arthropods [55,56]. Stable flies (*Stomoxys spps. e.g. S.calcitrans*) are capable of transmitting the infection; however, the most effective vectors are biting flies from the family Tabanidae. The EIA virus can also be transmitted on the mouth parts of horseflies and deerflies when they feed on an infected horse, and then feed on another horse within a fairly short period (approximately four hours). There is no evidence that the virus is transmitted by mosquitoes. Transmission is much more likely to occur from a horse when he is showing signs of illness, because of the increased amount of virus in the bloodstream (viraemia); however, transmission from apparently healthy but persistently infected carriers is possible, especially if exposed to stress [15,16].

A vertical transmission, (from the mare to the fetus in utero) as well as the transmission in the milk to nursing foals have also been described [57-59]. The risk of vertical transmission is more likely if the mare presents with clinical signs before foaling [60-63]. Foals born to EIA-positive mares are unlikely to be infected, particularly if the mare had no signs of EIA while pregnant [59]. Although foals are susceptible to infection after birth, antibodies in the colostrum from the mare appear to offer some protection for the first several months of life. There is also an iatrogenic transmission by the use of contaminated needles or veterinary/dental equipment as well as by blood transfusions and use of blood-contaminated equipment such as surgical and dental instruments, hoof knives and hypodermic needlesl [60,61]. The virus can survive for up to four days on a hypodermic needle at room temperature.

Pathology

The general pathological lesions seen on necropsy of EIA-infected equines have been reported by various authors. These included generalized lymphadenopathy, splenomegaly, hepatomegaly, accentuated hepatic lobular structure, mucosal and visceral hemorrhages, ventral edema, evidence of anemia, icterus, and thrombosis [50,62]. On histopathological examination, lymphocytic proliferation is observed in the spleen and lymph node [63-66]. Other microscopic lesions included infiltration of lymphocytes as well as macrophages in different organs such as the liver (in periportal areas), spleen, bone marrow, adrenal gland, heart, kidney, and meninges [49]. There is hyperplasia of Kupffer cells containing hemosiderin aggregates [50,62,64]. Accumulation of hemosiderin is also found in the infiltrated macrophages in the lymph nodes, spleen, and bone marrow [8]. In about 75% of EIAV-infected animals, there may be macroscopic lesions of glomerulitis with increased cellularity and thickening of glomerular tufts [49,62].

Diagnosis

Clinical signs of EIA virus infection are very similar to other

diseases, such as equine viral arteritis, anaplasmosis, edema, fever, anemia, or thrombocytopenia/ecchymoses [43]. So, in order to arrive at the right diagnosis, serological tests are applied. Demonstration of EIAV-specific antibody present in the serum of the suspected animals. The most reliable serological test used is the Agar Gel Immunodiffusion (AGID) test or Coggins test. It is the gold standard for the diagnosis of EIA [65]. The Polymerase Chain Reaction (PCR) is also used [66]. ELISA has also been employed [67,68].

Treatment and control

Unfortunately, there is no treatment for EIA virus infection. It is always recommended that sero-positive animals are to be euthanized [43,61]. According to Issel, et al, supportive treatment has no effect on controlling the virus [61].

So far, no vaccine is available to be used in prevention of the disease [44]. With the absence of treatment or prophylactic measures to be taken, then the major effective method of controlling the disease is to break the transmission cycle from by the insect mechanical vectors, to avoid iatrogenic transmission by applying strict hygienic measures, identification of the EIAV positive animals from the susceptible population, their quarantine or euthanasia [43,61].

Although EIA was first described many years ago, screening of equids for detection of EIA cases was not possible until the discovery of AGID or Coggins test in 1972. International regulatory bodies including OIE also recommend the sero-surveillance of susceptible equine populations for the international trade and imposition of restrictions on the trade or movement of the serologically positive equid [43,45,61].

Constant monitoring and surveillance associated with quarantine and elimination of seropositive animals under the appropriate legal provisions followed by regulation of movement of horses coupled with other sanitary and phytosanitary measures under the national policy on control of EIA resulted in successfully controlling EIA in India. Veterinarians also need to report properly to their respective regulatory authorities if they diagnose any new case of EIA [61].

Great care should be taken when introducing new horses to a herd. They should be tested for EIA before introduction.

CAPRINE ARTHRITIS ENCEPHALITIS

Caprine Arthritis and Encephalitis (CAE) infection of goats is caused by a lentivirus of the family *Retroviridae* [69]. Adult goats are mainly infected showing polysynovial-arthritis and can cause a less progressive paresis in kids called leukoencephalomyelitis [1]. Prevalence of infection increases with age but is not influenced by sex. Most goats are infected at an early age, remain virus positive for life, and develop disease months to years later [69]. CAE virus infection is widespread among dairy goats but uncommon in meat- and fiber-producing goats [69]. The disease is most common in industrialized countries but rare among indigenous goat breeds of developing countries unless they have been in contact with imported goats [70,71]. Phylogenetic analysis and reclassification of caprine and ovine lentiviruses based on 104 new isolates: evidence for regular sheep-to-goat transmission and worldwide propagation through lifestock trade.

Clinical manifestations

The clinical manifestations can be seen in goats from the age of six months and older [69,72-75]. The main manifestation of infection is polysynovitis-arthritis that mostly involving the carpal joints [71]. On-set of infection can start suddenly but progression. Although the disease can cause encephalomyelitis, but is generally seen in young kids aging 2-4 months, but can be seen in older kids and adult goats. Affected goats lose condition and usually have poor hair coats. Encephalomyelitis is generally seen in kids 2-4 months old but has been described in older kids and adult goats [69,70,72]. Affected kids initially exhibit weakness, ataxia, and hind limb placing deficits. Hypertonia and hyperreflexia are also common. Over time, signs progress to paraparesis or tetraparesis and paralysis [73]. Depression, head tilt, circling, opisthotonos, torticollis, and paddling have also been described. The interstitial pneumonia component of CAE virus infection rarely produces clinical signs in kids. However, in adult goats with serologic evidence of CAE virus infection, chronic interstitial pneumonia that leads to progressive dyspnea has been documented. The “hard udder” syndrome attributed to CAE virus infection is characterized by a firm, swollen mammary gland and agalactia at the time of parturition [74]. Milk quality is usually unaffected. Although the mammary gland may soften and produce close to normal amounts of milk, production remains low in many goats with indurative mastitis [74].

Transmission

Usually, CAE virus is transmitted during the neonatal period from an infected adult doe to the kid through consumption of colostrum and milk [6-8]. The chief mode of spread of CAE is through ingestion of virus-infected goat colostrum or milk by kids. The feeding of pooled colostrum or milk to kids is a particularly risky practice, because a few infected does will spread the virus to a large number of kids [74-76]. Horizontal transmission also contributes to disease spread within herds and may occur through direct contact, exposure to fomites at feed bunks and waterers, ingestion of contaminated milk in milking parlors, or serial use of needles or equipment contaminated with blood [74-76].

Transmission from the pregnant doe to the fetus has been reported. CAEV transmission by experimentally infected semen has been reported [77]. Direct transmission from goat to goat through saliva, urine, feces, semen, milking machines and failure to use hygienic measures during handling of goats for the different purposes like clinical examinations or surgical interferences [69,70,74-76].

Introduction of new animals into a herd can be a major source of infection [69,70].

Persistence of the CAE virus in the host is facilitated by its ability to become sequestered as provirus in host cells [69,70,74-85]. Infection induces a strong humoral and cell-mediated immune response, but neither is protective.

There is no evidence that the CAE virus is transmissible to humans [86].

Pathology

The gross pathologic lesions of CAE virus infection are generally described in details in several references [69-71]. Briefly, the lesions are usually manifested by lymphoproliferative with degenerative mononuclear cell infiltration. Lesions in joints are characterized by thickening of the joint capsule and marked proliferation of synovial villi. Lungs of affected goats are firm and gray-pink with multiple, small, white foci, and do not collapse. The bronchial lymph nodes are invariably enlarged. In chronic cases, soft-tissue calcification involving joint capsules, tendon sheaths, and bursae

is not uncommon. In advanced cases, severe cartilage destruction, rupture of ligaments and tendons, and periarticular osteophyte formation have also been described [69,70,78]. The reported histopathological lesions, are described as multifocal, mononuclear cell inflammatory infiltrates and varying degrees of demyelination. In the respiratory tract, chronic interstitial pneumonia with mononuclear cell infiltration in alveolar septae and in perivascular and peribronchial regions is seen. In does with udder induration [67], mononuclear infiltration of periductular stroma obliterates normal mammary tissue [78].

Diagnosis Treatment and control

The clinical signs and history of the condition are highly diagnostic. However, differential diagnoses from similar conditions, especially in young kids, such as progressive paresis, paralysis exhibited by young kids, enzootic ataxia, spinal cord abscess, cerebrospinal nematodiasis, spinal cord trauma, and congenital anomalies of the spinal cord and vertebral column has to be made [69,70,74]. If the neurologic examination indicates brain involvement, polioencephalomalacia, listeriosis, and rabies should be considered as possible causes. To confirm that the condition is a CAE, serological tests are to be considered [69,70,79,80]. The agar gel immunodiffusion test (AGID) and ELISA [80-82], are considered reliable in confirming a CAE infection. Virus isolation or PCR to demonstrate presence of viral antigen in tissues are also used for diagnosis of CAE virus [70,83,84]. Indeed, definitive diagnosis of clinical CAE should be associated with demonstration of characteristic lesions in biopsy specimens or at necropsy [70].

Treatment

As a virus disease, there are no specific treatments for any of the clinical syndromes associated with CAE virus infection [70,85]. However, supportive treatments may benefit individual goats. The condition of goats with the polysynovitis-arthritis may be improved with regular foot trimming, use of additional bedding, and administration of NSAIDs such as phenylbutazone or aspirin [60,70,85]. Goats with encephalomyelitis can be maintained for weeks with good nursing care [85]. Antimicrobial therapy is indicated to treat secondary bacterial infections that may complicate the interstitial pneumonia or indurative mastitis components of CAE virus infection. Provision of high quality feed to CAE-positive goats, is advisable to prevent or minimize the possible supervene of the wasting syndrome [85].

There are no known treatments for any of the clinical forms of CAE, and animals will not recover. Animals with mild cases of the arthritic form can be made more comfortable by providing regular, correct hoof trimming, providing easily accessible feed and water, and by long-term veterinary care.

Control

In commercial herds, one or more of the following have been recommended for control of CAE [69,70,85]. 1) Permanent isolation of kids beginning at birth; 2) feeding of heat-treated colostrum (45°C (113°F) for 60 min) and pasteurized milk; 3) frequent serologic testing of the herd (semiannually), with identification and segregation of seronegative and seropositive goats; and 4) eventual culling of seropositive goats. If the control program includes segregation of herds into seropositive and seronegative groups, groups should be separated by a minimum of 6 ft (1.8 m), and shared equipment should be disinfected using phenolic or quaternary ammonium compounds [69,70,85].

CONCLUSION

HIV-1 and HIV-2 are the two main types of the HIV virus. Most people living with HIV have HIV-1.

Both types of HIV weaken the immune system, but HIV-2 tends develop more slowly and is less easy for people to transmit than HIV-1.

Genetic differences between the two viruses mean that there are some differences in how healthcare providers diagnose and treat HIV-1 and HIV-2.

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