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Bovine herpesvirus 1 (BoHV-1): A review on latency and persistence of infection in cattle

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Abstract
Bovine herpesvirus 1 (BoHV-1) is a well known pathogen of cattle responsible for polymicrobial disease such as infectious bovine rhinotracheitis, vulvovaginitis, and balanopostitis. The disease caused by virus is ranging from acute form having active replication of virus to chronic form resulting in latency stage of virus. The lifelong latency is well established in the sensory neurons of infected cattle. There are different latency-related (LR) gene loci, which are expressed in latently infected neurons. Many predisposing factors like corticosteroids, environment stressors result reactivation of latency stage of virus. This ability of virus to reactivate from latency stage in cattle made it an attractive for studying the replication mechanism of virus. Therefore, mechanism and different genes responsible for BoHV-1 latency-reactivation in cattle are discussed in this review.

Keywords: BoHV-1, latency, IBR, abortion

Introduction
Bovine herpesvirus 1 (BoHV-1) is an economically important pathogen of cattle and buffalo responsible for various disease conditions like infectious bovine rhinotracheitis (IBR), vulvovaginitis, balanopostitis, abortion, encephalitis in calves and fatal multisystemic infection in newborns (Wyler *et al.,* 1989) [33]. This virus has also been associated with other clinical disease manifestations like conjunctivitis and generalized systemic infections etc. (Gibbs *et al.*, 1977) [9]. The clinical manifestations of Infectious bovine rhinotracheitis (IBR) are intense inflammation of the upper respiratory passages and trachea and accompanied by dyspneoa, depression, nasal discharge and loss of condition (Mckercher, 1959) [1]. Cornea usually remains unaffected but if secondary bacterial infection occurs, keratitis and corneal ulceration may result in permanent scaring of cornea (Turin and Russo, 2003) [30]. In adult cows, it causes loss of production, milk drop for 3-5 days accompanied with fever (over 104ºF or 39.6ºC), runny nose and eyes. Abortion is seen in some cases particularly during 4-9 months of pregnancy. Chronic pneumonia may subsequently develop in adult cows with the development of lung abscesses. Although there are high levels of viral replication inside the body system, humoral and cellular immune responses may clear the virus along with establishment of lifelong latency in ganglionic neurons (Jones *et al.,* 2011) [17].
The major characteristics feature of BoHV-1 is establishment of lifelong latency in sensory neurons of the peripheral nervous system after replication in mucosal epithelium. BoHV-1 is thought to penetrate the terminus of the sensitive nerves distributed in the infected epithelium and transported along the microtubules of the axons to reach the neuron body in the nervous ganglion (Enquist *et al.,* 1998) [5]. The authors have reported that lymph nodes and nasal mucosa are also considered to be sites of latency (Engels and Ackermann, 1996) [6]. Latency may be present in tonsillar lymphoid cells and peripheral blood lymphocytes (Mweene *et al.*, 1996) [23]. Latent virus only produces latency-related proteins, which protect latently infected cells from apoptosis.

Productive infection
BoHV-1 enters the animal through the mucous membrane in the respiratory or genital tracts. The main mode of disease transmission is direct nose-to-nose contact between an infected and a susceptible animal (Muylkens *et al*., 2007) [22]. This is made possible because of the virus sloughing off into the mucus. Aerosols have to be exhaled, sneezed, or coughed from an infected animal during viral shedding in order for transmission to occur (Mars *et al*., 1999) [19]. Transmission also originates from contaminated semen through use of live breeding or artificial insemination (AI); bulls that have been affected genetically may shed the virus through their semen.

Acute infection of BoHV-1 induces programmed cell death, inflammation and high levels of virus shedding. Viral gene expression during productive infection occurs in three different phases: immediate early (IE), early (E) or late (L). IE transcription unit 1 (IEtu1) encodes two crucial viral regulatory proteins; bICP0 and bICP4, which activate viral gene expression and DNA replication. IEtu2 encodes bICP22. A viral tegument protein, VP16 (also known as bTIF), is a viral structural protein present in the tegument that specifically trans-activates IE promoters. VP16 interacts with two cellular proteins (Oct1 and HCF-1) and this complex binds specific sequences in IE promoters. E genes, in general, encode nonstructural proteins that promote viral DNA replication. L genes encode proteins that comprise infectious virus particles (Jones., 2016) [15].

Establishment of latency

BoHV-1 virus can become latent following a primary infection with a field isolate or vaccination with an attenuated strain. The reactivated virus is transported intra-axonally back to the periphery, to the original portal of entry, where it is available for transmission to other susceptible hosts. After infection, BoHV-1 spreads from a local infection to the nervous system by entry of virus into peripheral neural cells. The virus reaches the sensory ganglion such as trigeminal and lumbosacral ganglions, where latency can be established. The local immune response may be too weak to prevent virus shedding completely, depending on the period of time elapsed between the initial infection and reactivation.

During latency, a latency related transcript (LRT) region is expressed in BoHV-1 leading to the inhibition of the lytic cycle and the induction of an anti-apoptotic state of the infected cells (Henderson *et al.,* 2004) [11]. A protein corresponding to the N-terminus of ORF2 in LRT was detected in high amounts during latency by western blotting (Hossain *et al.,*1995; Jiang *et al.,* 1998) [12, 14]. Inhibition of apoptosis (Ciacci-Zanella *et al.,* 1999) [3], S phase entry (Schang *et al.,* 1996) [26] and bICPO expression (Geiser *et al.,* 2002) are attributed to the functions of LRT. Reactivation from latency can occur after natural stimulus exposure (Thiry *et al.,* 1985; 1987) [28, 29] or corticosteroid treatment (Sheffy and Davies, 1972) [27] culminating in recurrent virus transmission to non-infected animals generally without clinical signs. A wide variety of stimuli such as stress, pregnancy, vaccination transport and treatment with corticosteroids may lead to reactivation from latency (figure 1). Once reactivated in the neurons of the trigeminal ganglion, BoHV1 initiates a new replication cycle. The infected cattle may be regarded as lifelong potential shedders of BoHV-1. The latent virus represents a long-term reservoir in an immune host which becomes relevant upon reactivation.

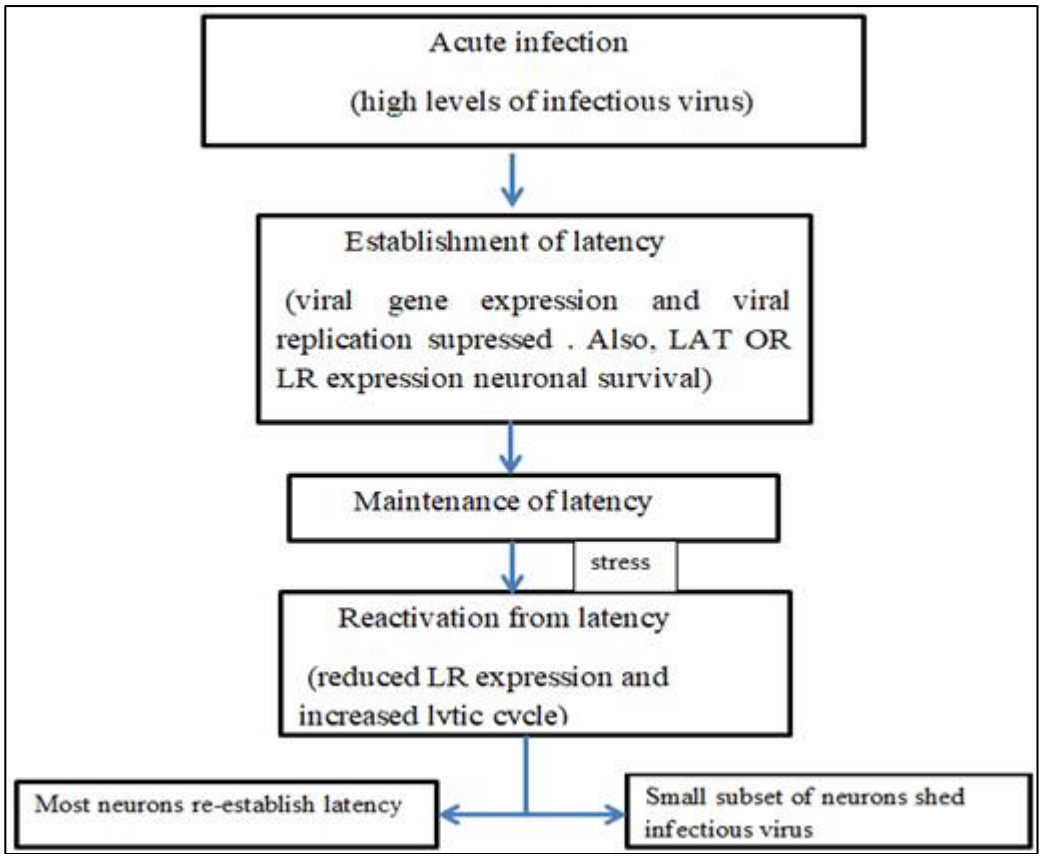

Fig 1: Latency reactivation cycle of BoHV-1 virus

Genes related to latency

Role of LR-gene in latency

In contrast to the 70-80 genes that are expressed during productive infection, LR-RNA is the only abundantly expressed transcript during latency (Kutish *et al.,* 1990; Rock *et al.,* 1987; Rock *et al.,* 1992) [18, 29, 25]. *In situ* hybridization localizes LR-RNA to the nucleus of the latently infected neurons. The full LR gene is approximately 2 kbp long (980 bp of promoter and 1180 bp of transcribed region) and it is transcribed antisense to the bICP0 mRNA (Rock *et al.,* 1987; Jones *et al.,* 1990) [24]. The LR gene sequence includes two well defined open reading frames (ORFs) (ORF1 and ORF 2) and two reading frames lacking an initiating ATG (RF-B and C).

The LR fusion protein interacts with two proteins that can induce apoptosis (Bid and Cdc42) and with CCAAT enhancer

binding protein alpha (C/EBP-alpha) shown in figure 2 (Meyer *et al.*, 2007) [20]. Moreover, the LR fusion protein also interacts with human or insect C/EBP-alpha. C/EBP-alpha protein expression is induced in TG neurons of infected calves and after dexamethasone-induced reactivation from latency. Wild-type C/EBP-alpha, but not a DNA binding mutant of C/EBP-alpha, enhances plaque formation in bovine cells. We hypothesize that interactions between the LR fusion protein and C/EBP-alpha promote the establishment of latency.

Role of miRNA in latency

There are 10 microRNA (miRNA) genes which are encoded by the BoHV-1 genome that are processed into 12 detectable mature miRNAs as determined by ultra-high throughput sequencing bioinformatics analyses of small RNA libraries and expression studies (Glazov *et al.*, 2010) [10]. They found that four of the miRNA genes were present as two copies in the BoHV-1 genome, resulting in a total of 14 miRNA encoding loci.

In the viral genome, the LR gene has a 463-bp region (present within the XbaI-PstI [XP] fragment) that inhibited the level of bICP0 protein and RNA expression in transiently transinfected mouse neuroblastoma cells. These XP fragment encodes small noncoding RNAs (sncRNAs) (20 to 90 nucleotides in length), which were detected in transiently transfected mouse neuroblastoma cells (Jaber *et al.*, 2010) [13]. There are two families of sncRNAs, which were cloned from this region and each family was predicted to contain a mature microRNA (miRNA). Both family of miRNAs were base pair with bICP0 mRNA sequences, resulting in reduction of bICP0 levels. XP-specific sncRNA levels were reduced during dexamethasone-induced reactivation from latency, showing that these sncRNAs support the establishment and maintenance of life long latency in cattle.

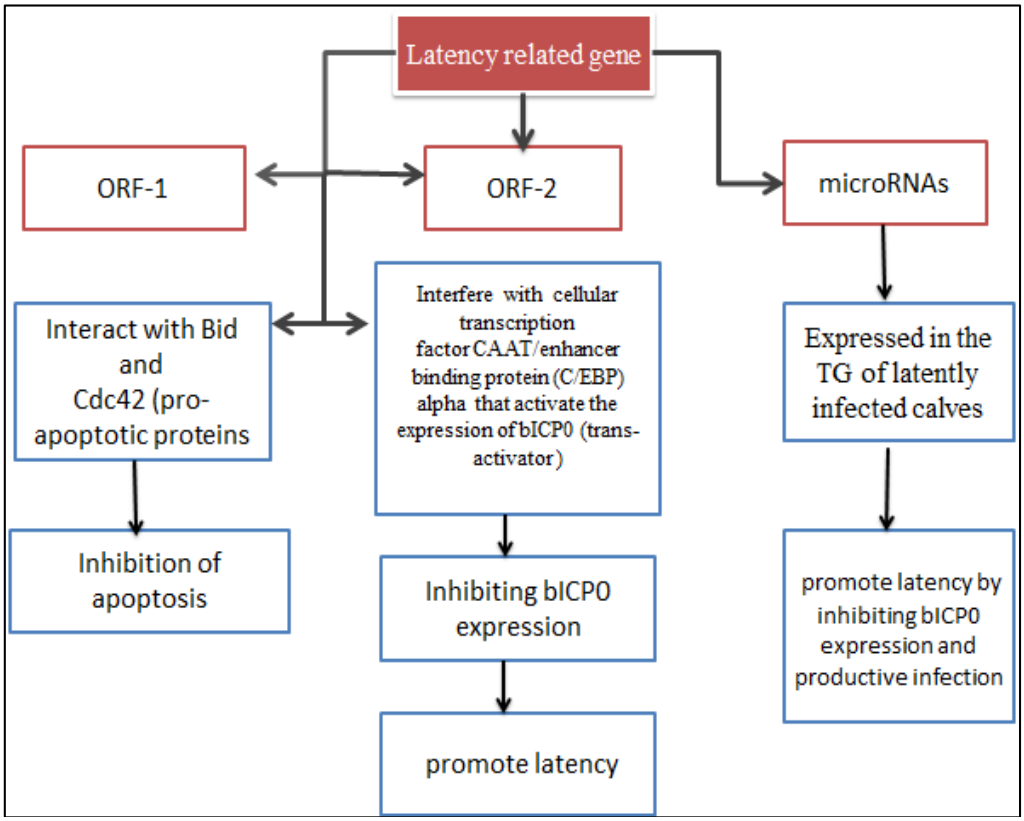

Fig 2: Overview of the role of latency related genes

Detection of latent BoHV-1 from various tissues

Bitsch (1978) [2] reported that BoHV-1 can establish latent infections. The latent virus persists during the life of the animal and may be reactivated under certain stressful conditions. Shedding of the virus may or may not be accompanied with clinical signs.

The nucleic acid samples prepared from the trigeminal ganglia from the calves has also been found positive for BoHV-1. BoHV-1 was detected by PCR in both BoHV-1 inoculated calves and BoHV-5 was detected by PCR in both BoHV-5-inoculated calves and in one of the contact control calves (Ashbaugh *et al.*, 1998). Further, Southern blotting of trigeminal PCR products and sequential hybridization with BoHV-1 and BHV-5 probes (or vice versa) was used to confirm the BoHV-1 or BHV-5 origin of products.

Delhon and Jones, 1997 [4] found that the XhoI-XbaI fragment is important for LR-RNA expression in neurons. They utilized electrophoretic mobility shift assays (EMSA) to identify regions of the LR promoter that specifically bind factors present in dorsal root ganglia of cattle. The dorsal root ganglia of cattle and rat pheochromocytoma nuclear extracts cells (PC12) contains abundant factors which specifically bound to a 72 bp XhoI-XbaI fragment. The 72 bp fragment was adjacent to the major start sites of LR transcriptional in trigeminal ganglia of latently infected cattle. However, the nuclear extracts from non-neural cells, such as bovine turbinate or rat-2, did not exhibit similar binding patterns showing that these factors had reduced binding affinity or were absent in non-neural cells. The binding was only localized to a 20 bp region present in the XhoI-XbaI fragment seen by EMSA and Exonuclease III footprinting. The deletion of XhoI-XbaI fragment resulted in repression of promoter activity of LR in PC12 cells.

The bovine herpesvirus type 1 (BoHV-1) has also been detected in whole-blood samples derived from naturally infected cattle (Fuchs *et al.,* 1999) [7] It was observed that the viral DNA was detectable in the peripheral blood of subclinically infected cattle. The gE-specific PCR allowed discrimination between wild-type (WT) virus infected and vaccinated animals. The results further showed that doubtful serological results could be verified or falsified and that individual animal could be monitored for the presence or absence of WT BoHV-1 or gE-negative virus in cattle herds. The results also indicated the simultaneous presence of WT and gE-negative vaccine virus in the PBLs of several cattle.

The BoHV-1 has also been detected in the tonsils of latently infected calves (Winkler *et al.,* 2000) [32]. Detection of the latency-related transcript (LRT) in tonsils of latently infected calves required nested reverse transcription-PCR (RT-PCR) suggesting that only a few cells contained viral DNA or that LRT is not an abundant transcript. bICP0 (immediate-early and early transcripts), ribonucleotide reductase (early transcript) and glycoprotein C (late transcript) were not detected by RT-PCR in latently infected calves. When reactivation was initiated by dexamethasone, bICP0 and ribonucleotide reductase transcripts were detected. Following dexamethasone treatment, viral nucleic acid was detected simultaneously in trigeminal ganglionic neurons and lymphoid follicles of tonsil. LRT was detected at 6 and 24 h after dexamethasone treatment but not at 48 h.

Wang and co-workers examined peripheral blood mononuclear cells (PBMCs) from 5 calves (3 controls and 2 vaccinates) used in a bovine herpesvirus 1 (BoHV-1) vaccine study with a BoHV-1 cooper strain challenge that were collected 6 months after challenge (Wang *et al.,* 2001) [31]. It was seen that the PBMCs from the control animals were positive by immunofluorescence for the BoHV-1 glycoprotein D (gD) while the vaccinates were negative. The PBMC samples from 4 of the 5 animals were examined for BoHV-1 DNA by polymerase chain reaction (PCR) and for gD immunofluorescence at 8 months after challenge. The BoHV-1 DNA and viral antigen were detected in PBMC samples at 8 months post infection, but no virus was isolated.

In conclusion, the latency-reactivation mechanism of BoHV-1, is regulated by a complex series of virus and host proteins. There are many LAT-encoded micro-RNAs and small noncoding RNAs which are supposed to have function in the latency stage of virus.

References

1. Ashbaugh SE, Thompson KE, Belknap EB, Schultheiss PC, Chowdhury S, Collins JK. Specific detection of shedding and latency of bovine herpesvirus 1 and 5 using a nested polymerase chain reaction. J VetDiagn Invest. 1997; 9(4):387-394.
2. Bitsch V. The P37/24 modification of the infectious bovine rhinotracheitis virus serum neutralization test. Acta Vet Scand. 1978; 19:497-505.
3. Ciacci-Zanella J, Stone M, Henderson G, Jones C. The latency-related gene of bovine herpesvirus 1 inhibits programmed cell death. J Virol. 1999; 73(12):9734-9740.
4. Delhon G, Jones C. Identification of DNA sequences in the latency related promoter of bovine herpes virus type 1 which are bound by neuronal specific factors. Virus research. 1997; 51(1):93-103.
5. Enquist LW, Husak PJ, Banfield BW, Smith GA. Infection and spread of alphaherpesviruses in the nervous system. Adv Virus Res. 1998; 51:237-347.
6. Engels M, Ackermann M. Pathogenesis of ruminant herpesvirus infections. Vet Microbiol. 1996; 53(1, 2):3-15.
7. Fuchs M, Hubert P, Detterer J, Rziha HJ. Detection of bovine herpesvirus type 1 in blood from naturally infected cattle by using a sensitive PCR that discriminates between wild-type virus and virus lacking glycoprotein E. J Clin Microbiol**.** 1999; 37:2498-2507.
8. Geiser V, Inman M, Zhang Y, Jones C. The latency-related gene of bovine herpesvirus-1 can inhibit the ability of bICP0 to activate productive infection. J Gen Virol. 2002; 83(12):2965-2971.
9. Gibbs EPJ, Rweyemamu MM. Bovine herpesviruses. Part I, Commonwealth Bureau of Animal Health. The Vet Bull 1977; 47:317-343.
10. Glazov EA, Paul F, Horwood, Assavalapsakul W, Kongsuwan K, Mitchell RW *et al*. Characterization of microRNAs encoded by the bovine herpesvirus 1 genome. J Gen Virol. 2010; 91:32-41.
11. Henderson G, Perng GC, Nesburn A, Wechsler S, Jones CJ. The latency related gene of bovine herpesvirus 1 can suppress caspase 3 and caspase 9 during productive infection. J Neurovirol. 2004; 10:64-70.
12. Hossain A, Schang LM, Jones C. Identification of gene products encoded by the latency-related gene of bovine herpesvirus 1. J Virol. 1995; 69(9):5345-5352.
13. Jaber T, Workman A, Jones C. Small Noncoding RNAs Encoded within the Bovine Herpesvirus 1 Latency-Related Gene Can Reduce Steady-State Levels of Infected Cell Protein 0 (bICP0). J Virol. 2010; 84:6297-6307.
14. Jiang Y, Hossain A, Winkler MT, Holt T, Doster A, Jones C. A protein encoded by the latency-related gene of bovine herpesvirus 1 is expressed in trigeminal ganglionic neurons of latently infected cattle and interacts with cyclin-dependent kinase 2 during productive infection. J Virol. 1998; 72(10):8133-8142.
15. Jones C. Latency of Bovine Herpesvirus 1 (BoHV-1) in Sensory Neurons, Herpesviridae, Jozsef Ongradi, Intech Open, 2016; 9:237-261.
16. Jones C, Delhon G, Bratanich A, Kutish G, Rock D. Analysis of the transcriptional promoter which regulates the latency-related transcript of bovine herpesvirus 1. J Virol. 1990; 64(3):1164-1170.
17. Jones C, Silva-da LF, Sinani D. Regulation of the latency-reactivation cycle by products encoded by the bovine herpesvirus 1 (BHV-1) latency-related gene. J Neurovirol. 2011; 17:535-545.
18. Kutish G, Mainprize T, Rock D. Characterization of the latency-related transcriptionally active region of the bovine herpesvirus 1 genome. J Virol 1990; 64(12):5730-5737**.**
19. Mars MH, Bruschke CJ, van Oirschot JT. Airborne transmission of BHV1, BRSV, and BVDV among cattle is possible under experimental conditions. Vet. Microbiol 1999; 66(3):197-207. doi:10.1016/s0378-1135(99)00009-7. PMID 10227122.
20. Meyer F, Perez S, Geiser V, Sintek M, Inman M, Jones C. A protein encoded by the bovine herpesvirus 1 latency-related gene interacts with specific cellular regulatory proteins, including CCAAT enhancer binding protein alpha. J Virol. 2007; 81(1):59-67.
21. Mckercher DG. Infectious bovine rhinotracheitis. Adv Vet Sci Comp Med 1959; 5:299-328.

22. Muylkens B, Thiry J, Kirten P, Schynts F, Thiry E. Bovine herpesvirus 1 infection and infectious bovine rhinotracheitis. Vet Res. 2007; 38(2):181-209.
23. Mweene AS, Okazaki K, Kida H. Detection of viral genome in non-neural tissues of cattle experimentally infected with bovine herpesvirus 1. Jpn J Vet Res. 1996; 44:165-174.
24. Rock DL, Beam SL, Mayfield JE. Mapping bovine herpesvirus type 1 latency-related rna in trigeminal ganglia of latently infected rabbits. J Virol. 1987; 61(12):3827-3831.
25. Rock D, Lokensgard J, Lewis T, Kutish G. Characterization of dexamethasone-induced reactivation of latent bovine herpesvirus 1. J Virol. 1992; 66(4):2484-2490.
26. Schang LM, Hossain A, Jones C. The latency-related gene of bovine herpesvirus 1 encodes a product which inhibits cell cycle progression. J Virol. 1996; 70(6):3807-3814.
27. Sheffy BE, Davies DH. Reactivation of a bovine herpesvirus after corticosteroid treatment. Proceedings of the society for ExpBiol Med 1972; 140(3):974-976.
28. Thiry E, Brochier B, Saliki J, Pirak M, Pastoret PP. Excretion and reexcretion of thermo sensitive and wild-type strains of infectious bovine rhinotracheitis virus after co-infection or two successive infections. Vet. Microbiol. 1985; 10:371-380.
29. Thiry E, Saliki J, Bublot M, Pastoret PP. Reactivation of infectious bovine rhinotracheitis virus by transport. Comp Immunol Microbiol Infect Dis 1987; 10(1):59-63.
30. Turin L, Russo S. BHV-1 infection in cattle: an update. Veterinary Bulletin. 2003; 73(8):15-21.
31. Wang DJ, Hurley LJ, Braun C, Chase CL. Detection of bovine herpesvirus-1 in peripheral blood mononuclear cells eight months post infection. J Vet Diagn Invest. 2001; 13:424-427.
32. Winkler MTC, Doster A, Jones C. Persistence and reactivation of bovine herpesvirus 1 in the tonsil of latently infected calves. J Virol 2000; 74:5337-5346.
33. Wyler R, Engels M, Schwyzer M. Infectious bovine rhinotracheitis/vulvovaginitis (BHV-1), In G. Witman (ed.), Herpesviruses diseases of cattle, horses and pigs, developments in veterinary medicine. Kluver Academic Publishers, Boston. 1989, 172.