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Understanding Primate Herpesviruses

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Abstract

Viruses related to the herpes simplex viruses of humans are present in all nonhuman primate (NHP) species tested and cross species transmission has been documented. The herpesvirus present in macaques, Herpes B virus (BV) rarely causes disease in its natural macaque host. However, when transmitted to a nonnative host, BV has occasionally caused severe and even fatal disease if not treated immediately. Here we present a comprehensive review of the taxonomy, molecular biology, physiology, epidemiology, diagnosis and treatment of BV. We also summarizes what is known about related herpesviruses of other NHP species and the zoonotic potential of these viruses.

Keywords

α-Herpesviruses; Herpes B; BV; *Macacine herpesvirus* 1; Primates; Macaques; Macaca; Papiine; Cercopithecine; Saimirine; Ateline; HSV1; HSV2; ChHV; HVP2; SA8; HVS1; Sahv1; HVA1; AtHV1

α-Herpesviruses of Nonhuman Primates

Like humans, nonhuman primates (NHPs) are naturally infected with several herpesviruses. There are eight different human herpesviruses that are divided into three groups: α-, β- and γ-herpesviruses. Viruses related to all the human herpesviruses have been isolated from or detected in many different species of NHPs. Herpesviruses usually do not cause serious infections in healthy members of their natural host species, most such infections being asymptomatic. A hallmark of herpesviruses is their ability to establish latent infections that endure for the life of the host with no clinically apparent signs of infection. In response to various stimuli, latent virus can reactivate and undergo lytic replication resulting in shedding of infectious virus that can then be transmitted to a naïve host, thereby perpetuating existence of the virus. Consistent with this intimate association between host and virus,

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numerous phylogenetic analyses have concluded that herpesviruses have co-evolved with their host species.

Since humans and NHPs are genetically and physiologically similar, it is not surprising that some herpesviruses of NHPs can infect humans, and vice versa. While most such cross-species infections are likely abortive (i.e., the virus cannot complete its replicative cycle to produce an active or latent infection or cause clinically apparent disease), some herpesviruses produce serious or lethal infections when transmitted to a non-natural host species. The most notorious NHP virus in this respect is monkey B virus (BV) of macaques. While this review focusses primarily on BV, available information on the zoonotic potential of other NHP α-herpesviruses will also be summarized.

Herpes B Virus

Herpes B virus (BV) occurs naturally in Asian monkeys of the genus *Macaca* [1–5]. Although known by several names over the years since its isolation in 1932 [6] (most commonly *Herpesvirus simiae*, monkey B virus, and Herpes B), BV is officially designated *Macacine herpesvirus* 1 by the International Committee on Taxonomy of Viruses [7]. BV is a member of family *Herpesviridae*, subfamily *Alphaherpesvirinae*, genus *Simplexvirus*. The simplexviruses of human and nonhuman primates are summarized in Table 1. These viruses are all closely related, although the degree of relatedness generally reflects that of the relatedness of their host species [8,9]. The same holds true for the primate β- and γ-herpesviruses.

Molecular Biology of BV

BV is closely related to HSV, so much of what is known regarding HSV structure, protein functions and viral replication likely applies to BV as well. BV has the typical virion structure of α-herpesviruses, with a linear DNA genome of ~155 kbp enclosed within a 125 nm icosahedral capsid embedded in an amorphous protein tegument surrounded by a lipid membrane envelope [10,11]. As expected from the comparatively large size of the viral genome, herpesviruses are complex in both their structure and replication. Like other members of the *simplexvirus* genus, BV encodes over 70 proteins as well as a number of miRNAs [12–15].

BV has a wide host range *in vitro*, productively infecting most cell lines tested. The lytic replication cycle of BV begins with attachment of the virion to a host cell, presumably mediated by binding of glycoprotein C (gC) to cell surface heparin sulfate. This allows the gD glycoprotein to specifically bind cell surface molecules which in turn alters the structure of the gB and gH/gL glycoproteins to initiate fusion of the viral envelope with the cell plasma membrane. While five gD receptors have been identified for HSV, BV appears to recognize only nectin-1 [16–18]. Furthermore, while gD is essential for entry of several α–herpesviruses, gD does not appear to be essential for BV entry [19]. When the viral envelope fuses with the host cell membrane, the virion nucleocapsid and tegument proteins are released into the cytoplasm. The nucleocapsid is then transported to a nuclear pore where the

viral genome is released into the nucleus [13]. The BV replication cycle is fairly rapid, with extracellular progeny virus appearing about 6–8 hrs post infection [20].

One tegument protein of HSV [UL41, the "virion host shutoff (vhs) protein] plays a central role in circumventing the innate immune response. Once released into the cytoplasm, UL41 degrades cellular mRNAs, thereby abrogating initiation of a β-interferon (IFN-β) response by the cell. Deletion of the BV UL41 coding sequence or mutation of the UL41 RNase active site prevents mRNA degradation and allows continued synthesis of host cell proteins. As a result the infected cell is able to generate an IFN-β response, indicating that the BV UL41 functions similarly to HSV UL41 [21]. Another HSV gene that plays an important role in modifying the host cell for viral replication is RL1 (or γ-34.5). The HSV γ34.5 protein is not only a determinant of neurovirulence in mice, but also functions in egress of progeny virions from the cell and inhibiting surface expression of MHC II proteins [22–25]. Despite its importance in HSV, BV and related simian viruses do not have a homologue of the RL1 gene. One antiviral response of a cell to infection is shutdown of protein synthesis by phosphorylation of translation initiation factor eIF-2α. The HSV γ-34.5 protein dephosphorylates eIF-2α, thereby allowing protein synthesis to continue [24]. Lacking an RL1 homologue BV does not dephosphorylate eIF-2α, yet viral protein synthesis continues in the BV infected cell [unpublished]. Consistent with this, deletion of the region of the BV genome where an RL1 homologue would be located does not affect BV replication, inhibition of the cellular IFN-β response, or neurovirulence of BV in mice [unpublished]. Thus, while BV is certainly similar to HSV, there are significant differences as well.

In 1971 Hull [26] reported the formalin inactivation of a BV isolate from a rhesus macaque (*Macaca mulatta*) for use as a vaccine, and this BV strain (E2490) has since served as the "standard" BV strain. The genome sequence of this BV strain has been determined [27–29] although there are a number of minor differences between sequences determined by different laboratories. Sequences of a number of individual genes from various isolates of BV have also been reported [30–33]. The genomic sequence of a BV strain isolated from a captive colony bred long tailed macaque (*M. fascicularis)* with a fatal BV infection has also been reported [34]. Recently, a genome sequence for 14 rhesus BV isolates has been determined as well as BV isolates from pigtail (*M. nemestrina*) and lion-tailed (*M. silenus*) macaques [unpublished]. All BV genomes have a very high G+C content of ~75% and are similar to HSV2 and ChHV in their genetic organization. Comparing genome sequences of the reference E2490 strain with other rhesus isolates of BV, all coding sequences and miRNAs are highly conserved. The most prominent differences lie in the long and short repeat regions (RL & RS, resp.) in areas that do not encode either proteins or miRNAs. There are several areas of repeated sequences in the BV genome, and strain-specific differences occur in the number of iterations of repeated sequences, sequence of the repeat units, and length of homopolymeric tracts of G or C. [unpublished]. BV isolates from non-rhesus macaque species are very similar to rhesus BV isolates, with all coding sequences and miRNAs being conserved. Based on DNA sequence data, variation in the amino acid (AA) sequence identity of homologous BV and HSV proteins averages 62.5% [29]. In contrast, average AA sequence identity values are approximately 95% among BV strains, 87% between BV and HVP2, and 83% between BV and SA8 [27,35,36]. This level of AA sequence homology is consistent with previous studies that detected antigenic cross-reactivity of almost all BV

proteins with homologous HSV proteins [37–41] and with the extensive antigenic cross-reactivity observed between BV and HSV in ELISA, western blot and neutralization assays [37,40–46].

As discussed in more detail below, the conserved nature of most BV proteins is very important in diagnosing zoonotic BV infections. Although most BV proteins do have cross-reactive antigenic determinants, many also possess BV-specific epitopes. BV-immune sera react more strongly with BV antigen than HSV antigen, and vice versa. In addition, some BV glycoproteins are not strongly conserved with their HSV counterparts and so stimulate non-cross-reactive (or BV-specific) antibodies. Both the gG and gC glycoproteins have been found to be largely BV-specific antigens with respect to HSV, but they still exhibit substantial cross-reactivity with the homologous glycoproteins of HVP2 and SA8 [29,47,48].

Biology of BV in the Natural Macaque Host

Our understanding of the biology of BV in macaques comes almost entirely from work on captive bred macaques. BV is normally transmitted horizontally between macaques via direct contact and exchange of bodily secretions [2,3,5,49,50]. The prevalence of BV infections in macaque populations (both captive and wild) as measured by the presence of anti-BV serum IgG is related to age. The incidence of infected individuals increases progressively from infants to juveniles, adolescents, young adults, and mature adults [51–58]. Sexually immature macaques can be infected following intimate contact with an infected mother or other infected animals in the troop, usually as an oral infection. There is a marked increase in BV exposure via genital infections as animals become socially and reproductively active in the prepubescent and pubertal period (2–4 years of age). In both wild macaque populations and conventional captive breeding colonies, where animals are not segregated, the prevalence of BV in mature adults ranges from 70% to nearly 100% [58–60].

Most macaques experiencing a primary BV infection do not exhibit overt clinical signs of disease, although upon close inspection orofacial or genital lesions can sometimes be seen [2,3,5,49,61]. Initial virus replication occurs locally in the mucosal epithelium at the site of infection and induces an immune response, resulting in the appearance of both anti-viral antibody and cell-mediated immune responses. As the virus replicates, it enters unmyelinated sensory nerve endings present in the epidermis and is transported intra axonally to the neuron cell body in the sensory ganglion. In the normal course of infection, the virus then becomes latent in sensory neurons where it is maintained in a non-replicating state [50,62–65]. In comparatively rare instances, usually in infants or the very young, primary infections may not end with establishment of latency, but continues to progress as a generalized infection that spreads throughout the body and is usually fatal [61,66–68].

Once a latent infection has been established, the virus remains in sensory neurons for the life of the host [2,5,64,65,69,70]. Periodically in response to various stimuli, BV will reactivate from the latent state. Such recurrent infections result in shedding of infectious virus that can then be transmitted to a naïve host. Most recurrent infections are not accompanied by

clinically apparent lesions; thus, healthy macaques can shed infectious BV without any outward signs of infection. The frequency of virus shedding appears to be quite low (2–3%) in captive macaques under typical husbandry conditions [3,71–73]. Stress related to social challenges, transportation, immunosuppression, or a new housing environment have all been linked to reactivation and shedding of BV [63,70,74]. However, in seasonal breeding macaque species like rhesus, reactivation, shedding and transmission of BV occurs primarily during the breeding season [50,70–72]. Thus, potential factors associated with reactivation due to stressors and breeding could relate to hormonal changes.

The genus *Macaca* includes at least 17 species. While all macaques appear to harbor BV, BV isolates obtained from different macaque species do show differences at the molecular level. PCR amplification and sequencing of a limited region of the genome from BV isolates obtained from several macaque species revealed the existence of different “genotypes” of BV, each being particular to a specific macaque species [32,75,76]. While differences among BV genotypes are readily evident by DNA sequencing, there have not been any differences noted at the biological level; different BV genotypes appear to behave the same in their natural macaque hosts.

BV Infections in Non-Macaque Monkeys

Cross-species transmission of BV has been reported in a number of monkey species which had contact with macaques. While most reported cases have been lethal infections, some monkeys have survived BV infections. Lethal infections have been reported in Debrazza’s monkeys (*Cercopithecus neglectus*), a patas monkey (*Erythrocebus patas*) and a black and white colobus monkey (*Colobus spp.*) [76–78], all of which were housed near macaques in zoos. In the case of the DeBrazza’s monkeys, the origin of the infection appears to have been lion-tailed macaques (*M. silenus*) housed in an adjacent cage. Clinically apparent disease was noted in 7/8 DeBrazza’s monkeys, but only 3/7 died. BV has also been reported in a colony of brown capuchin monkeys (*Cebus apella*) [79]. These animals had been housed in the same room as BV-positive macaques. Of particular note, while 5/7 monkeys were seropositive for BV and 7/7 were positive when tested by PCR, none showed any clinical symptoms of infection. Thus while BV infections in non-macaque monkeys can be lethal, not all such infections are lethal or even symptomatic.

Experimental Pathogenesis Models of BV

Little experimental research on BV pathogenesis has been reported. Rabbits have historically been used in BV research since they are extremely sensitivity to infection, succumbing rapidly when inoculated by almost any route including inhalation [80,81]. However, no pathogenic studies in this species have been reported. BV pathogenesis in newborn mice has been reported, but this model system has not found widespread use [82,83]. More recently a mouse model using intramuscular injection (i.m.) or skin scarification for virus inoculation simulating presumed routes of zoonotic infection has been developed [84–86]. While variation in the neurovirulence of different rhesus isolates of BV were observed using i.m. inoculation, all BV strains tested produced lethal infections when inoculated by skin scarification and have LD_{50}s that are not statistically different from one

another [unpublished]. Also, there is no difference among isolates of different BV genotypes (isolates from different macaque species) when iniocculated i.m., suggesting that rhesus isolates of BV are likely not inherently more neurovirulent than BV isolates from other macaque species [unpublished].

Diagnosis of BV Infections in Macaques

Various test methods have been used to diagnose BV infections in macaques including virus isolation, virus neutralization, ELISA and PCR. PCR is very sensitive and specific, and a number of PCR assays for detection and quantitation of BV have been described [87–93]. However, PCR has not found widespread use for identification of BV infected macaques since only those monkeys actually shedding virus at the time of sampling would test positive; latently infected animals not actively shedding virus would not test positive. Consequently, serological testing by ELISA is most widely used to identify BV infected macaques. While assays using BV antigen are most desirable for such testing, production of BV antigen preparations involves significant biohazard concerns. Taking advantage of the close genetic and antigenic relationship between BV and related primate α-herpesviruses, serologic assays have been developed that utilize HVP2 or SA8 antigens [43,94–97]. These assays are nearly as sensitive as assays using BV antigen for detection of BV-positive macaques. While HSV1 has also been used as an alternative antigen, the assay sensitivity is not as great as with HVP2 or SA8 antigen [94]. Notably, none of these ELISAs, including ELISAs using BV antigen, specifically identifies what virus a positive monkey is actually infected with; it is implicitly assumed that positive macaques are infected with BV. Even so, it should not be assumed that sero-positive animals are shedding virus. This erroneous assumption has led to the needless destruction of several macaque colonies [98,99].

Diagnosis of Zoonotic BV Infections

Diagnosis of BV infections in humans is a much more difficult problem [100,101]. Although serologic testing is possible, such assays rely on detection of antiviral antibodies which do not appear until 7–10 days after infection. The antigenic cross-reactivity between BV and HSV represents a major challenge for diagnosis of zoonotic BV infections. Most adult humans are infected with HSV1 and/or HSV2, and anti-HSV antibodies cross-react with BV antigens. Also, when BV infects an HSV-immune person, an anamnestic response to cross-reactive antigens occurs similar to the “original antigenic sin” phenomenon noted with sequential influenza virus infections [102, 103]. This results in high levels of antibodies directed against cross-reactive antigens, making detection of BV-specific antibodies all the more difficult [100,101]. Furthermore, many suspected/potentially infected BV patients are treated prophylactically with antiviral drugs immediately after a BV exposure incident. This can impede BV replication, thereby preventing or lessening the intensity of the anti-BV immune response [104]. Given all these challenges, serologic assays for detection of zoonotic BV infections must be both sensitive and virus-specific to detect antibodies directed against BV.

Development of serologic assays that can reliably differentiate zoonotic BV from HSV infections in humans is not a simple problem. One approach used is to adsorb the human test

serum with HSV antigen, thus removing antibodies that react with HSV antigen prior to testing for anti-BV antibodies [42]. Although this approach reduces assay sensitivity, it has been used to successfully diagnose BV infections. Another approach is utilization of recombinant DNA technology to express BV genes, producing recombinant proteins for use as diagnostic antigens [33,39,47,105–108]. Recombinant BV antigens are safe to use, economical to produce, and can easily be standardized. The high G+C content of BV genes makes efficient prokaryotic expression of BV genes difficult and inefficient, but expression using the insect baculovirus system has proven more successful [47]. Since most BV proteins possess cross-reactive antigenic determinants, expression of only part of a BV protein has been used to produce antigens that are more BV-specific. The combined use of several such recombinant BV proteins (glycoprotens gB, gC, gD & gG) has provided improved sensitivity and specificity for detection of antibodies to BV [47,108].

Monoclonal antibodies (mAbs) are very specific, and have been developed for BV serological testing [109,110]. Not surprisingly, the vast majority of anti-BV mAbs produced recognize epitopes common to BV and HSV. Although BV-specific mAbs have been isolated, the epitopes they are directed against have not proven to be consistently recognized by infected macaques, thus limiting their usefulness in diagnostic assays [111,112]. In one case, a BV-specific mAb to the gB glycoprotein (which is consistently recognized in infected animals) was produced, but the mAb was not diagnostically useful because its binding was inhibited by cross-reactive antibodies presumably directed against a nearby epitope, resulting in poor binding of the BV-specific mAb and thus false-negative results [111].

As mentioned above, PCR assays have the advantage of being able to rapidly and specifically detect minute quantities of viral DNA rather than relying on development of a host immune response to the virus. Thus, PCR testing of swabs from a bite or scratch wound site can be used to detect the presence of BV. In the case of bites or scratches resulting from a captive monkey, the animal itself can also be tested to determine whether it was actively shedding BV at the time of the exposure incident, thereby providing some measure of the likelihood of BV having been transmitted to the patient. Many PCR assays for detection of BV have been described, and several have been used to diagnose human infections due to BV versus HSV [90,113, R Mukai, perscomm]. Although its extreme sensitivity makes PCR ideal for detecting small amounts of virus in diagnostic specimens, this sensitivity can also be a limitation. Different BV genotypes exhibit substantial DNA sequence variation in regions of the genome, and sequence variation even occurs among different strains of BV from rhesus monkeys [29,32,34,75]. The limited number of published BV genome sequences makes it difficult to quantitatively assess the full extent of sequence variation among BV isolates in order to design primers reliably able to detect all BV isolates. PCR assays for use in diagnosis need to be specific for BV versus HSV but also able to detect different BV strains and genotypes.

As is apparent from the above discussion, the type of sample to be submitted for diagnosis depends on the goal of the testing to be done. The National B Virus Reference Laboratory is most widely used for testing of human samples where zoonotic infections are suspected, and relevant information regarding sample collection and specimen shipping are available on the

National B Virus Reference Laboratory website. There are also several commercial testing laboratories that will test macaque samples.

Zoonotic BV Infections

In 1932 Dr. WB Brebner, a young physician, was bitten on the finger by a rhesus macaque being used in poliovirus research [6,114,115]. Dr. Brebner developed herpetic lesions on the finger, but unlike herpetic whitlows caused by HSV, the infection progressed to involve the central nervous system (CNS). Dr. Brebner died several weeks later from an acute ascending myeloencephalitis. A herpesvirus was isolated from several tissues and, although initially identified as HSV, was subsequently shown to be distinct from HSV and was designated as 'the B virus' [6,114]. While the exact number is not available, a fairly small number of additional human BV infections (~50–100) have occurred sporadically over the ensuing years through contact with captive macaques or macaque tissues [2,4,5]. Although extremely rare, zoonotic BV infections are notorious for their severity. Untreated, zoonotic BV infections have a fatality rate of 70–80%, with many survivors having marked neurologic deficits. Survivors can also experience progressive deteriorative neurologic sequelae.

To date, all confirmed cases of zoonotic BV have been in persons working with captive monkeys; no cases of zoonotic BV due to contact with wild macaques have been reported. Humans typically acquire BV by direct contact with an infected macaque or contaminated materials (eg. dirty cages, primary cells preparations). Although aerosol infection has been achieved in the laboratory setting [81,116] and has been suspected in two zoonotic BV cases [4,5], there is no definitive evidence that aerosol transmission of BV occurs naturally. The vast majority of human BV infections have been associated with bites or scratches from macaques. However, additional modes of transmission have been documented including splashing of macaque urine into the eye [117], needle stick injury [118], contamination of cuts with material from primary macaque cells in the laboratory [119], and person-to-person transmission [120,121]. It is noteworthy that the only documented cases of persons infected with BV have been animal care personnel, veterinarians, and laboratory researchers working with macaques (or in one case the spouse of a caretaker). There have been no confirmed zoonotic infections in persons having been bitten by wild or pet macaques [122,123].

The clinical course of BV infection in humans can vary [4,11,124]. Initial symptoms of infection usually develop within 1–3 weeks of an exposure incident, but in some cases initial symptoms may develop considerably later. The nature of initial clinical symptoms can also vary but always include nonspecific flu-like symptoms (fever, muscular pain, fatigue, and headache); vesicular herpetic lesions at the site of inoculation are not present in all cases. Later in the disease course symptoms indicative of involvement of the peripheral and/or central nervous systems develop. Progression of clinical symptoms associated with advancing infection also varies among individual patients and can include symptoms as diverse as vesicular lesions, lymphadenitis, lymphangitis, nausea/vomiting, and abdominal pain. At some point in the infection BV gains access to the nervous system where it spreads along sensory nerves to the spinal cord and ascends to the brainstem, often resulting in encephalomyelitis and respiratory failure in terminal stages of the infection. Once the infection reaches the brainstem, the final outcome is almost invariably death of the patient.

Since BV invades the sensory nervous system, the potential exists for patients surviving BV infections to harbor latent BV. The appearance of clinical BV infections in persons having a history of working with macaques but without any known potential exposure immediately prior to the appearance of clinical signs (including one case lacking any potential exposure for 10 years prior to disease onset) [4,5,124] or recurrence of disease after resolution of an initial BV infection [121,125,126] both suggest that BV latency not only occurs in humans but also that reactivation of latent BV can be associated with clinical disease. In one case where three animal care personnel at one facility acquired BV from infected macaques or contaminated cages, testing of over 130 other persons including health care personnel having contact with the patients failed to detect additional cases of BV (with the exception of BV transmission to one patient's spouse) [120]. Similarly, testing of sera from >300 animal handlers that had worked with macaques did not detect any evidence of asymptomatic BV infection despite long term and/or repeated contact with sero-positive macaques [127]. It thus appears that the risk of BV transmission is low.

Geographic Restriction of Zoonotic BV Infections

It is curious that all zoonotic BV cases to date have occurred in the US, Canada or Europe. Throughout Asia (India, Nepal, China, SE Asia) people often live and work in close proximity to macaques and experience bites and scratches. Yet despite the hundreds of thousands of such exposures that occur annually in Asia [128–132], there has not been a single reported case of zoonotic BV infection. Wild macaques are known to be seropositive for BV, and a number of studies have documented the frequent occurrence of bites and scratches among both monkey temple workers and tourists visiting these sites [59,60,133–135]. Unpublished serologic analysis of monkey temple workers suggests that some may have experienced BV infection, but none of these workers had a history of having experienced any clinical signs indicative of pathogenic BV infection.

The apparent lack of fatal BV infections in Asia where macaques are ubiquitous and both residents and international tourists are bitten and scratched at rates that dwarf exposure rates reported in US and Europe is perplexing. It is possible that captive macaques raised for biomedical research may be in an environment inherently more stressful than that of urban, temple, pet or wild macaques, resulting in more frequent shedding of BV or shedding of greater quantities of infectious BV, thereby presenting a greater likelihood of zoonotic transmission of BV. However, over the past 10–15 years several Asian nations have developed large captive macaque breeding facilities that operate similar to US captive breeding facilities, yet none have reported transmission of BV to animal care personnel.

Another possible explanation for the lack of clinical BV cases in Asia is that BV infections may not be diagnosed accurately, particularly in rural areas with limited healthcare. However, tens of thousands of macaques are free-ranging in large metropolitan areas in Asia where access to healthcare, diagnostics and case follow-up is readily available (e.g. Singapore and Hong Kong) and yet no cases of zoonotic BV have been detected. Similarly, international tourists who are exposed at monkey temple sites in places like Bali or India typically have access to advanced medical diagnostics on returning home and they or their physicians would almost certainly posit a connection between a monkey bite in Asia and

symptoms typically associated with zoonotic BV infection. The reasons underlying the restriction of fatal zoonotic BV infections to the US and Europe remains a mystery.

Drug Sensitivity of BV

Sensitivity of BV to various anti-herpetic drugs has been investigated *in vitro*, and BV has consistently been found to be less sensitive than HSV to all drugs tested [136–138]. The drug most widely used to treat HSV infections is acyclovir (ACV), and while BV is susceptible to ACV it is ~10-fold less sensitive than HSV. The BV thymidine kinase enzyme does not efficiently phosphorylate ACV (or related acyclic nucleoside analogs) which is a prerequisite for antiviral effectiveness of these drugs [137]. BV is sensitive to other drugs besides ACV including penciclovir (PCV), ganciclovir (GCV), cidofovir (CDV), and an experimental drug FEAU [137,138]. Notably, mutants of HSV that are resistant ACV and GCV are not uncommonly encountered in patients, and a similar spontaneous GCV-resistant mutant of BV has been described [139].

The *in vitro* efficacy of drugs does not always accurately predict their efficacy *in vivo*. ACV has been tested *in vivo* using a rabbit model, and while protection could be attained it required comparatively high concentrations of ACV administered over several weeks [136,140]. Consistent with observations from clinical human cases, once neurological signs of CNS involvement were evident, oral ACV was found to be ineffective although intravenous GCV did provide some protection [140]. More recently, a mouse model has been used to assess *in vivo* efficacy of several drugs in protecting against lethal BV infection [84]. While ACV, PCV, GCV and CDV were all found to be about equally effective against BV *in vitro*, these drugs varied considerably in their *in vivo* efficacy. ACV was completely ineffective and PCV provided only slight protection. In contrast, complete protection against lethal infection could be achieved with GCV or CDV. Initiation of drug treatment could be delayed up to 48 hrs after infection and still provide complete protection. While GCV treated mice surviving BV infection still developed signs of neurological involvement, most surviving mice treated with CDV did not exhibit any clinical signs of neurological involvement. Consistent with this, GCV treated survivors developed a strong serum IgG response while CDV treated survivors developed a weak or no serum anti-BV IgG response. These results suggest that CDV may be much more effective against BV than GCV.

Ideally, a treatment regimen that is non-toxic but effective in preventing BV replication at the site of inoculation before the virus can invade the nervous system is needed. Preliminary experiments testing the efficacy of topical drug treatment following inoculation by skin scarification in the mouse model suggest that this approach holds great promise as a means of providing effective prophylactic treatment immediately following an exposure incidence without the concerns for drug toxicity or the expense of in-patient care [unpublished].

Treatment of Zoonotic BV Infections

Although fewer than 100 cases of zoonotic BV have been reported since its discovery, their severity has resulted in development of guidelines for first aid after an exposure incident, testing of persons potentially exposed to BV and the monkey involved, and

recommendations for prophylactic antiviral treatment [141,142]. These guidelines were developed with research and veterinary personnel in mind; persons exposed to macaques in Asia (residents and tourists) are rarely if ever treated following these guidelines. Also, very little research has been done on drug treatment for BV infections; current treatment recommendations are based on a very few published experimental studies performed in rabbits using only two drugs. Due to the comparative rarity of zoonotic BV infections, there is little financial incentive for corporate entities to develop BV-specific drugs. Consequently, drugs developed for treatment of HSV infections are currently used to treat BV infections. Current recommendations for treatment of zoonotic BV infections advise prophylactic use of oral ACV (or val-ACV), PCV or GCV, and intravenous GCV if nervous system symptoms are evident. Both ACV and GCV have proven effective in preventing disease progression in some cases [118,121,125], but have been completely ineffective in others [117,121,125,143]. Of particular note, once infections have progressed to involve the CNS, treatment is rarely effective.

The poor potency of ACV against BV in both the rabbit and mouse models raises a serious concern regarding current treatment recommendations for prophylactic treatment of suspected zoonotic infections (i.e., oral ACV or val-ACV). If ACV is as poorly effective against BV in humans as it is in mice and rabbits, prophylactic use of ACV following an exposure incident may allow BV to continue to replicate at the site of inoculation to a level eventually sufficient to invade the CNS. While there are no published experimental data demonstrating efficacy of prophylactic ACV treatment, there is a single published clinical case where neurological involvement did not develop following oral ACV treatment despite BV being detected by PCR in the wound site [118]. In contrast, there are several published cases where treatment with ACV failed to prevent advancement of BV infection (i.e., patients treated with ACV developed an overt/lethal infection) [125,144] as well as multiple cases where patients receiving no ACV or treatment with other drugs unrelated to ACV recovered from clinically overt BV infection (the ~20% non-lethal BV cases) [124,125,145]. Thus, the actual efficacy of ACV against BV in humans remains unclear. GCV, the most effective treatment currently recommended for zoonotic BV infection, is usually reserved for use once neurological symptoms are evident. Even so, GCV is not completely effective [117].

Zoonotic Infections by Other NHP Herpesviruses

As summarized in Table 1, herpesviruses related to BV have been isolated from chimpanzees [146], baboons [147–150], vervets [151], langurs [43] and several species of South American monkeys [152–155]. Serologic studies indicate the existence of related α-herpesviruses in other NHP species as well [41,156–162]. If herpesviruses have co-evolved with their host species as phylogenetic analyses suggest, all NHP species are likely to have their own unique α-herpesviruses that are genetically and antigenically related to known NHP herpesviruses. Virtually nothing is known about the herpesviruses of langurs and spider monkeys, but some of the other NHP herpesviruses can cause fatal disease when they cross the species barrier. While we often think in terms of zoonoses, we also need to be aware of the ability of human viruses to infect NHPs. While not always serious, HSV has been transmitted to a variety of NHP species, in many cases with fatal results [77,163–175].

One herpesvirus closely related to BV is *Cercopithecine herpesvirus* 2 (simian agent 8; SA8). SA8 was originally isolated in South Africa from a vervet (*Cercopithecus aethiops*) and subsequently from a chacma baboon (*Papio ursinus*) [150,151]. As a result of its isolation from two species, SA8 was long considered to be a virus present in all African monkeys. It was later recognized that the herpesvirus found in savannah (olive and yellow) baboons (*P. anubis* & *P. cynocephalus*, resp.) while very similar to SA8, was distinct from SA8 [148]. A virus assumed to also be SA8 has since been isolated from a vervet [176]. However, careful serological analyses found that vervets do not appear to recognize SA8-specific antigens, suggesting that at least the reference strain of SA8 (B264) may not actually be a vervet virus [41]. Nonetheless, vervets are likely infected with an α-herpesvirus related to BV. While translocated vervets from the Caribbean are all sero-negative for SA8, other vervets have been reported to be sero-positive [41].

In one case reported as a zoonotic BV infection, a patient was bitten on the hand by a vervet [177]. The following day she sought treatment for pain and swelling at the wound site and two days later developed fever and flu-like symptoms, but eventually improved. Three weeks after the bite incident, the wounds on the hand had healed but the patient developed swelling and tingling in the forearm and swelling of regional lymphnodes. She also recovered from this without specific treatment, but 2 weeks later again developed itching and pain in the hand and forearm. At this point BV infection was suspected and the patient was placed on a 25 day course of oral ACV. The patient completely recovered and remained free of symptoms for 11 months. Since BV is not found in African NHPs, it is likely this infection was due to a vervet herpesvirus rather than BV.

A case often included in historical summaries of zoonotic BV cases involved an individual who had a history of contact with only African NHPs (no contact with macaques) and was bitten by a vervet (*Cercopithecus aethiops*) [4]. Both the monkey and patient exhibited increasing titers to BV. Given the lack of exposure to macaques, it seems likely that this infection was not due to BV, but rather to SA8 or a related virus of vervets. Such an infection would produce the same serological results given the tests used at the time (circa 1959).

Baboons carry a herpesvirus designated *Papiine herpesvirus* 2 (Herpesvirus papio 2; HVP2) [148–150,178,179]. HVP2 is very closely related to SA8 and was originally considered to be the same virus. Only with the advent of molecular genetics analyses did it become clear that HVP2 was a distinct virus [148]. In baboons HVP2 behaves just as BV does in macaques or HSV in humans, producing oral or genital infections and becoming latent in sensory neurons with subsequent reactivation and shedding of the virus [147,149,180,181]. Also like BV in macaques, HVP2 can produce fatal infections in infant baboons [182,183]. HVP2 and BV are very closely related at the molecular level to the point that HVP2 has found use as an alternative antigen to replace BV antigen in serological assays [94,95]. Most HVP2 isolates are just as neurovirulent in mice as the most neurovirulent strains of BV [86,184]. Also like BV, HVP2 can produce lethal cross-species infections in other NHPs [185]. Despite the close similarity of HVP2 and BV, zoonotic HVP2 infections have never been reported. Serological testing of animal care personnel at one baboon breeding facility similarly failed to detect any evidence of zoonotic HVP2 infections [unpublished].

An α-herpesvirus isolated from squirrel monkeys (*Saimiri spp.*) designated *Saimirine herpesvirus* 1 (Herpesvirus saimiri 1; HVS1) should not to be confused with the γ-herpesvirus (Herpesvirus saimiri 2) which is usually referred to as "Herpesvirus saimiri". HVS1 was originally isolated from tamarins (*Saguinus spp.*) that succumbed to lethal generalized disease soon after importation to the US, and so was variously referred to as Herpes tamarinus, Herpes T, or marmoset herpesvirus [152,155]. The tamarins had been imported together with squirrel monkeys, and subsequent studies confirmed that squirrel monkeys are the natural host of this virus [158,186–189]. Like BV and HVP2, this virus rarely causes serious disease in its natural host. Although most adults are infected, oral lesions (when present) are observed primarily in young animals [189, unpublished].

When transmitted to other South American NHPs (marmosets, owl monkeys), HVS1 produces severe and frequently fatal disease with disseminated multifocal necrosis of visceral organs and occasional involvement of the CNS [154,158,190–193]. While no conclusive reports of zoonotic infections exist, there have been several unconfirmed reports of human HVS1 infection. One was a case of encephalitis following a squirrel monkey bite where IgG titers to HVS1 increased, but no virus was ever isolated [194]. In two other incidents, customers at pet shops were bitten by a squirrel monkey and developed herpetic-type lesions on the finger, but both patients declined any testing [unpublished]. Thus, there is reason to believe that HVS1 can infect humans.

Serological testing of captive chimpanzees housed in US zoos suggested that chimpanzees (and bonobos) are infected with one of three related herpesviruses: HSV1, HSV2 or a related but distinct virus [157]. There have been two cases where an α-herpesvirus has been isolated from chimpanzees. In one case the virus was identified as HSV2 [169]. More recently, a herpesvirus (ChHV) was isolated from a chimpanzee with oral lesions [146]. While this virus is very closely related to human HSV2, both genomic sequencing and phylogenetic analyses confirmed that it is a distinct, albeit very closely related virus [195,196]. Serological testing suggested that this virus likely represents the third unidentified virus detected in some zoo-housed chimpanzees [157]. Although ChHV does not produce serious infections in mice, nothing is known about the zoonotic potential of this virus. However, given the ability of HSV2 to infect chimpanzees and the similarity of the two viruses there is no reason to expect that ChHV is not capable of infecting humans. Interestingly, recent phylogenetic analyses suggest that humans originally acquired a virus (ChHV) via cross-species infection from chimpanzees, and that this virus subsequently evolved into HSV2 [196].

Summary

NHPs are natural hosts for many infectious agents. Being closely related to humans, many of these pathogens are capable of productively infecting humans and so represent zoonotic concerns. Herpesviruses are ubiquitous in NHPs and some have been associated with pathology in non-native hosts. Of particular note is BV which is present in almost all adult macaques. Severe disease is rare in healthy macaques, but pathology has been documented following human infections with BV. Except for a very few cases in the UK, all zoonotic BV infections have occurred in the US following exposure to captive macaques. Despite the

frequent, high-risk exposure incidents that routinely occur throughout Asia where millions of macaques are naturally distributed, there have never been any cases of zoonotic BV reported nor have cases with neurological symptoms consistent BV infection been linked to macaque exposures. Nonetheless, the perception continues in the peer reviewed scientific literature as well as the popular media that all exposures from macaques can lead to highly pathogenic zoonotic BV infections. Large scale, comprehensive, longitudinal epidemiological surveys of individuals at risk for BV infection are needed to determine the true public health significance of this virus. Additionally, the extent of variation among BV isolates and comparison of isolates from captive vs. wild macaques of known provenance should be examined in depth.

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Table 1

α-Herpesviruses Isolated from Nonhuman Primates

Host Species	Commonly Used Designation	Official ICTV Name (common name)
Human	HSV1, HSV2	Human herpesvirus 1, 2 (Herpes simplex virus)
Chimpanzee	ChHV	(Chimpanzee herpesvirus) *
Macaque	Herpes B, BV	*Macacine herpesvirus* 1
Baboon	HVP2	*Papiine herpesvirus* 2
Vervet, Baboon	SA8	*Cercopithecine herpesvirus* 2
Langur	HVL	(Langur herpesvirus) *
Squirrel monkey	HVS1, Sahv1	*Saimirine herpesvirus* 1
Spider monkey	HVA1, AtHV1	*Ateline herpesvirus* 1

* Not yet officially classified by ICTV