The controversial natural history of oral Herpes Simplex Virus Type 1 infection

Running title: oral HSV-1 natural history

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Stefano Petti [1], Giovanni Lodi [2,]

[1] Department of Public Health and Infectious Diseases, Sapienza University, Rome, Italy.

2 Department of Biomedical, Surgical, and Dental Sciences, University of Milan, Milan, Italy.

Corresponding Author

Prof. Stefano Petti

Department of Public Health and Infectious Diseases, c/o Sanarelli Building, Piazzale Aldo Moro 5, I-00185 Rome, Italy.

Email address, stefano.petti@uniroma1.it

Fax number, +3906 4991 4667

ABSTRACT

The natural history of oral Herpes Simplex virus Type-1 (HSV-1) infection in the immunocompetent host is complex and rich in controversial phenomena. Namely, the role of unapparent transmission in primary infection acquisition, the high frequency of asymptomatic primary and recurrent infections, the lack of immunogenicity of HSV-1 internalized in the soma (cell body) of the sensory neurons of the Trigeminal Ganglion, the lytic activity of HSV-1 in the soma of neurons that is limited in the sensory neurons of the Trigeminal Ganglion and often uncontrolled in the other neurons, the role of keratin in promoting the development of recurrence episodes in immunocompetent hosts, the virus-host Nash equilibrium, the paradoxical HSV-1 seronegative individuals who shed HSV-1 trough saliva, the limited efficacy of anti-HSV vaccines, and why the oral route of infection is the least likely to produce severe complications. The natural history of oral HSV-1 infection is also an history of symbiosis between humans and virus that may switch from mutualism to parasitism and vice versa. This balance is typical of microorganisms that are highly co-evolved with humans and its knowledge is essential to oral healthcare providers to perform adequate diagnosis and provide proper individual-based HSV-1 infection therapy.

1 | INTRODUCTION

Herpesviridae, a family of DNA viruses, personify the pattern of viral co-divergence with their vertebrate hosts, dating back hundreds of millions of years. More specifically, across the three subfamilies (Alpha-, Beta-, Gamma-herpesvirinae), there have been multitudes of within-host viral lineage duplications in which viral descendants followed the phylogenetic history of their host species. When chimpanzees and humans diverged from their common ancestor, 6 million years ago, Human Herpes Simplex virus Type 1 (HSV-1) and Chimpanzee Herpes Simplex virus (ChHV) also diverged from their common Herpes Simplex virus ancestor of the Alphaherpesvirinae subfamily. Conversely, a zoonotic ChHV infection to human forerunners occurred 1.5 million years ago, gave birth to Human Herpes Simplex virus Type 2 (HSV-2). Such temporally distinct but longer association of HSV-1 with human host explains the differences between HSV-1 and HSV-2 infections, and why HSV-2 is genetically closer to ChHV than to HSV-1 (Sehrawat, Kumar, & Rouse, 2018; Wertheim, Smith, Smith, Scheffler, & Kosakovsky Pond, 2014).

HSV-1 is, therefore, a highly successful pathogen. Nearly all human beings, by the time they reach adolescence, are infected with multiple herpesviruses, HSV-1 being the principal, this family of viruses accounts for 35-40 billion human infections worldwide, making herpesviruses among the most prevalent pathogens known to exist. This long co-evolution gave HSV-1 the ability to evade host immunity using a number of strategies. These include infection of tissues with limited accessibility to immune mediators, establishment of latency which allows minimal immune recognition and numerous active immunomodulatory procedures. Immune evasion is responsible for lifelong infection. In addition, immunomodulatory activity makes the HSV-1 infected hosts either more resistant or susceptible to other disease situations, such as other infections, allergies and tumors. For example, in immunologic models of cancer progression, herpesviruses display many mechanisms of interaction with the nascent cancer cells, including enhanced immunosurveillance, tumor elimination, or maintenance of precancerous equilibrium triggered by latency-driven immune modulation. In contrast, the immunomodulatory environment triggered by herpesvirus latency promotes more rapid tumor immune evasion and enhances the development or recruitment of immunosuppressive cells into the tumor microenvironment (Sehrawat et al., 2018; Wertheim et al., 2014).

The natural history of an infectious disease refers to the progression of the disease in individuals over time in the absence of any treatment. Most infectious diseases have characteristic natural histories, although the time frame and specific disease manifestations vary between individuals and are influenced by preventive measures (Centers for Disease Control and Prevention, 2012). The natural history of such an ancient human pathogen is also the history of co-infections, allergies, autoimmune diseases and cancers that have been promoted or prevented by chronic HSV-1 infection and is also the history of changing immunocompetence of the host throughout life (Sehrawat et al., 2018; White, Suzanne Beard, & Barton, 2012).

1.1 | Why another oral HSV-1 infection review

Unlike the many good reviews on oral HSV-1 infection (examples are Arduino, & Porter, 2008; Ballyram, Wood, Khammissa, Lemmer, & Feller, 2016; Fatahzadeh, & Schwartz, 2007; Kolokotronis, & Doumas, 2006), the present narrative review does not focus on clinical signs and symptoms of the disease, but on the pathogenesis of the various stages and manifestations of such infection. The ultimate goal of this review is, therefore, of improving healthcare providers' knowledge about oral HSV-1 infection, thus promoting better infection control, diagnosis and treatment procedures. This history does not account for the many diseases prevented and promoted by HSV-1 infection, particularly in immunocompromised individuals. An overview of the natural history is displayed in **Figure. 1**.

This is a narrative review and since there are no acknowledged guidelines available for narrative review writing (Ferrari, 2015), this paper was written according to the journal style for narrative reviews (see, for example, Rahman et al., 2018; Sannigrahi, Sharma, Panda, & Khullar, 2018).

2 | PRIMARY ORAL HSV-1 INFECTION

2.1 | Transmission and penetration into the oral mucosa of the susceptible host

Humans are the only known HSV-1 reservoir, and since HSV-1 is short-lived on external surfaces, transmission is due to intimate contacts with carriers who shed live viral particles through HSV-1

infectious lesions (exudates or active lesions), or secretions (mostly saliva). Indeed, most viruses are transmitted through saliva and Epstein-Barr virus, Cytomegalovirus, Herpes Zoster virus (Guidry, Birdwell, & Scott, 2018; Wong, Richards, Pei, & Sereti, 2017), Zika virus, (Leão, Gueiros, Lodi, Robinson, & Scully, 2017; Wiwanitkit, 2017), Adenoviruses (Alevizos et al., 2017), Hepatitis B virus (Portilho et al., 2017), Polyomaviruses (Figueiredo et al., 2017), Human Papillomaviruses (Camacho-Aguilar et al., 2018), are only examples.

Lesions could be so mild that patients do not recall them. In addition, asymptomatic carriers with undetectable or even no lesions also exist, thus making it often impossible the recall of the event that led to infection development (Kaufman et al., 2005; Knaup, Schünemann, & Wolff, 2000; Okinaga, 2000; Ramchandani et al., 2016). Live HSV-1 particles are occasionally recovered from skin up to two hours after contamination with the virus, but the skin must be humid or wet. Thus, HSV-1 transmission could occur through contaminated moistened hands touching oral lesions of susceptible hosts. Although HSV-1 has been recovered from environmental surfaces, such as doorknobs and toilet seats, transmission without a direct contact between carriers and susceptible hosts seems unlikely (Barker, Stevens, & Bloomfield, 2001).

HSV-1 infects the susceptible host through epithelial breaks due to mechanical, physical, or chemical injuries. However, infection could also be promoted by preexisting infections due to pathogens or overgrowth of commensals that induce the inflammatory response of the oral mucosa with consequent disturbance of epithelial integrity and loss of the barrier function. This event explains why individuals with poor oral hygiene, from low socio-economic classes, and with coexisting oral infections, are more likely to develop primary HSV-1 infection (Beydoun, Dail, Ugwu, Boueiz, & Beydoun, 2010; Thier et al., 2017).

The HSV-1 infectious dose is not clear, although experimental studies on rhesus macaques show that 10^4 viral units are necessary for the transmission to occur efficiently (Fan et al., 2017). Following the entry of a number of viral particles sufficient to cause infection, HSV-1 rapidly spreads in the oral epithelia thanks to its lytic activity (i.e., cellular destruction) specifically directed against the epithelial cells.

2.2 | Penetration into the sensory-neuron axons of the Trigeminal Nerve

Within the oral mucosa there lie the sensory-neuron axon free endings of the fifth cranial nerve (CR-5, Trigeminal Nerve) (Otth, Acuña-Hinrichsen, Leyton, Martin, & Concha, 2016; Perng, & Jones,

2010). CR-5 carries the sensory innervation of the skin of face and anterior scalp, the conjunctiva, and the nasal and oral mucosae; it does not carry sensory innervation of the posterior third of tongue, oropharynx and upper esophageal tract. The incoming nerve axons of the three Trigeminal Nerve branches converge on the Trigeminal Ganglion (Semilunar or Gasserian Ganglion), where there are the soma (cell bodies) of the sensory neurons. The Trigeminal Ganglion is analogous to the dorsal root ganglia of the spinal cord, which contain the cell bodies of incoming sensory fibers from the rest of the body.

The sensory-neuron axon free endings are enveloped in the Blood-Nerve Barrier, that protects them from physical and biological injuries. However, inflammation caused by HSV-1 infection and, possibly, preexisting infections produce an increase in Blood-Nerve Barrier permeability –which is less efficient than the Blood-Brain Barrier that protects the Central Nervous System, through substances, such as interferon-γ (IFN-γ), TNF-α, Interleukin-6, Reactive Oxygen Species (Egan, Wu, Wigdahl, & Jennings, 2013; Varatharaj, & Galea, 2017). HSV-1 particles are thus internalized into the free endings and reach the soma of the neurons in the Gasserian Ganglion through retrograde transport, where viral latency is usually induced.

In order to understand the natural history of HSV-1 infection it is important to anticipate that although the epithelial and the neuronal infections originate from the same event, they evolve independently.

2.3 | Why most primary HSV-1 infections in children and elderly are asymptomatic

Primary HSV-1 infections are generally mild or asymptomatic because productive infection (i.e., viral replication) and lytic activities are minimal. Such event is not accidental, but is due to the aforementioned long co-evolution between pathogenic viruses and human hosts.

Viral infections were long thought to produce only acute clinical diseases, while the majority do not produce pathological signs, and are subclinical or asymptomatic (Baron, 1996). This happens because local infection and HSV-1 internalization into the epithelial cells of the infection site and into the CR-5 neurons are two different events. Namely, while viral particles are rapidly internalized into sensory-neuron free endings, anti-viral defenses of the host may arrest the progression of the epithelial infection before disease manifestation. Indeed, the immunologic neutralization of the epithelial infection occurs in two phases, one innate and the other adaptive. During the innate phase, epithelial cell infection induces the production of interferon-β (IFN-β)

that activates the innate immune cells, which in turn secrete interferon-α (IFN-α). IFN-α and IFN-β induce an antiviral state in the infected and surrounding epithelial cells. Interleukin-18, released from dendritic cells, activates natural killer cells that secrete IFN-γ and granzymes A and B. During the following adaptive phase the dendritic cells that engulf the HSV-1 virions travel to the draining lymph node and activate naive B and T cells. Activated B and T cells travel back to the site of the primary infection. The antigen specific response ultimately results in the lysis of infected epithelial cells with the development of a detectable lesion. However, during the innate phase, the neutralization of HSV-1 virions may occur, thus preventing the development of the epithelial lesion and, therefore, patients remain asymptomatic (Egan et al., 2013; Wuest, & Carr, 2008). In addition, if the innate immunity is particularly efficient, it is possible that the adaptive stage does not occur at all and patients remain seronegative.

2.4 | Primary herpetic gingivostomatitis

Typical primary oral HSV-1 infection is characterized by productive infection and lytic activity directed against the epithelial cells and limited to the site of entry. The consequent local inflammatory process, possibly enhanced by coinfection, leads to the development of the Primary Herpetic Gingivostomatitis (PHGS) after an incubation of 2-20 days.

The oral mucosa develops exudate containing pin-head vesicles, that are rarely seen. Vesicles break down rapidly, coalesce and produce small painful red lesions. Red color is due to hyper-vascularization of underlying connective tissue occurring during inflammation, while pain is due to the loss of the barrier function provided by the epithelial cells and exposure of underlying sensory-nerve endings. Initial lesions enlarge slightly promoting the formation of central ulcerations, due to exposure of the lamina propria and connective tissue. Ulcerations are then covered by yellow-grey pseudomembranes (membrane color is due to the characteristics of the exudate). Adjacent lesions may coalesce to form irregular ulcerations. PGHS is often accompanied by local lymphadenopathy.

PHGS lesions occur on the tongue, vermillion, gingival, buccal, hard and soft palatal mucosae and, less frequently, pharyngeal (with pharyngo-tonsillitis) and nasal (with rhinitis) mucosae (Arduino, & Porter, 2008; Kolokotronis, & Doumas, 2006). Clinical signs comprise diffuse, purple, boggy gingival swelling. The ulcers heal gradually in 10-14 days without scarring. In three fourth of patients with PHGS perioral lesions occur affecting lips, cheeks, and chin. Sporadically,

eye infections (ocular herpes or herpetic keratoconjunctivitis) and infections of the digits (herpetic whitlow) also may occur (Amir, Harel, Smetana, & Varsano, 1999).

PHGS lesion development is preceded by prodromal, non-pathognomonic, general signs and symptoms, such as fever, chills, nausea, loss of appetite, lethargy, irritability, malaise and headache. Sometimes, prodromal symptoms are the only signs of primary HSV-1 infection and sometimes they can be so mild (or even lacking) that the affected subjects cannot recall them. Anyway, only 10-12% PHGS cases among children are so severe that parents notice them. Elders who develop PHGS usually show mild lesions and no lymphadenopathy. Conversely, PHGS developed among younger adults is more severe (Ajar, & Chauvin, 2002; Petti, 2018).

Childhood, between 6 months and 5 years of age, and adolescence –in developing countries, or adulthood, between 20 and 40 years of age –in affluent countries, are the age peaks of PHGS onset (Whitley, & Roizman, 2001).

Clinically severe forms of PHGS may also occur. Severe PHGS show signs, such as lymphadenopathy, oral malodour and coated tongue, that are due to accumulation of bacteria and yeasts on the tongue, which in turn is due to soreness. The latter leads to limited function of the oral muscles, with consequently reduced bacterial clearance from the oral cavity and, to minor extent, to poor oral hygiene and coinfections. Extra-oral symptoms may be present, such as initially macular and later purpuric cutaneous rash, and arthralgia. Intra-oral symptoms include dysphagia and odynophagia, which could be so severe that subjects require hospitalization (Ajar & Chauvin, 2002; Husein-ElAhmed, O'Valle, Aneiros-Fernandez, Gutiérrez Salmerón, & Arias-Santiago, 2011).

Every year more than 20,000 Emergency Department visits are due to PHGS complications only in the US, resulting in more than 7,000 hospitalization days. Almost one half of these visits involve children aged 0-3 years. Among subjects visited in the Emergency Departments, impaired nutrition due to PHGS is responsible for severe fluid and electrolyte disorders (reported in 65% patients), hypertension (8%), and weight loss (4%) (Allareddy & Elangovan, 2014). 10% patients have bacteremia and may develop bacterial infections (Amir et al., 1999; Shouval, Bilavsky, Avitzur, Shapiro, & Amir, 2008). Almost one tenth of children presenting at the Emergency Departments require hospitalization, while 10% return to the Emergency Departments for a second and even third time, and 25% of them are then hospitalized (de Suremain et al., 2019). The economic burden of severe PHGS is high and the annual cost for the only hospitalization in the US is of almost 35 million USD (Allareddy & Elangovan, 2014).

Globally, the proportion of children who develop severe PHGS is low compared to those with mild PHGS and asymptomatic children. Many of these children have important comorbidities. The most frequent of them are anemia, neurologic disorders, solid tumors, leukemia, lymphoma, liver disease, and renal failure, each reported in at least 3% subjects, while HIV infection does not seem responsible for severe PHGS (Allareddy & Elangovan, 2014; Tovaru, Parlatescu, Tovaru, & Cionca, 2009). Another important element, once associated to high case-fatality ratio, is malnutrition, particularly frequent in the past and in developing countries (Adegbola et al., 1994; Hansen, 1961; Johnson, Salimonu, & Osunkoya, 1981). Poor socio-economic level is frequent in families of hospitalized children (Allareddy & Elangovan, 2014). The latter is not only a problem of lack of resources, since the services offered in Emergency Departments and in most hospitals are free, especially for children. The problem of poor socio-economic level is partly explained by the Inverse Equity Hypothesis, a corollary of the Inverse Care Law, which states that public and private healthcare services are prevalently used by the wealthier segments of the population that need them least (Hart, 1971; Victora, Vaughan, Barros, Silva, & Tomasi, 2000). Indeed, an analysis in US among children with severe PHGS showed that subjects from families that were under government-sponsored insurance programs, which cover the healthcare of the poorest people, did not routinely seek for free oral and dental care and were, therefore, more likely to seek for emergency care than children from affluent families (Allareddy & Elangovan, 2014). The factors responsible for this paradoxical effect must be searched in comorbidities and fatalism. Comorbidity regards the whole family and not only physical diseases, the most typical is psychological distress. Fatalism is the belief of being powerless to contrast the events that have already been decided by the destiny. Fatalism, widespread amongst low-income communities, groups and countries, is dramatically associated with poor oral health outcomes (Petti, 2010; Petti, 2011).

2.5 | Encephalitis

If the viral load that causes the primary infection is particularly high, and/or the infected subject is immunocompromised or lacks specific anti-viral activity (Abdelmagid et al., 2016; Casrouge et al., 2006; Pourchet, Modrek, Placantonakis, Mohr, & Wilson, 2017), HSV-1 particles surpass the Trigeminal Ganglion and reach the Geniculate Ganglion (Facial Nerve, CN-7) via the lingual nerve and, from there, the Vestibular Ganglion (Vestibulocochlear Nerve, CN-8) through facio-vestibular

anastomoses. Although latency can be induced into these ganglia, HSV-1 infection control by the host is less efficient and complications, such as Bell's palsy (Geniculate Ganglion), sudden hearing loss, and vestibular neuritis (Vestibular Ganglion) may occur (Arbusow et al., 2010; Himmelein et al., 2017). Ultimately, entry in the Central Nervous System could occur with latency in the cerebellum, olfactory bulb, frontal cortex, hippocampus, or HSV-1 encephalitis (HSE) development. It is not clear, however, whether HSE is due to primary or recurrent HSV-1 infection (Duarte et al., 2019; Steiner, Kennedy, & Pachner, 2007).

This is the trigeminal pathway of HSE and is one of the three Central Nervous System invasion routes, the other routes being the olfactory nerve pathway –through primary infection of the nasal mucosa and infection of the Olfactory Nerve (CN-1), and the hematogeneous route –that can directly lead to primary Central Nervous System infection. The trigeminal pathway is the least likely route leading to HSE. Indeed, in patients who died from HSE, HSV-1 antigens have not been detected in regions associated to this pathway, but in those associated to the olfactory pathway that seems the preferential route, while the primary infection option is supported by the finding that at least half of HSE cases are caused by another HSV-1 strain different from the strain responsible for oral HSV-1 infection (Otth et al., 2016; Steiner et al., 2007).

The Central Nervous System infection through the trigeminal pathway is an unlikely strategy for successful HSV-1 infection, as it disrupts host-pathogen equilibrium. Indeed, HSE is often fatal and represents a "dead-end" for both pathogen and host (Koyuncu, MacGibeny, & Enquist, 2018).

With an estimated annual incidence rate of 3-4 cases per million population, HSE is an uncommon event. Nevertheless, HSV-1 is the most frequent pathogen responsible for infectious encephalitis and its case-fatality ratio is as high as nearly 20% (Boucher et al., 2017; Jørgensen, Dalgaard, Østergaard, Nørgaard, & Mogensen, 2017). HSE usually, but not exclusively, affects older adults aged 50-70 years and is lethal in subjects with comorbidities, such as cerebrovascular diseases and chronic pulmonary diseases (Jørgensen et al., 2017).

3 | LATENT HSV-1 INFECTION

3.1 | Viral replication inhibition into the soma of the sensory neurons of the Trigeminal Ganglion

As anticipated, while PHGS is progressing independently in the oral mucosa, other viral particles cross the Blood-Nerve Barrier and are internalized into the axons of the sensory-nerve free endings of CN-5 and reach the soma of the neurons in the Trigeminal Ganglion.

Although human neurons are naturally permissive for HSV-1 replication (Pourchet et al., 2017), this activity is limited into the Gasserian Ganglion of the immunocompetent host, owing to the intervention of immune cells and mediators that prevent HSV-1 spread into the Central Nervous System (Arbusow et al., 2010; Theil et al., 2003). Indeed, soon after viral internalization into the axons, massive infiltration of lymphocytic cells (CD8+ T-cells, CD68 macrophages) that cross the Blood-Nerve Barrier also occurs. This infiltration is persistent in the Trigeminal Ganglion with production of cytokines (IFN-γ, TNF-α) that hamper viral replication, and chemokines that attract other immune cells in the ganglion (Theil et al., 2003).

This lymphocytic infiltration results in chronic inflammation in the Trigeminal Ganglion and ultimately in HSV-1 latency (Arbusow et al., 2010; Theil et al., 2003). During latency, HSV-1 DNA is circularized in the nucleus. Specific neuronal histones assembled on the viral DNA allow transcription of only a small segment of the viral genome, with the expression of noncoding RNAs known as the Latency-Associated Transcripts (LATs). LATs in turn modify the chromatin on the viral genome promoting stable but reversible transcriptional silencing. LATs are detectable in the soma of all infected neurons that are converted into a lifelong reservoir of recurrent infections (Cliffe, & Wilson, 2017; Koyuncu et al., 2018). During latency, therefore, both inhibition of viral replication and expression of viral antigens occur and, seemingly paradoxically, both the host and the HSV-1 cooperate in controlling the spread of the infection.

3.2 | Nash equilibrium and HSV-1 latency into the Trigeminal Ganglion

This cooperation between the infecting pathogen and the infected host in maintaining the intracellular latent infection is a typical strategy of pathogens that are coevolved with the human host, such as Herpesviruses, Human papillomavirus, *Mycobacterium tuberculosis* and *Helicobacter pylori*, and is known as Nash equilibrium. Nash equilibrium is the solution for a non-cooperative game in which no single player dominates the other in decision making (Blaser, & Kirschner, 2007; Kodaman, Sobota, Mera, Schneider, & Williams, 2014).

Chronic infection is crucial for survival and evolution of pathogens that have the human host as unique reservoir. Indeed, pathogens have two options, intracellular and extracellular infection. While the intracellular compartment is relatively safe, as pathogens are relatively protected from immune recognition and serum mediated extracellular killing, extracellular compartment provides pathogens an easy access to the external environment that is necessary for dissemination to other hosts. Thus, pathogens face a trade-off between safety of the intracellular compartment and relative ease of dissemination via the extracellular compartment. The infected host also has two options, killing the infected cells, thus eradicating the infection, or killing only extracellular pathogens limiting the spread of the infection to other sites but tolerating pathogen persistence. The first option would be desirable but produces damages to the infected organs and apparatuses and, possibly, death (Eswarappa, 2009).

The Nash equilibrium between humans and HSV-1 is efficiently described by James Lovelock's quote "An inefficient virus kills its host. A clever virus stays with it" (reported by Steiner, & Benninger, 2013). Nash equilibrium is indeed the best compromise for both HSV-1, that has the chance of transmission to other susceptible hosts during reactivations, although its reproduction within the infected host is limited, and for the host that cannot eradicate HSV-1 infection, but inhibits virus propagation, thus preventing serious complications such as HSE.

The selective entry of HSV-1 into the axons of the Trigeminal Nerve neurons is an essential part of the natural HSV-1 life cycle that promotes Nash equilibrium installation. Namely, animal studies and studies on human corps show that while HSV-1 presence in the Trigeminal Ganglion is extremely frequent (77% of the seropositive individuals), presence in other sites of the Nervous System, such as the Olfactory Bulb and the Central Nervous System, is less frequent, that is, 15% and 30%, respectively (Baringer, & Pisani, 1994). In addition, viral replication is efficiently controlled in the Trigeminal Ganglion, where the median number of detectable viral particles is very low (300 per 10^5 cells), while it is out of control in the Vestibular and the Geniculate Ganglia, where the median number of viral particles is as high as 83,000 and 4,000 per 10^5 cells, respectively (Hafezi et al., 2012; Otth et al., 2016). Clinical data corroborate this hypothesis, since recurrent herpetic infection in individuals with HSE is as frequent as in the general population, thus suggesting that past HSV-1 infection is not a risk factor for HSE development (Steiner, & Benninger, 2013).

These data confirm that the optimal control over HSV-1 replication occurs only into the trigeminal neurons, while the alternatives rarely result in latency, and lead to complications.

4 | Reactivation

4.1 | Animation, Full Reactivation and Anterograde Transport

HSV-1 Reactivation, pivotal for viral life cycle, occurs in two phases, Animation and Full Reactivation. During Animation, one or more stressors induce the activation of the Neuronal Stress Pathway that results in more permissive viral chromatin. Subsequently, a generalized burst of HSV-1 gene transcription and translation with synthesis of several viral regulatory factors occurs. During Full Reactivation these factors promote the transcriptional capability of all viral genes allowing HSV-1 DNA replication and new viral particle assembly. Noticeably, although all latently infected neurons are exposed to the stressor leading to the Animation phase, only a subset will undergo Full Reactivation. It seems that the number of viral regulatory factors produced during Animation must be higher than a given threshold to induce Full Reactivation. Other hypotheses are that neurons respond differently to stressors, and that noncoding miRNAs could be involved (Roizman & Whitley, 2013).

The Reactivation process is due to a combination of two concurrent events, that is, the suppression of the immune response that controls viral replication during latency, and the presence of exogenous signals. An example of the former event is the production of specific viral proteins during Animation, that have the power to neutralize the IFNs produced by the T cells surrounding the infected ganglia, that block Animation and/or Full Reactivation (Linderman et al., 2017). Examples of the latter are traumatic injuries, UV irradiation, heat shock, fever, change in hormone levels, and other events that damage the innervated tissues and induce the deprivation of the Neuronal Growth Factor, an essential component in maintaining latency (Suzich & Cliffe, 2018), while epithelial infections from other alpha herpesvirus trigger the viral-tegument mediated reactivation pathway (Koyuncu et al., 2018).

The Neuronal Stress Pathway can be induced by different stressors listed in **Table 1**, investigated through in vitro, animal, and clinical studies (Arduino, & Porter, 2008; Cliffe, & Wilson, 2017; Koyuncu et al., 2018; Roizman, & Whitley, 2013). The earliest recognized stressor is fever, hence the name of fever blister given to herpes labialis, but the stressor most frequently associated to recurrences is exposure to UV rays, typical of skiers, fishermen, and open water swimmers. Psychological stress and menstruation are also frequent. Genetic susceptibility of the

host also seems to be important in determining recurrence frequency and severity, particularly the C21orf91 gene, located in the long arm of the chromosome 21. Conversely, no specific viral genes seem directly responsible for recurrences. Nevertheless, the viral load at the time of the primary infection is associated to these events, and the neurons harboring large copy numbers of viral DNA are more likely to undergo Full Reactivation than the remaining infected neurons (Roizman, & Whitley, 2013).

The presence and the severity of recurrence symptoms depend on the number of new viral particles that are produced (Cliffe, & Wilson, 2017; Koyuncu et al., 2018). The newly formed viral particles leave the nucleus and travel to the nerve endings (Anterograde Transport) using the highly specialized secretory pathway used for transport and exocytosis of neurotransmitters and neuropeptides in the neuronal synapses. More specifically, Anterograde Transport occurs through microtubules that are in the cytosol and is as fast as 4-5 mm per hour. At synapsis level the microtubules are anchored to the plasma membrane by cytoplasmic linker associated proteins, and virus particle exocytosis occurs (Hogue, Bosse, Hu, Thiberge, & Enquist, 2014). Egressed viral particles are internalized into epithelial cell by fusion at the plasma membrane or by endocytosis (Devadas et al., 2014). The epithelial cells in relatively undifferentiated state, such as the basal layer, the lower prickle cell layer, and the cells of the basement membrane are the only permissive cell to HSV-1 internalization, while epithelial cells in a differentiated state are not (Yura et al., 1987). Full Reactivation closely resembles primary infection (Cliffe, & Wilson, 2017).

4.2 | Recurrence and Recrudescence

In general, viral reactivation from latency resulting in asymptomatic shedding is called recurrence, while reactivation resulting in clinical disease is called recrudescence (Fatahzadeh, & Schwartz, 2007). However, there is no consensus on whether to use the term recrudescence for detectable lesions, and any reactivation from latency is occasionally referred to as recurrence.

Reactivation may have different manifestations depending on the number of re-infected epithelial cells, namely,

- Asymptomatic infection, in individuals without prodromal symptoms who do not develop any detectable lesion.
- False prodromal symptoms, in individuals with prodromal symptoms who do not develop any detectable lesion.

- Recurrent oral herpetic infection, in individuals with detectable lesions (recrudescence), namely, herpes labialis and recurrent herpetic stomatitis, with or without prodromal symptoms.

Very importantly, during reactivation all individuals are contagious irrespectively of the manifestation of the recurrent infection.

Prodromal symptoms, due to viral replication in the epithelial cells in the area of the viral egression from the sensory axons (Fatahzadeh, & Schwartz, 2007), are focal itching, burning or tingling sensation of the lip, paraesthesia, tenderness and sometimes pain. Prodromal symptoms usually start 24-48 hours before the lesion development, they can last few hours, but may occasionally persist after the lesion development and even after healing (Arduino, & Porter, 2008; Ramchandani et al., 2016; Tilliss, & McDowell, 2002).

According to older studies (Spruance, 1984) most lesions occur without prodromal symptoms. This is probably due to the fact that prodromal symptomology may seem confounding to the patient at initial occurrence, however, for those frequently experiencing recurrent herpetic lesions, these symptoms are often recognizable. Therefore, lack of prodromal symptoms is probably only apparent and due to the occurrence of mild symptoms that are often overlooked by patients (Tilliss, & McDowell, 2002).

4.3 | Asymptomatic recurrent infection is very frequent

The first scientific report of HSV-1 recovered from the mouths of individuals with no clinical evidence of recurrent herpetic infection dates back to 1953 (Buddingh, Schrum, Lanier, & Guidry, 1953). Since then, several studies longitudinally investigated recurrence and recrudescence development in immunocompetent subjects (reviewed by Miller, & Danaher, 2008). Five follow-up studies on seropositive individuals were used here to assess the incidence of the various manifestations of HSV-1 reactivation (Kaufman et al., 2005; Knaup et al., 2000; Okinaga, 2000; Ramchandani et al., 2016; Spruance, 1984). Although average estimates could not be assessed, due to different study designs, it is evident from **Table 2** that asymptomatic viral shedding is even more frequent than both lesion development and false prodromal symptoms.

The fact that the majority of HSV-1, as well as most viral infections are asymptomatic (Baron, 1996) is not due to chance. Indeed, co-evolution between pathogens and hosts led to develop host defense mechanisms to prevent the spread of epidemics. One of these mechanisms,

known as Behavioral Immune System, is intended to recognize and respond negatively to individuals who show signs of infectious diseases (Schaller, 2006). This system, the first line of defense against potentially harmful pathogens, has deep evolutionary roots, as it is also observed in social insects such as ants, bees, and termites (Shakhar, 2019). However, the Behavioral Immune System is so fixed in humans that leads to paradoxical behaviors, such as those observed during the greatest Ebolavirus Disease (EVD) epidemics. Indeed, the key measure proposed by the World Health Organization with the collaboration of the US Centers for Disease Control and Prevention to prevent the importation of cases from West Africa was to "Conduct exit screening of all persons at international airports, seaports and major land crossings for unexplained febrile illness consistent with potential Ebola infection" (World Health Organization, 2014). In addition, several healthcare workers from Western countries were infected and some died from EVD despite the use of impenetrable Personal Protective Equipment in the EVD units (Petti, Protano, Messano, & Scully, 2016). Both the WHO/CDC measures and the infection of healthcare workers did not account for asymptomatic Ebolavirus carriers and focused only on sick individuals. Asymptomatic infection can be thought as a measure developed by co-evolved pathogens to counteract this collective host behavior and ensure viral spread to other susceptible hots, thus preventing pathogen extinction.

Asymptomatic carriers have an important role in infection dissemination throughout the population, thus also helping explain why the event that leads to infection transmission is often not recalled by patients with primary infection. From the epidemiologic standpoint, if asymptomatic infections and false prodromal symptoms are considered, the true prevalence of oral HSV-1 infection is much higher than prevalence calculated considering only the clinically detectable lesions (Sacks et al., 2004).

The investigation of oral HSV-1 epidemics is further complicated by the presence of seronegative and asymptomatic individuals who shed HSV-1 (Kaufman et al., 2005).

4.4 | Persistently seronegative individuals with HSV-1 in saliva

A relatively small proportion, roughly 3%, of adult subjects with clinically detectable PHGS do not develop either IgM or IgG (Yoshizumi, 2000). In addition, some seronegative individuals shed HSV-1 in saliva and tears acting as hidden carriers (Hatherley, Hayes, & Jack, 1980). Such an event is relatively frequent (Kaufman et al., 2005) and seems to occur when both the epithelial and the

neuronal infections do not lead to IgG production. While the neuronal infection in the Trigeminal Ganglion is almost never immunogenic during latency, due to lack of viral antigen expression on the external surfaces of the soma of the neurons (Cliffe, & Wilson, 2017), the situation is different for the epithelial infection. This event is probably explained by the development of specific T-cell immunity that precedes and replaces specific IgG production, as suggested by the report that there are persistently seronegative individuals who are immune against HSV-1 thanks to such T-cell immunity (Posavad et al., 2010).

4.5 | Recurrent extra-oral herpes and herpes labialis

Herpes labialis, also known as cold sores or fever blister, is the best known recrudescence in immunocompetent individuals. Recrudescent extra-oral herpes may affect any site along the involved sensory division of CN-5, such as the skin of the nose, chin or cheek, but the most frequent and typical location is the vermilion border, the mucocutaneous junction of the lips. The clinical lesions are characterized by virally induced epithelial damage and go through different stages,

- Development of a cluster of small, erythematous fluid filled papules (microvesicles).
- Microvesicle rupture within 2 days to form irregular, superficial erosions that can be pustular or ulcerative (erosions).
- Erosions crust over within 3-4 days.
- Complete healing without scarring within 1-2 weeks.

(Fatahzadeh, & Schwartz, 2007; Kolokotronis, & Doumas, 2006; Spruance, 1984).

The average area involved is 70 (range, 4-250) mm^2, usually lower than 100 mm^2. The mean duration is 7 (range, 2-16) days. Pain is intense at the outset, but resolves within 4-5 days. Virus shedding is the highest after microvesicle rupture and is often present for 2-3 days, but longer periods are likely even after resolution of clinical signs. Recurrent herpes labialis may coexist with recurrent herpetic stomatitis (Kolokotronis, & Doumas, 2006; Spruance, 1984).

Data from **Table 2** suggest that three to four annual episodes are normal, however, in a proportion ranging between 5% and 25% immunocompetent individuals, up to twelve episodes may occur. Recurrent herpes labialis is more frequent in women than in males, and in younger individuals (Arduino, & Porter, 2008; Fatahzadeh, & Schwartz, 2007; Kolokotronis, & Doumas, 2006).

4.6 | Recurrent herpetic stomatitis and the key role of the keratinized oral mucosa

Recurrent herpetic stomatitis (RHS) is also known as recurrent intraoral herpes. Like the recurrent herpes labialis, it is often, but not necessarily, preceded by prodromal symptoms and can develop anywhere along the involved sensory division of the Trigeminal Nerve.

The typical course of RHS is similar to herpes labialis, namely,

- Development of a cluster of microvesicles.
- Microvesicle rupture and tiny ulcer formation.
- Ulceration coalescence in larger irregular ulcers (diameter <5 mm, up to 1 cm).
- Development of a yellowish-white pseudomembrane surrounded by erythematous halo on the ulcer.
- Ulceration crusts.
- Complete healing without scarring.

Clinicians may confuse RHS with recurrent aphthous stomatitis (RAS). The main difference between RHS and RAS is that while RAS affects only the non-keratinized mucosa, RHS usually, but not exclusively, affects the keratinized mucosa and is accompanied by herpes labialis in one fourth of episodes. Multiple lesions are more frequent than single lesions. Lesions heal in 1-3 weeks, but anomalies exist and one case of 4 year duration in an immunocompetent host is reported (Stoopler, Alfaris, Alomar, & Sollecito, 2016). These features, reported by patients who sought for healthcare, are probably more severe than those typical of mild RHS (Arduino, & Porter, 2008; Eisen, 1998; Fatahzadeh, & Schwartz, 2007; Tilliss, & McDowell, 2002; Tovaru, Parlatescu, Tovaru, Cionca, & Arduino, 2011). Indeed, Spruance, who followed seropositive patients longitudinally reported an average development of one RHS every three months with lesions that were often single, and smaller and their average duration was only 2.5 days (Spruance, 1984).

Differential diagnosis between primary and recurrent herpetic gingivostomatitis could be difficult in patients who seek for care for the first time. Indeed, as previously explained, mild or asymptomatic PHGS could be not recalled and patients could seek for care for the first time for an episode of RHS. Patients' age could be an important discriminatory factor, particularly if subjects are younger than five years, typical of PHGS, while the presence of stressors is suggestive of RHS. Perhaps, the most reliable method to determine past exposure is the serological test for anti-HSV-

1 IgG, taken within a period 10-14 days from symptom onset, with negative test results suggesting PHGS and positive results RHS (Whitley, & Roizman, 2001).

Nevertheless, more than one episode of PHGS in patients infected with multiple HSV-1 strains could occur, since different HSV-1 strains within a single host have been occasionally detected (Lewis, Leung, Jeffrey, & Warren, 1984).

The hard palate and the upper attached gingiva are the preferential RHS sites and account for more than half intra-oral episodes (Eisen, 1998; Tovaru et al., 2011). RHS is twice as frequent on the keratinized mucosa, than on the non-keratinized mucosa (**Table 3**). Paradoxically, in the immunocompromised hosts, such as patients with leukemia and HIV infection, recrudescence occurs within keratinized and non-keratinized mucosa with the same probability (Friedman, 2006; Greenberg, Cohen, Boosz, & Friedman, 1987; Tilliss, & McDowell, 2002). This apparently puzzling phenomenon is not due to higher HSV-1 affinity for keratinized mucosa, as epithelial cells in a differentiated state are not permissive to HSV-1 internalization (Yura et al., 1987).

The explanation is different (Friedman, 2006). Indeed, HSV-1 anterograde transport occurs anywhere in the epithelia where there are free endings of the Trigeminal Nerve sensory axons, thus, reinfection occurs on both keratinized and non-keratinized oral mucosae. At the epithelial level, reinfection is responsible for inflammation with exudate production and consequent formation of several, small, and undetectable microvesicles, precursors of those described previously.

These microscopic microvesicles tend to grow due to exudate formation. Now, under the robust keratinized epithelium, they have the opportunity to overgrow without breaking. Overgrowth, in turn, produces the compression of the surrounding tissues and the sensory axon free endings, with consequent development of focal prodromal symptoms (paraesthesia, tenderness, pain, itching, burning, tingling sensations). This increase in size also promotes coalescence and microvesicles become clinically detectable. When the internal pressure overwhelms the resistance of the keratinized epithelia they break, thus alleviating the symptoms due to compression, while virions are shed and the subject becomes contagious. HSV-1 release induces the intervention of secretory IgA (ubiquitous on the mucosal surfaces and active against infectious and toxic agents thanks to the activation of Natural Killer T-cells) (Janeway, Travers, Walport, & Shlomchik, 2001; Mestecky, 1987), that prevents further lesion growth in the immunocompetent host. The situation is different in the fragile, non-keratinized epithelium. Indeed, the microscopic microvesicles break earlier before they can overgrow becoming

detectable, and often before the development of focal symptoms due to compression. HSV-1 virions are shed through broken microvesicles and subjects, even without symptoms, are contagious. Like in the keratinized epithelia, the intervention of secretory IgA in the immunocompetent host prevents further lesion growth. Secretory IgA cannot properly intervene in immunocompromised patients and the lesions have the opportunity to grow, thus explaining why in these patients clinically detectable recurrence occurs indifferently in keratinized and non-keratinized epithelia.

In summary, recurrence may occur everywhere in the area of the Trigeminal Nerve. However, asymptomatic carriers who shed HSV-1 are individuals who develop recurrence in non-keratinized epithelia, while symptomatic carriers are individuals who develop recurrence in keratinized tissues. This model can elegantly explain why –clinically detectable- recurrence is more frequent in the hard palate, and why there are many asymptomatic carriers at the same time.

This hypothesis is corroborated by the histological observation of intra-epidermal microvesicle overgrowth that is not found in non-keratinized mucosa (Friedman, 2006). Another indirect support to this hypothesis comes from the trials on the efficacy of HSV glycoprotein-D-subunit vaccine against genital HSV infections. Indeed, such vaccine did not prove effective in previously infected seropositive women, who kept on developing recurrent lesions on the keratinized mucosae where the virus could overgrow undisturbed by immunity effectors. Conversely, this vaccine proved effective against primary HSV infection that requires a contact of the host with a source of infection, but the mucosae of vagina, exocervix and medial aspect of the labia minora resulted protected by activated secretory IgA (Stanberry et al., 2002).

5 | Complications of recurrent oral HSV-1 infection

5.1 | Herpetic pneumonia

Herpetic pneumonia is uncommon and almost exclusively observed in immunocompromised hosts such as HIV positive, malnourished, leukemic individuals, bone marrow transplant recipients, subjects with extensive burns and those with severe pulmonary diseases. Occurrence in immunocompetent adults is rare (Libraty, Bocelli, & Fraire, 2013; Mills, Ratra, El-Bakush, Kambali, & Nugent, 2014; Reyes, & Bolden, 2009). The pathogenesis is associated to retrograde contiguous extension of oral primary or recurrent herpetic stomatitis or aspiration of HSV-1 viral particles

from oral and lip lesions (Reyes, & Bolden, 2009). This hypothesis is supported by the case of an immunocompetent man, cannabis user and infected with hepatitis C virus, with herpetic bronchiolitis and acute pneumonia, who showed evidence of a healed ulcer on the lateral side of his left upper lip (Libraty et al., 2013). Herpetic pneumonia can be serious, as it is often unrecognized, but once proper diagnosis and antiviral therapy are performed, remission of respiratory symptoms occurs (Libraty et al., 2013; Mills et al., 2014; Reyes, & Bolden, 2009).

5.2 | Herpetic esophagitis

The esophagus is the visceral organ most commonly involved in herpetic infection, with a prevalence of 1.8% among serial autopsy cases. This suggests that the burden of herpetic esophagitis is underestimated, as the diagnosis is probably limited to symptomatic and severe episodes. The typical lesions are similar to RHS, namely, small, single or multiple vesicles and ulcers that may be confluent into one lesion, that has the shape of a map (Itoh et al., 2003). Symptoms, such as odynophagia and retrosternal chest pain, typical of esophagitis occur in subjects with large lesions. Herpetic esophagitis in the immunocompetent host affects adults and adolescents. It is preceded by oro-labial recurrent HSV-1 infection in 25% cases. For this reason, herpetic esophagitis development is believed to be due to ingestion of viral particles from oro-labial lesions. Disruption of the integrity of the esophageal mucosa, due to gastroesophageal reflux or esophageal instrumentation, is necessary to promote HSV-1 infection (Canalejo Castrillero, García Durán, Cabello, & García Martínez, 2010).

5.3 | Erythema multiforme

Erythema multiforme is an acute, immune-mediated, muco-cutaneous condition caused by infectious agents, mainly HSV, and the use of certain medications. Erythema multiforme with cutaneous and mucosal involvement is called major, without mucosal involvement is called minor. Oral lesions are common and sometimes are the only lesions (mucosal erythema multiforme). Erythema multiforme is called recurrent if at least three episodes are reported annually (Sokumbi, & Wetter, 2012; Wetter, & Davis, 2010).

Oral lesions initially manifest with edema, erythema, and erythematous macules of the lips and labial mucosa, followed by the development of multiple vesicles and bullae that quickly

rupture and result in pseudomembrane formation. The lips tend to become swollen and show diagnostically distinctive bloody encrustations (Al-Johani, Fedele, & Porter, 2007; Celentano et al., 2015). Cutaneous lesions are typically target shaped with three concentric zones, the center disk is red and may show bullae as a sign of epidermal involvement (Lerch, Mainetti, Terziroli Beretta-Piccoli, & Harr, 2018), while the first ring is paler and consists of palpable edema (Al-Johani et al., 2007).

Erythema multiforme is often associated to HSV-1. Indeed, follow-up studies report that more than 60% erythema multiforme episodes are preceded by episodes of recurrent herpes labialis, while the anti-HSV-1 drug acyclovir is effective in the treatment of some cases of erythema multiforme maior and in the prevention of recurrences (Scully, & Bagan, 2008; Wetter, & Davis, 2010). In addition, HSV-DNA from lesional skin biopsies has been detected in 27% single and 60% recurrent episodes of erythema multiforme preceded by herpes labialis and in 25% single and 50% recurrent episodes of idiopathic erythema multiforme, not preceded by herpes labialis (Ng, Sun, Tan, & Tan, 2003). These data collectively suggest that oral HSV-1 infection could be responsible for recurrent erythema multiforme, mucosal erythema multiforme and erythema multiforme maior.

The pathogenesis of HSV-associated erythema multiforme is complex. In most patients with this condition viral fragments in the site of the lesion are detected and persistently present. This anomalous situation is due to defective CD34+ cells that are unable to eliminate HSV-1 particles after phagocytosis completely. Such abnormality, typical of individuals who develop erythema multiforme, does not occur in healthy subjects. These fragments are immunogenic and lead to the local intervention of the T-cell mediated immune response, that is ultimately responsible for the development and the severity of the lesion (Ono, Sharma, Smith, Burnett, & Aurelian, 2005).

5.4 | Periodontal disease and apical periodontitis

Several studies reported high prevalence and high copy counts of Cytomegalovirus, Epstein-Barr virus and HSV-1 in patients with aggressive (Alzahrani, 2017; Li et al., 2017) and, to a lesser extent, chronic (Zhu et al., 2015) periodontitis. Herpesviruses are not merely more frequent in saliva, periodontal pockets, biopsy tissue samples of periodontitis patients than in healthy individuals (Slots, 2015), but they are also more frequent in periodontal lesions than in clinically healthy sites

within periodontal patients. In addition, HSV-1 in periodontal pockets is associated to detection of periodontal pathogens, such as *Porphyromonas gingivalis*, *Tannerella forsythia*, *Fusobacterium periodonticum* (Passariello et al., 2017). HSV-1 microRNA (small, non-coding fragments of RNA that regulate viral and host gene expression) "miR-H1" is detected in periodontitis patients and undetected in healthy subjects (Naqvi et al., 2018).

Although these elements do not confirm a causative role of HSV-1 in periodontitis development, it has been suggested that periodontal pathogen bacteria alone cannot produce destructive periodontitis, while the interaction between these bacteria, herpesviruses, and chronic inflammation may lead to the development of aggressive periodontitis (Slots, & Slots, 2019).

Apical periodontitis occurs as a result of microbial, mechanical or chemical damage of the dental pulp, and can be acute or chronic, symptomatic or asymptomatic. Apical periodontitis may even be responsible for adverse pregnancy outcomes due to systemic inflammation (Harjunmaa et al., 2018). More than 400 different taxa have been detected in apical periodontitis lesions including bacteria, archaea, fungi, bacteriophages, and viruses. For the majority of them, however, their involvement in lesion development is unclear. Herpesviruses, particularly, Human Cytomegalovirus, and Epstein-Barr virus have been frequently detected in periapical lesions (Jakovljevic et al., 2018).

Well-designed observational studies to investigate an hypothetical etiologic role of HSV-1 in apical periodontitis are difficult to perform for technical and ethical issues. Indeed, in one half the studies on HSV-1 (reviewed by Hernández Vigueras et al., 2016), there are no controls. Nevertheless, according to Hernández Vigueras and colleagues, there were 16 HSV-1/HSV-2 positive samples from a total of 283 (HSV prevalence, 5.7%) in apical periodontitis and 2 positive samples from a total of 37 (HSV prevalence, 5.4%) in healthy tissues. These data do not seem to confirm a causal role of HSV-1 in apical periodontitis.

6 | Conclusions. HSV-1 between mutualism and parasitism

Despite recent changes in HSV-1 infection spread in western countries (Bradley, Markowitz, Gibson, McQuillan, 2014; Chaabane, Harfouche, Chemaitelly, Schwarzer, & Abu-Raddad, 2019; Miyachi, & Imafuku, 2017; Woestenberg et al., 2016), oral HSV-1 infection remains highly prevalent and is probably the most common human viral infection. This infection is characterized by continuous transitions between chronic-latent and acute-recurrent stages, giving the

microorganism the opportunity to evade immunity and warrant the transmission to other susceptible hosts at the same time. On the other hand, the damage to the host is minimal, excluding for neonates and immunocompromised individuals. Although data suggest that HSV-1 infection may protect against other pathogens, inflammation, allergy and even cancer, the discussion over the host benefits from oral chronic HSV-1 infection is open and is not an aim of this review.

Thus, the natural history of oral HSV-1 infection is also the history of unapparent transmission, asymptomatic primary and recurrent infections, non-immunogenic latency, recurrent infection development promoted by keratin, Nash equilibrium, contagious individuals who are HSV-1 seronegative, limited efficacy of anti-HSV vaccines (Rajčáni, Bánáti, Szenthe, & Szathmary, 2018). The so-called "war metaphor" (i.e., HSV-1 invades the host, the host mounts specific anti-HSV-1 defense, and the virus uses sophisticated means to evade host defense and install chronic infection) should be substituted with the evolutionary-ecological perspective that HSV-1 represents a co-evolved symbiont. Symbiosis connotes an intimate relationship between two species. Some symbiotic relationships provide benefits for both species and are called mutualistic, others provide benefit for just the microorganism and are called parasitic. Importantly, the HSV-1-human symbiotic relationship is not purely parasitic or mutualistic. Indeed, the natural history of oral HSV-1 infection is an history of a symbiosis that may switch from mutualism to parasitism and vice versa according to changes in developmental and environmental conditions (White et al., 2012). This balance between these two conditions is typical of pathogens that are highly co-evolved with humans (Artzy-Randrup, & Pascual, 2014) and its knowledge is essential to healthcare providers to perform adequate diagnosis and provide proper individual-based HSV-1 infection therapy.

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Table 1. Stressors responsible for oral HSV-1 infection reactivation.

Stressors investigated through in vitro and animal studies	
Withdrawal of trophic support to neurons	Heat shock
Mechanical traumatic injury to neurons	Local infections from alpha herpesviruses
Stressors investigated through clinical studies	
Ultraviolet light exposure	Fatigue
Emotional stress	Fever
Common cold and other viral infections	Menstruation
Oral trauma	Sideropenia
Iatrogenic stressors (surgery, epidural morphine, immunosuppressants, chemotherapy, etc.)	

Table 2. Incidence of various manifestations of oral HSV-1 reactivation according to different follow-up studies with different designs (study characteristics reported below). Recrudescence and false prodromal symptoms are expressed as number of events per person per year, asymptomatic infection as number of viral shedding days per person per year.

Study	Recrudescence*	False prodromal symptoms**	Asymptomatic infection
Kaufman et al., 2005	not reported	not reported	219.4
Knaup, Schünemann, & Wolff, 2000	1.6	not reported	26.5
Okinaga, 2000	0.4	not reported	1.9
Ramchandani et al., 2016	4.8	13.3	63.9
Spruance, 1984	9.3	1.8	14.4

*herpes labialis and/or recurrent herpetic stomatitis; **prodromal symptoms without lesions

Table 3. Distribution of Recurrent Herpetic Stomatitis oral sites (pooled estimate from Eisen, 1998 and Tovaru et al., 2011).

Site	Number of lesions	Relative frequency	95% confidence interval
Hard palate*	56	37.3%	24.7-50.0%
Maxillary attached gingiva*	31	20.7%	6.4-34.9%
Mandibular attached gingiva*	16	10.7%	<0.0-25.8%
Tongue (unspecified)	3	2.0%	<0.0-17.8%
Buccal mucosa**	17	11.3%	<0.0-26.4%
Soft palate**	20	13.3%	<0.0-28.2%
Alveolar mucosa**	7	4.7%	<0.0-20.3%

*keratinized mucosa and special mucosa; **non-keratinized mucosa

FIGURE 1 Overview of the natural history of oral Herpes Simplex Virus Type 1 infection in the immunocompetent host