An Updated Overview of Herpes Simplex Virus-1 Infection: Insights from Origin to Mitigation Measures

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Purpose: High prevalence of recurrent HSV-1 (Herpes Simplex Virus 1) and its facile mode of transmission requires an elaborated understanding of the virus for mollification. To mitigate its pervasive nature that greatly affects both men and women, a thorough understanding of the viral genome and epidemiology are prerequisites. The review focuses on the existing facts of HSV-1 and acknowledges the prospect of ongoing epidemiological studies.

Findings: Recent data indicates a surge of HSV-1 infection in the age ranged 30-50 years along with the emergence of neonatal cases. The newfound receptors indicate the effect and degree of susceptibility of the host and support the statistical data of HSV-1 seropositivity. Recent studies also show that the evolving virus has gained resistance against widely used antiviral drugs such as Acyclovir (ACV). Therefore, trials of several vaccines (eg. GEN-003 and HerpV) are garnering attention as a possible prevention method.

Summary: As most natural viruses are radically evolving, ensuing rather fatal consequences than previous wild types, every virus requires to be tackled with equal importance. Developing vaccines and potent drugs to eradicate viruses from infected subjects’ systems can be the only way to prevent future viral epidemics or pandemics. Therefore, early detection of the virus with accurate assay following immediate treatment can only prevent the cases from future catastrophe.

Keywords: herpes simplex virus, infection, neonatal HSV-1, pathogenesis, vaccine

INTRODUCTION

Herpes viruses are double-stranded DNA viruses belonging to the Herpesviridae family [1,2]. It consists of spiky enveloped particles (180 nm in diameter) and has a capsid (100-110 nm in diameter) oficosahedral shape which encompasses a large DNA of genome size around 152 kbp. Herpesviruses can be categorized into three subfamilies: alpha, beta, and gamma whereas the alphaherpesvirus subfamily comprises Herpes Simplex Virus-1(HSV-1) in humans [3-5]. The first form of the Herpes virus is responsible for the appearance of characteristic febrile vesicles which normally affect the facial skin, also called herpes simplex labial. *Herpes labialis*, commonly known as cold sores or fever blisters in the lip, is a common skin condition caused by Herpes Simplex Virus type 1 (HSV-1) [2,6]. HSV-1 is a recurrent virus that causes relapse in approximately one-third of all the infected patients [7,8] with mild morbidity, it can be harmful to it’s frequent and/or severe recurrence [9]. There is currently no cure for herpes labialis outbreaks [6,10]. The prevalence of herpes labialis is 2.5 per 1000 patients per year and its average incidence is 1.6 per 1000 patients per year [7,11]. Approximately 20–40% of adults are affected by HSV-1 at some point in their lives [6,12].

The mode of transmission of HSV-1 is by direct contact with body fluids. Also, if an individual comes in contact with the injuries of an infected person, the virus can be transmitted to that individual. Transmission can also take place even if symptoms are absent in an infected individual. It is predominantly transmitted by oral-to-oral contact that leads to oral herpes infection, employing contact with the HSV-1 virus in saliva, sores, and surfaces surrounding the mouth. Moreover, HSV-1 can be transmitted via sexual contact and genital herpes may also occur due to the transmission of HSV-1 by oral-genital contact [2,6]. Direct lytic infection or the reactivation of viruses inside latently infected neurons following by the transportation to the infected sites is the major phenomenon before bruise formation. Besides these conventional signs, HSV-1 can induce lesions at other regions, for example, on fingers (known as herpetic whitlow), at abrasion sites (called herpes gladiatorum), and on eyelids (also called herpes blepharitis). In addition to that, HSV-1 can cause inductive infections in the tissues of the cornea that leads to herpes keratitis and conclusively results in corneal scarring and vision impairment or blindness. The HSV-associated disease becomes malignant when the virus gets access to the central nervous system, which may result in herpes encephalitis [1,13,14]. This article provides a comprehensive overview of the
mutation and recombination history taking place in a period of
relation with the alphaherpesvirus subtypes HSV-1 and HSV-2 as
mammalian HSV-1 is related to genomic phenomena such as
that the patterned codivergence of the herpesvirus into HSV-1
primate family Cercopithecidae to the superfamily called
the analysis placed the ChHV in the same clade as the two
specification and codivergence, which may give rise to novel
possible resistant strain formation as a consequence. The
approximately a million years, during which period the current
recombinant or mutant strains of current HSV-1 strain and
form of a virus evolved to be able to infect humans, can link the
specific genomic causes of pathogenesis.

MODE OF TRANSMISSION

HSV-1 is a pervasive pathogen that is mostly restricted to
primates and prolonged infection. HSV-1 is a pervasive
pathogen that is mostly restricted to primates and well known
for its lifelong infection [2]. Generally, the transmission of HSV-1
occurs via the contact of an infected person to an uninfected
person [22]. The virus can be transmitted through physical
contact if exchange or exposure of saliva, oro-facial lesion,
mucous membrane, genital fluids occurs or if corneal
transplantation from an infected to healthy person occurs.
Moreover, Viral load is found maximum in fluids of oral labial or
genital lesions. Thus, the risk of transmitting the virus
increases if these fluids are exchanged [23]. Furthermore, the
transmission of the virus during childbirth generally happens
as the neonate is exposed to HSV-1 in the vaginal tract of an
infected mother, where the viral shedding is frequent in case of
genital herpes simplex virus infestation. The risk of
transmission is significantly greater in women, infected by HSV
during pregnancy than women who have longstanding
infections [24,25]. Besides, involvement in sexual contact with
the person of asymptomatic and symptomatic carriers may
lead to high-risk of infection [26].

The list of primates hosts the viruses are given in Table 1.
There are in total eight forms of herpes virus. Alpha herpes virus
shows a wide range of host diversity, showing latent infection
in most of the cases and exhibit less severity to its host [27].
Whereas, Herpes B virus, naturally occurring host is Asian
Monkeys of genus MACACA. Which generally, don't infect the
human primates, seen to be infected with HVP-2, MHV-1, HVA-
1 occurs via the contact of an infected person to an uninfected
person and exchange of viral load [22]. The virus can be transmitted through physical
contact if exchange or exposure of saliva, oro-facial lesion,
mucous membrane, genital fluids occurs or if corneal
transplantation from an infected to healthy person occurs.

The prospect of understanding the evolutionary history of
mammalian HSV-1 is related to genomic phenomena such as
specification and codivergence, which may give rise to novel
recombinant or mutant strains of current HSV-1 strain and
possible resistant strain formation as a consequence. The
mutation and recombination history taking place in a period of
approximately a million years, during which period the current
origin, hosts, pathogenesis, sign and symptoms, diagnosis
methods, and mitigation measures about the HSV-1 infection.
The scientific essence of this study contribute to understand
the modes of HSV-1 infection, its management, treatment, and
preventive measures and to uphold the research efforts on this
virus.

EVOLUTIONARY DATA ON HSV-1

The herpesvirus has evolved alongside the evolution of
humans and its primate ancestors, co-diverging from the older
ancestors to the newer ones throughout the millions of years of
primate speciation. Among all the strains of alphaherpesvirus,
HSV-1 has supposedly co-speciated with its primate hosts by
creating viral duplications among the different species and
transmitting the viral DNA among its descendants [15, 16]. The
analysis based on the molecular clock of primates suggests that the patterned codivergence of the herpesvirus into HSV-1
has occurred through human ancestors such as the largest
primate family Cercopithecidae to the superfamily called
Ceboidea [17]. As the genera Homo and Pan are proved to have
developed through speciation process occurring approximately
more than 6 million years ago, one of the mammalian herpesvirus called ChHV found in chimpanzee (Pan troglodytes) and the human simplex virus or HSV are
linked through host-virus codivergence due to the close
relation between ChHV, HSV-2 and HSV-1 [17,18,19]. The
phylogenetic analysis of ChHV via ELISA confirmed its close
relation with the alphaherpesvirus subtypes HSV1 and HSV2 as
the analysis placed the ChHV in the same clade as the two
human simplex virus types [20]. By conducting MUSCLE v2.0 on the
ChHV and HSV-1 genomes’ 12 conserved regions, the HSV-1
is indicated to have codiverged from the ChHV approximately
6 million years ago [17] (Figure 1). Furthermore, an analysis
based on molecular dating and phylogenesis was conducted
the most conserved region of HSV-1 (US7 and USB of the HSV1
genome) of the strains having least number of recombinations
among their genomes which showed the most recent common
ancestors to have developed approximately 710,000 years ago,
indicating the viral-host divergence phenomenon of HSV-1
[21]. This phenomenon indicates that the herpes simplex virus
has evolved itself from its ancestral strains to infect its hosts
which had evolved from the previous older and new world
monkeys to become a much more complex homo species.

The prospect of understanding the evolutionary history of
mammalian HSV-1 is related to genomic phenomena such as
specification and codivergence, which may give rise to novel
recombinant or mutant strains of current HSV-1 strain and
possible resistant strain formation as a consequence. The
mutation and recombination history taking place in a period of
approximately a million years, during which period the current

![Genomic Organization of Herpes Simpex Type 1 virus](image)

**Figure 1.** Genomic organization of the HSV-1. The genome is around 152 kbp in length containing two terminal regions in both ends, two internal regions and two unique regions.
maintain during childbirth of an HSV infected mother to have the neonates safe.

**PATHOGENESIS OF HSV-1 INFECTION**

HSV1 can carry out lytic (or primary) as well as latent infections [41-43]. The oral mucosa contains epithelial cells where lytic infections usually occur and subsequently lead to cold sores and lesions. The primary infection site is predominantly the oral mucosa whereas genital mucosa can rarely be infected as well. Not only that, but the other epithelial zones at the periphery are also jeopardized by this infection. Patients with no existing antibodies to HSV-1 are the victim of the primary infection. The mucosa or abraded skin must come in direct contact with the virus for the occurrence of the infection. Thus, sexual contact is considered as a route of transmission in young people [41,44,45]. If a child comes in contact with primary exposure to HSV-1 and gets infected, it may cause a clinical symptom called acute herpetic gingivostomatitis after 5–10 days of the infection. On the contrary, as the consequence of the primary infections in adults, pharyngitis skin may be produced as well as a mononucleosis-like syndrome that may occur that includes blisters and raw throats. The viral envelope interacts with a host cell membrane through the receptor-mediated fusion. Envelope protein is a structural protein that facilitates the fusion of the virus inside the host cell (Figure 2) The envelope of HSV-1 contains glycoprotein gD that must bind to any of its receptors to ensure the entry inside the cell [45,46].

“Herpesvirus entry mediator” (HVEM) and nectin-1 are the two well-identified receptors for HSV-1 by which the host cell membrane is fused with the viroid envelope. Hence the infectious cycle of HSV-1 is commenced. Adequate numbers of glycoproteins (gD, gB, and the heterodimeric complex gH/gL) in the envelope of HSV-1 are required for this intricate process called fusion [46-48]. Fusion is followed by the release of viral capsid into the cytoplasm. Once discharged into the cytoplasm, viral capsids are imported along with the microtubules towards the microtubule-organizing center (MTOC) and hence to the nuclear envelope. After the association of the capsids with nuclear pores, the viral genome becomes uncoated which penetrates the nucleoplasm via the nuclear pore. Later on, the lytic replication takes place and thus primary infection occurs that results in some ordinary symptoms including blisters or oral sores. But, the primary infection may also be asymptomatic that leads the virus to the latency phase [49].

The virus moves towards the sensory ganglion, dorsal root ganglia (DRG) innervating the primary lesion, migrating forward to latent infection, and becomes inactive or dormant [14,50-52]. During latent infection, virus particles get entry to the neuronal axons and move to neuronal nuclei of the cell body in the tri-germinal ganglion, the place where the viral genome, as an extra-chromosomal element, is integrated into a repressed chromatin structure. Although tens to hundreds of viral genomes may take place in the individual latently infected neurons, the viral genes of the lytic cycle remain unexpressed. The majority of the genome undergoes silent transcription apart from the latency-associated transcripts or LATs.

| Virus Abbreviation | Virus Abbreviation | Host Latin Name | Host common name | References |
|--------------------|--------------------|----------------|-----------------|------------|
| Chimpanzee herpes virus | ChHV | Pan troglodytes | Chimpanzee | [31] |
| Baboon herpesvirus 2 | HVP-2 | Papio spp. | Baboons | [32] |
| Cercopithecus herpesvirus 2 | CheV-2 | Chlorocebus pygerythrus | African green monkey | [33] |
| Macacine herpes virus 1 | MHV-1 | Macaca spp. | Macaques | [34] |
| Saimiriine herpes virus | HVS-1 | Saimin sciureus | Squirrel monkey | [35] |
| Langur herpesvirus | HVL | Semnopithecus | Langur | [36] |
| Herpes simplex virus 1 | HSV-1 | Homo sapiens | Human | [37] |
| Herpes simplex virus 2 | HSV-2 | H. sapiens | Human | [38] |
| Spider monkey herpes virus | HVA-1 | Ateles geoffroyi | Spider monkey | [39] |

Table 1. List of primates prone to HSV-1 pathogen and transmission

Figure 2. Structure of the HSV-1. HSV-1 includes lipid envelope surrounded by the envelope proteins. It contains viral genome occupied inside the nucleocapsid. The figure was created in BioRender.com and exported under the terms of premium subscription.
Consequently, no or very few replications of viral DNA occurs. During this period, HSV-1 outsmarts the human immune system via several mechanisms. One of them is the induction of an intercellular accumulation of CD1d molecules in antigen-presenting cells. Hence, latently infected neurons are maintained for a long period and as the virus cannot be evacuated, the infected individuals bear the virus for life. Neurons containing the latent HSV-1 genomes are concentrated in the trigeminal ganglion because these predominantly innervate epithelial cells of the oral region. The virus may reactivate when people undergo certain stresses. This is also called recurrence which is triggered by genotoxic stress, fever, certain illness, ultraviolet light exposure, fatigue, hormonal imbalance (e.g. during menstruation), immune depression, and mental shock to a site or a nerve region where earlier HSV infection took place [14,41,49,53].

After the stimulation of reactivation, the early genes (α or β) of HSV-1, are expressed. At first, the replication process initiates in the neuron; it then advances from the neuron to the authentic site of infection in the oral epithelial cell nucleus. Thus the same process as the lytic infection is reiterated in the oral epithelium that results in oral lesions and other symptoms [14,41,54]. Mostly, DNA replication takes place in viral replication compartments that are located in the nucleus. The first step in this event is assumed to be the cooperation between the viral transcription factor, Infected-cell polypeptide 4 (ICP4) with parental viral genomes [55] (Figure 3).

Recurrent viruses like HSV-1 undergo quite a strategic manner during infection. Therefore, further study on the pathogenesis of the virus should be conducted later on to determine every possible way to prohibit the virus could be understood more precisely. Moreover, it is undoubtedly momentous to understand the process in which the virus lingers in the body life-long for generating more potential treatment strategies to combat the viral infection.

**SYMPTOMS AND CLINICAL DELINEATIONS**

Primary infection of HSV-1 usually spreads in the system of the host without showing visible symptoms. But when the immune system initiates suppression of the virus, the symptoms vary from children to adults e.g. formation of blisters around lips or fever usually occurs among children whereas adults may have sore throats or swelling of cervical lymph node [55,56]. Symptoms may cling to the patients for up to a couple of weeks and change form through a range of phases. Initially, itching and the inflammation occur at the site of infection which may wind up the formation of blisters or mini-papules around the site of infection [57]. Subsequently, the mini-papules fuse and for the larger blister which is highly itchy and aching either. Thereafter, renewal of the skin takes place beneath the scrabies that result in the formation of Meier complex later on which feels pain and highly itchy as well [58].

Recurrent viruses are sometimes highly critical to be observed because, they can be asymptomatic for weeks to
HSV interacts with both TLR-2 and TLR-9. Interaction with TLR occurs on the surface. Whereas interaction with TLR-mediator in creating innate immunity against this virus [64]. In production [66].

The role of interferon (IFN-alpha and beta) in reducing the viral load of IFN-α, β, γ does play a role in the initial response of the body against HSV [61-63]. The DCs [65]. However, this interaction stimulates the production there [60].

Herpes simplex virus causes a variety of illnesses depending on the pathway it enters and the host it’s infecting. HSV-1 usually infects the system of a possible host when body-fluids containing viral load enters through the damage of the skin/mucosa layer, genital tract, and mouth cavity. Then it enters the sensory neuron transport to the dorsal root ganglion by retrograde axonal transport. It develops lifelong latency there [60].

Interferon, macrophages, NK cells, and γδ T cells plays vital role in the initial response of the body against HSV [61-63]. The role of interferon (IFN-alpha and beta) in reducing the viral load and protection against HSV has been revealed in murine models. However, toll-like receptors (TLRs) are an important mediator in creating innate immunity against this virus [64]. In general, HSV interacts with both TLR-2 and TLR-9. Interaction with TLR occurs on the surface. Whereas interaction with TLR-9 occurs within endosome and particularly of Plasmacytoid DCs [65]. However, this interaction stimulates the production of IFN-α, as plasmacytoid DCs are the main effectors of IFN-α production [66].

Besides, the immune system of the body must need to maintain the latency and inhibit the reactivation of the virus. In that case, non-cytolytic CD8+ T cells play crucial rules in producing INF-γ. These non-cytolytic CD8+ T cells are specific for HSV structural protein and lie in the apposition to neurons. A recent study on the mice model, by knocking out INF-γ or addition of INF-γ revealed the role of non-cytolytic CD8+ T cells in controlling the viral latency period possibly by inhibiting early viral protein ICP0 with the help of CD4+ T cells [67].

In the case of infected epithelium cell, CD4+ T cells secrete IFN-γ which restores the major histocompatibility complex (MHC) class I protein expression, thus overcoming the induced blockage of expression of MHC-I by HSV ICP47 and allowing recognition with CD8+ cytotoxic T cells [68, 69]. Throughout the lesion, INF-γ stimulates MHC class II expression in keratinocytes to recognize by CD4+ T cell. Production of β-Chemokines, IL-12 and IFN-α, -β, -γ from hepatic lesion epithelial cell and immune cell play a crucial role in controlling this cytopathic virus [70, 71]. β-Chemokines attract monocyte and T cell into the area of the lesion, IL-12 stimulates the secretion of CD4+ in a Th1 pattern which plays a role in activating cytotoxic T cells. Then, CD8+ cytotoxic T cells correspond started to clear the virus from the lesion [72, 73] (Figure 4).

When our body cannot defend this virus, symptoms are shown up and infection occurs. That’s why much more research needed in this field to explore the mechanism of our body’s immune system against this virus to get a clear understanding and accelerate the process of vaccine and antiviral drug development.

**GLOBAL SCENARIO OF HSV-1 PREVALENCE**

**Europe**

In a serological study conducted in two universities located in Germany and Spain, students (age range between 17-41) were tested for HSV-1 and oral lesions caused by the virus while considering the risk factors like alcohol consumption, coital...
activity, hygiene, etc [74,76]. In Navarra Public University, Spain 596 students were observed and from University of Bielefeld, Germany 174 students were selected for the assay. Although the sample size differs in the sites, the manifestation result and risk factors were the same for both of them. 55.3% of the entire sample population tested positive for HSV1 among whom 27.4% had oral lesions in the 12 months during or before the experiment timeline. As for the risk factor for students who were engaged in unsafe coitus, 95% (OR= 1.88, CI: 1.31-2.69) were prone to contracting the virus. Another study supports this fact as it showed that healthy lifestyle aimed to manage hygiene and specific gender behaviors prevents sexually transmitted diseases (STDs) by 18.2% in a sample size of 650 students of German universities [76].

The high prevalence of HSV1 in the french population was proved by a study with significance (p<0.001) and 67% positive result for HSV-1 which was conducted on a sample of 4412 subjects (female 66.5%, males 33.5%) [77,78]. Indicating that two-thirds of the population was affected by HSV. The study was by an epidemiological inquiry titled HERPIMAX which was a cohort study associated with SU.VI.MAX [79-81]. Higher seroprevalence was observed among aged groups female however no significant age disparity was observed among men.

North America

The prevalence in neonates aged two months or lower at the time of experiment in Canada during the period October, 2000 to September, 2003, was reported to be 5.9 per 100,000 live births and among the test subjects, 62.5% tested positive for HSV-1 [75]. Among the total case, 28.1% was born prematurely and 24.6% of the live birth was conducted via cesarean. 51.7% of the neonates were female and 48.3 of the subjects were male. Another comparison study conducted on genital isolates obtained from the United States tested positive for HSV-1 in 2001, however during 1993 it accounted for 31% [80,82,83]. A nationwide study done in the United States showed a demographic, racial, and gender-based comparison statistical analysis of HSV-1 positive people. The highest rate of prevalence was in the 40-49 years age range with 59.7% which is almost twice the population aged 14-19 years as the latter group tested positive for only 27.0%. Females tested positive more than males as the former group is 50.9% [84] and the latter 45.2% [85]. Also, seroprevalence for HSV-1 was 53.9% during 2005-2010 in the United States and among both men and women the rate of infection deline in a continuous manner over the course of two decades [86,87]. This gradual infection rate decrease (men= 2.84% & women= 2.2%) is a significant indicator of the improvement of hygiene practice in the population that lowered the transmission of HSV-1 [87].

Asia

In a prospective study conducted via ELISA using gG1 and gG2 type-specific antigens for samples collected from 463 Bangladeshi female sex workers showed 87.5% were seropositive for HSV-1 [88]. In an integrated study conducted on samples collected from India, Estonia, Morocco, Brazil, and Sri Lanka. The data of India and Sri Laka indicated that the seropositivity for HSV-1 was proportionally linked with the age of the subjects. 31.4% of the sample from children above or equal to 1 year tested positive for HSV-1 on another hand people aging 45 years and above had 95.5% seropositivity for HSV-1. In the same study, 82% of the isolates obtained from 45year or above people tested positive for HSV-1 [89]. Women from Osaka were more prone (88%) to the infection than
Table 3. The identification methods of HSV-1 antibody from serum samples

| Method name       | Commonly used commercial kit                  | Type of sample for test | Mechanism                                                                 | Result output method                                                                 | Reference |
|-------------------|-----------------------------------------------|-------------------------|---------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-----------|
| Western blotting  | Euroimmun made Euromimmun Anti-HSV-1/HSV-2  | Blood serum             | The strips of the kit contain pure protein and antigenic mixtures such as | The binding percentage depicts antibody seroprevalence. The strips are evaluated and interpreted via a scanner comprising | [21, 34, 40, 106, 107] |
|                   | Euroimmun WB (IgM/IgG)                        |                         | as gG-1 for HSV-1 (that is electrophoretically separated), the antigen binds with the HSV-1 antibody | University of Washington’s WB result to measure specificity, sensitivity positive predictive value. SPSS was used to define behavioral and demographic frequency. |           |
| Immunodot enzyme assay | HerpeSelect HSV-2 ELISA IgG or HerpeSelect HSV-1 ELISA IgG (Conventional) | Blood serum             | Purified gG1 antigen located in the kit identifies and binds with the antibody of HSV-1 present in serum or saliva sample | The ELISA result output was analyzed by setting the reference standard as the University of Washington’s WB result to measure specificity, sensitivity positive predictive value. SPSS was used to define behavioral and demographic frequency. | [21, 34, 36, 108, 109] |
| PCR, RT-PCR       | Conventional PCR machine, Real Time PCR machine | Periodontal, cutaneous source, mucocutaneous source, corneal impression membrane | The amplifying primers were designed to be specific for the thymidine kinase gene region of the HSV-1 | The PCR procedure was conducted via the general method. The statistical analysis was performed via a statistical package made for windows named Statistical package for social science (SPSS) | [44, 110] |

Pregnant women from Tokyo, whose population accounted for 50%. In the diverse demographic group seroprevalence for HSV1 increased steadily with age and relatively higher than HSV2 [90,91]. In Eastern China women were more prone to HSV1 (94.2%) than males (89.1%) shown in a study conducted on 2141 samples. In the overall tested population, 92.0% HSV-1 seroprevalence was present, which was linked to increasing age as well [92]. From a more recent study conducted in the last decade, it was evident that HSV-1 prevalence varies in age group as both males and females of the infected population were among the 20-39 age group (men=68.2% & women=72.6%), and infected individuals from older age group were lesser [92,93]. Similar studies from middle east supports the fact that seroprevalence for HSV-1 is linked with increasing age as samples from children under age 10 was lowest at 60.5%, however highest in people over or equal to 30 years (94.3%) [94, 95].

In retrospect, several woman-oriented studies were done in Bangladesh to observe the HSV-1 prevalence. In one study conducted from 2006 to 2007, 111 pregnant women were tested for the seroprevalence of HSV-1 along with a group of infectious diseases abbreviated as TORCH (Toxoplasmagondii, Rubella, Cytomegalovirus, HSV-1 & 2). 90.09 % samples showed HSV-1 antibody presence after being processed by immunoglobulin G (IgG) specific ELISA [96]. In 2002, a study focused on the underprivileged sex workers from Dhaka and the severity of HSV-1 among the demographics. In 1879 women who visited a local healthcare system in Dhaka were tested for multiple sexually transmitted diseases. Among them, 97% of the tested subjects tested positive for HSV-1 antibody without further observation [97].

Africa

In Egypt a total of 98% males aged from 30 to 39 and 100% males aging 45-49 years were tested positive for HSV-1 [98]. In another study seroprevalence for HSV1 was 98.8% Moroccan pregnant women [99]. Also, it was reported that the HSV-1 was more prevalent in the older population than younger [100].

South America

In Natal, Brazil 261 women were tested in a cross-sectional study between January 2000 and December 2003 in a cross-sectional study which showed a higher prevalence of HSV-1 than HSV-2 along with a link of HSV-1 infection rate with age. About 80% women above 30 years of age tested positive for HSV1 whereas 72% women tested positive who were less sexually active and above 50 years [101] Supporting evidence of the higher prevalence in Brazil was found as 83.5% and 63.4% were found positive in HSV-1 and HSV-2 respectively. [102].

Australia

A nationwide study in 1999-2000, which showed 76% of the population carrying HSV1 that differed based on age, race, gender [103] Another study indicated the increasing seroprevalence of HSV-1 as in a study combining 25,372 subjects during 1980 and 2003, 15.8% of tested patients were found positive for HSV-1 in 1980, however, 34.9% were positive in 2003 [104]. Meanwhile in a recent, HSV-1 infection prevalence seems to be higher in female population as a 16% increaseal has occured in 2017 compared to the 45% female HSV-1 patients observed in the 2004 data obtained from Melbourne Sexual Health Center, Australia [105].

DIAGNOSIS METHODS OF HSV-1 INFECTION

Identification of the pathogen is vital to initiate treatment procedures as well as for the containment of the virus. Every step of the procedure, from the point of collecting the specimen from a suspected patient to the point of molecular identification of viral DNA in the sample, is essential to prove a medical prognosis when it comes to HSV-1 patients. Using validated commercial kits to conduct molecular identification is a widespread practice around the world. A list of the methods used in previous researches shows that the viral protein structure is the target of most diagnostic medical laboratory kits.

The objective of a comparative review of the listed methods is to help researchers understand the degree of efficiency of each testing method and kits along with probable optimization options regarding sample collection and processing via the test kits.
CONVENTIONAL TREATMENT METHODS

As a persistent virus, HSV-1 causes lifetime latency in the host and recurrent labial ulcer lesions occur whenever the virus is reactivated by several factors (eg. radiation, stress, etc). The virus cannot be cured, however proper treatments can lower the degree of the labial lesion and oral infection caused by the viral population. The approaches for preventive measures are aimed to suppress the viral DNA replication either by the admission of nucleoside analogs (eg. Acyclovir or ACV, Acyclovir monophosphate, Acyclovir triphosphate valacyclovir, penciclovir) or helicase primase inhibitors (eg. Amenamevir. Pritelivir) [111-113]. The guanosine analog ACV is phosphorylated when the β gene of HSV synthesizes thymidine kinase and the activation of the topical drug leads to viral replication suppression [114]. Although reduction of the lesion was successfully done by ACV, its limitations are eradicated by prodrugs like valacyclovir and penciclovir. The latter has longer intracellular half-life post phosphorylation by thymidine kinase [113,115]. In contrast, valacyclovir can be used as a short term remedy for the genital lesion caused by HSV-1 [112,116]. After long term application of the acyclovir (ACV) topical ointment, the HSV-1 may show some degrees of resistance or give rise to resistant strain [117, 118]. To remedy this problem, the activity of 6-(2-hydroxy-3-hydroxymethyl but-1-yl) guanine otherwise known as BRL against HSV-1 can be utilized that show thymidine kinase activity in few of its mutant form that shows resistance against ACV [118]. Natural resources have also been explored to find a possible treatment by external application such as the Howyttuyna cordata containing anti-inflammatory activity [119-121]. Despite relieving irritation and degree of the lesion the natural resources show little replication inhibitory activities.

In the past decade, anti-viral vaccine development has been the focus of the preventive measure against HSV as the virus cannot be terminated once acquired and let to replicate inside the human system.

PROGRESSES IN HSV-1 VACCINE DEVELOPMENT

The vaccine is an acquired immunity stimulatory substance which is usually developed to make the physiological system ready to fight against one or multiple diseases. This may contain a weaker form of the causative disease agent, its constituent, mutant form its protein product, etc. Vaccines are usually developed for two purposes. One is for prevention and another one is for treatment. A preventive vaccine, in the case of HSV-1, generally produces a high rate of the immune response against HSV-1 before get infected and creates high immunity to prevent secondary infection at high-risk populations. Whereas, Therapeutic vaccine for HSV-1, injected into a seropositive person who is infected by this virus before. This vaccine reduces the severity of disease and creates immunity against this pathogen [122].

Many vaccine candidates with a diverse platform have been studied in the preclinical phase, some of them are tested in clinical trials and early developmental stages with the financial help of government, Academic, Biotech institutions and several pharmaceutical companies are also seen to invest on it.

The most widely used vaccine for the human clinical trial is the Glycoprotein subunit vaccine, which is produced by mutating gD gene at amino acid residues 3 and 38 by altering alanine with cysteine and tyrosine with cysteine. This impaired mutant vaccine can’t get entry and create a huge immune response. Thus it is a novel candidate attenuated live HSV-1 vaccine [123]. The largest clinical trial occurs the subunit vaccine Herpevac in seronegative women which contain glycoprotein-2 (gD2) with alum/MPL adjuvant [Table 4] [124].

HSV529 a replication-defective, live attenuated virus deleted in gD2 enters into the Phase I trial for both preventive and therapeutic indications. It is the first developed virus to eliminate latency from the dorsal root ganglia [131]. Some vaccine candidates have entered into phase I/II trial within few years [Table 4]. These candidates have a novel stimulatory effect on T cell immunity. The GEN-003 which is a gD2/ICP4 protein subunit-containing vaccine with adjuvant of Matrix M has shown to 50% decline in Genital HSV shedding in primary trial results [127]. However novel delivery methods for glycoprotein D and intranasal delivery methods are being explored. Besides glycoprotein candidates with unique features are still being investigated. For instance, the trivalent vaccine containing gD/gC/gE glycoprotein in promising in mice [132]. There is also some latest work are performing in the field of vaccine development. To inhibit the corneal blindness, a prophylactic live attenuated vaccine is developed which successfully able to protect the ocular HSV-1 challenged in mice. This vaccine involved a T-dependent hormonal immune response and complement C3. Most importantly it works without doing any harm to eye [142]. Besides, a trial was conducted to analyze the efficacy of the Glycoprotein D dependent HSV vaccine and it was found that it shows 73% and 74% efficacy in women. But in the case of men, it shows no effect [143]. Again, to control HSV, a mutant virus was created where the glycoprotein H (gH) gene was deleted. As a result, the virus cannot perform a multi-cell cycle. It just able to continue one cycle and after that, it will disable. After insertion in the guinea pig, it was seen to increase the high degree of prevention against HSV-2, genital herpes, and observed to significantly reduce the recurrent infections [144]. Moreover, A improved recombinant strain is produced, CJ83193-like recombinant CJ9-gD, which has the deletions of an essential gene and contains an extra copy of the gene responsible for encoding glycoprotein D (gD). Mice immunized with CJ9-gD produce 3.5 fold higher HSV-1 neutralizing antibody and produce a strong HSV-1 T cell response and 80% reduction of the latent infection by HSV-1 wild type strain [145]. Lastly, a mammalian cell line constructed which secreted a soluble gH-gL complex, consisting of gH truncated at amino acid 792 and the full length of gL. To test its potentiality as a subunit vaccine, BALB/c mice were immunized with the complex, and the result was observed that the mice model shows a high level of virus-neutralizing activity, reduced primary lesions and show no secondary zosteriform lesions [146].

As evident in the global prevalence article of the review, more than one-third of the world’s population shows some degree of HSV-1 symptoms. Meaning that the possible carriers of the recurrent virus which will have until decease and will be able to transmit it to a non-healthy person. The current treatment methods are neither able to inhibit the recurrence of the pathogenic actions of HSV-1 nor they can ensure complete inhibition when a non-infected person is exposed to the virus. HSV-1 poses are fatal pathogens when it creates major organ-
related complications therefore immunity against it via vaccination will be vital to control it and lower the range of transmission. Such a vaccine can annihilate the virus to some degree in the same manner as Poliovirus has been suppressed in the last century.

CURRENT STATUS AND FUTURE PROSPECTS OF HSV-1 RESEARCH

According to the World Health Organization, about 417 million people in the world age ranging from 15-49 are affected by HSV-1 [147]. In most cases, people affected by it without showing any symptoms. Sometimes it may cause many acute complications such as corneal keratitis, nerve damage & may lead to azimuthal disease [148]. Researchers are working hard to find out the solutions of HSV-1. A good deal of researches is conducting with the funding of government, non-government research institutes, renowned universities, different pharmaceuticals and vaccine developing companies, etc.

Nowadays, scientists are working hard to discover effective anti-viral agents against HSV-1. As of this investigation, bioactive materials extracted by enzyme assisted hydrolysis from C. crispus (multiaxial filamentous tissue) and C. fragile (coenocytic tissue) exhibits anti-viral activity without creating any kind of cytotoxicity [149]. Besides, Chlorogenic acid (CGA) is found to obstruct the inflammatory reaction that occurs in HSV by suppressing Toll-like receptor (TLR)-2 & TLR9-Myd88 signaling pathways [150]. Moreover, the Researcher’s found geopropolis from Scaptotrigona postica as an anti-viral agent against HSV [151]. Furthermore, another group of scientists found Polyphenol rich extract, from natural shelled (NPRE) pistachios kernels (Pistacia vera L.) which have a remarkable inhibitory activity against HSV-1 [152]. Also, Arisaema tortuosum extracts Apigenin and luteolin demonstrate antiviral activity and successfully able to reduce virus progeny. Further, a compound name apigenin is found to create obstacles in the activity and successfully able to reduce virus progeny. Further, a compound name apigenin is found to create obstacles in the activity and successfully able to reduce virus progeny.

Table 4. All possible kinds of vaccines for HSV-1 that are under development and research in pre-clinical and post clinical trials. Here, X sign states on which phase the vaccine is now on; X(T), X(P), and X(P & T) sign refers to either the vaccine is therapeutic types, preventive types, or both respectively; POC refers as Proof of Concept Trial.

| Candidate name or Identifier | Institutions/ Company | Platforms /Antigens | Pre-clinical | Phase I | Phase II | Phase III | References |
|------------------------------|-----------------------|---------------------|--------------|---------|---------|-----------|------------|
| GEN-003 (gD2/ICP4/MM adjuvant) | Genocea Biosciences | Subunit vaccine: gD2/ICP4 with Matrix M2 adjuvant | X(T) | X | [125, 126, 127] |
| HerpV | Agenus | 32-mer peptides, complexed with HSP, QS-21 Adjuvant | X(T) | [128] |
| Codon optimized polynucleotide vaccine | Admedus | DNA vaccine-gD2 codon optimized/ubiquitin-tagged | X(T) | [129] |
| VCL-HB01/HM01 | Vical | DNA vaccine: gD2+-/UL46/Vaxfectin | X (T) | [130] |
| HSV529 | Sanofi | Replication-defective HSV-2 with deletions of UL5 and UL29 | X (P&T) | [131] |
| gD2/gC2/gE2 | Perelman School of Medicine at the University of Pennsylvania | Subunit vaccine: gD2/gC2/gE2 | X | [132] |
| HSV-2 2ΔNLS | Rational Vaccines | Live, attenuated replication-competent HSV-2 with deletion of ICP0 | X | [133] |
| HF10 | | Live, attenuated replication-competent HSV-1 mutated for UL43, UL49.5, UL55, UL56, LAT | X | [134] |
| ΔgD2 | Albert Einstein College of Medicine | Live, attenuated HSV-2 deleted in gD2 | X | [135] |
| AD472 | Medimmune | HSV-2 mutated for g34.5, UL43.5, UL55-56, US10, US11, US12 | X | [136] |
| CJ2-gD2 | | Non-replicating gD2 dominant neg HSV-2 | X | [137] |
| Prime-pull strategy | | “Prime” with live attenuated HSV-2 followed by “pull” with topical intravaginal CXCL9/CXCL10 chemokine | X | [138] |
| Inactivated HSV-2 in MPL/alum | Spector, University of California San Diego | with topical intravaginal CXCL9/CXCL10 chemokine Formalin inactivated HSV-2 | X | [139] |
| HSV-1 glycoprotein B lentiviral vector | | Lentiviral vector expressing gB1 | X | [140] |
| gB1s-NISV | | Intranasal non-ionic surfactant vesicles containing recombinant HSV-1 gB | X | [141] |
The development of advanced-level sequencing technique by 4sU tagging could lead to analyze real-time changes in RNA synthesis, processing, and translation at transcriptome level and could explore what type of changes occurring when a cell is infected by pathogens like HSV-1 [157]. Besides, an investigation found that HSV-1 & HSV-2 exhibit species specific modulation in programmed necrosis with the help of Viral Ribonucleotide Reductase Large Subunit RI. In mouse cell, it is found to directly activating programmed necrosis where as in human, it is blocked TNF (Tumor necrosis factor) induced necrosis by obstructing the induction of receptor interacting protein kinase-1 (RIP1) / receptor interacting protein kinase-3 (RIP3) necroosome [158].

CONCLUSION

HSV-1 continues to spread among different risk groups and possesses major threat to the global population. So far, proper hygiene, social ethical values and religious practices appear to be the most effective strategies to reduce the transmission of HSV-1. However, no approved licensed vaccines are currently available in the market to counter the HSV-1 infection and spread. Therefore, researchers are working hard to find out clinical solutions for HSV-1. Extensive epidemiological and genomic studies are also required to accelerate the process of vaccine development. Better further understanding of the pathogenesis with combining existing information and initiating further experiments can aid the chances of obtaining antiviral drugs with high efficacy to treat the infected patients. As a result, further researches and specific trials are warranted to combat worldwide HSV-1 infection.

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