DISCLAIMER: Rational Vaccines (RVx) does not advocate any specific course of action in the management of herpetic disease. Doctors are individually responsible for how they choose to use the information provided herein.

OVERVIEW: The Chief Science Officer of RVx, William P. Halford, has been studying the latency-replication balance of herpes simplex virus since 1991 (see Dr. Halford’s Biosketch). This document summarizes two areas of knowledge that may help doctors appreciate the concerns of herpes patients and understand present and future options for managing herpes patients:

1. The Relationship between Latent HSV Infections and Genital Herpes Disease.

OTHER RESOURCES:
- Warren, 2009. The Good News About the Bad News of Herpes: Everything You Need to Know
- RVx’s Accurate Info for Patients document, which reviews the biology of HSV infections

1. The Relationship between Latent HSV Infections and Genital Herpes Symptoms

- Over 3 billion people are infected with HSV-1, and HSV-1 is the predominant cause of genital herpes in younger age groups. Although many doctors are taught that HSV-2 is the primary cause of recurrent genital herpes, the evidence to support this supposition is limited at best. The literature of the past decade indicates that, in the 21st century, HSV-1 and HSV-2 are both significant causes of genital herpes.
- The most obvious functional difference between HSV-1 and HSV-2 is that (1) HSV-2 kills host cells more quickly (i.e., is more cytopathic) and (2) HSV-2 infection spreads cell-to-cell more rapidly than HSV-1. It would appear HSV-2 has evolved these more aggressive traits to allow it to efficiently superinfect persons already infected with HSV-1.
- The severity of primary HSV infection can be hugely influenced by two variables:
  - trauma to epithelium at time of HSV transmission (Fig. 1 of Halford, et al., 2004)
  - immune status at the time of primary HSV infection (Fig. 6 of Halford, et al., 2005)
- Examples of the first principle include women who have had a “Brazilian” pubic hair removal just prior to contracting HSV and men who shave over primary herpes lesions. In both cases, a compromised epithelial barrier promotes more severe herpetic disease.
- As the duration of primary HSV infection increases, the risk of recurrent herpetic disease increases. Primary genital herpes may last as long as 2 months with frequent recurrences spanning the first year. In contrast, 80% of primary HSV infections are so brief that no symptoms are noted. The duration of the primary infection will be proportional to (1) the number of HSV latently infected neurons colonized in the lower spine and (2) the copy number of latent HSV genomes an individual carries for the remainder of their life. This “viral DNA load” may vary widely from person-to-person, and may range from less than 1,000 to >1,000,000 copies of the latent HSV genome. As the reservoir of HSV latently infected neurons increases, so do the odds of recurrent herpetic disease.
- Among the greatest challenges for clinicians in diagnosing herpetic disease is that HSV infections may produce a wide variety of symptoms. Medical textbooks tend to emphasize “typical” herpes symptoms, but less than 20% of HSV-infected persons will present with
these symptoms. Likewise, only a subset of patients with recurrent genital herpes will have the “typical” 4 outbreaks per year. Patients who are latently infected with HSV may suffer from recurrent herpes symptoms that impacts them anywhere from 0 - 100% of the days in any calendar year. Rules are only useful when they are applicable most of the time. With recurrent genital herpes, it is simply not useful to think in terms of a “median case of herpes,” because 80% of HSV infections are completely asymptomatic and 1-2% are far more chronic and debilitating than the “typical” presentation.

- Clinicians should think of recurrent genital herpes as being highly variable in (1) frequency of outbreaks, (2) duration of outbreaks, and (3) spatial extent of skin symptoms (localized or widespread across more than one dermatome). Additionally, patients may exhibit symptoms that are more internal than external in nature, such as chronic herpes-induced neuralgia. The clinical presentation of herpes zoster provides some context for considering what is possible. HSV-1 and HSV-2 tend to cause more localized symptoms at any one point in time, but patients’ symptoms may alternate between the genitalia, buttocks, thighs, and/or anus (areas innervated by the sacral ganglia). The review of Beauman, 2007 considers some “atypical” presentations of genital herpes.

- Patients who experience the most protracted primary HSV-1 or HSV-2 infections are at the greatest risk for having high-level complications associated with recurrent genital herpes, including (1) chronic neuropathic pain and/or (2) multiple sites of HSV recurrences that rotate from the left and right sides of the body. The latter symptoms indicate that latent HSV infections were established in multiple spinal ganglia.

- Many so-called “atypical” herpes symptoms make a great deal of sense if one understands the theoretical underpinnings of the biology of HSV infections.

2. Strategies to Manage Genital Herpes: Present and Future

The biology of latent HSV infections is presented above in terms of an equilibrium model, which effectively reduces to three points:

1. When viral activators accumulate in HSV-infected neurons, the virus overcomes interferon (host)-induced repression and active replication occurs.

2. When viral activators fail to accumulate, HSV replication in neurons is suppressed by the host immune response.

3. Most HSV reactivation events do not appear to kill their host neurons. Hence, the reservoir of latently infected neurons does not shrink over time, and most sufferers experience their outbreaks at the same site over and over again because the same neurons repeatedly support reactivation events.

Below, the factors that influence recurrent genital herpes are described in the same terms. In essence, HSV reactivation is like an idling car that is temporarily stopped. There are two options to get it moving. You can (1) punch the gas to overpower the brakes (i.e., make more viral activators) or (2) release the brakes so the car starts rolling (i.e., compromise immune control of HSV). Triggers of HSV reactivation either i. increase production of viral activators; ii. interfere with host immune control of HSV; or iii. both.
2-A. **Avoidance of HSV Triggers.** Triggers include activities that increase levels of stress-related hormones, such as cortisol, or sunburn, local irritation of sites where herpes outbreaks occur, or damage to the HSV latently infected nerve fibers (e.g., a back injury). In animal models, such triggers tend to drive increased production of the viral IE activator protein ICP0, which promotes reactivation. Alternatively, triggers may dampen the host immune response that controls a latent HSV infection. Examples include alcohol consumption, anemia, systemic fever, or the progesterone spike that precedes menstruation. Additionally, many foods trigger herpes outbreaks in sufferers such as peanuts, chocolate, and coffee which have the potential to (1) drive expression of viral activators (particularly stimulants like coffee) and/or (2) trigger food allergies that would alter immune function. Knowing and avoiding activities that trigger herpes outbreaks is a simple strategy used by many herpes sufferers to reduce the frequency of their symptoms.

2-B. **Pros and Cons of Acyclovir-Like Drugs.** Acyclovir was developed in the 1970s, and functions as a chain terminator of viral DNA synthesis in HSV-infected cells. Although it is efficient at blocking HSV replication in a laboratory setting, acyclovir’s efficacy in patients is limited by its poor solubility, and oral acyclovir is additionally limited by poor absorption from the gut. Valacyclovir and famciclovir are related drugs that have the same mechanism of action, but which are slightly more soluble. In patients with recurrent genital herpes, acyclovir-like drugs may be taken episodically as needed to shorten the duration of herpes outbreaks. However, for this to be effective, the drugs must be taken at the earliest sign of the prodromal symptoms (nerve tingling or pain) that precedes an outbreak. Alternatively, some patients are placed on daily suppressive therapy to control their herpes outbreaks with acyclovir-related drugs. For some patients, daily antiviral drugs are effective, but for many this is not the case. In two studies in 1988, it was shown that patients who took daily acyclovir prophylactically exhibited a decrease in HSV-specific antibody levels. For others, acyclovir-related drugs may decrease the duration of skin symptoms, but are ineffectual in preventing the pain and tingling sensations (neuralgia) that accompany recurrent genital herpes. HSV-infected persons should absolutely consider acyclovir-related drugs to manage their disease. However, patients should be realistic that acyclovir-related drugs are not effective for controlling 100% of herpes symptoms in 100% of patients.

2-C. **Pritelivir: A Better Antiviral Drug?** In 2016, the first new class of anti-herpesviral drugs appears to be close to reaching U.S. markets. This drug, pritelivir, functions as a helicase-primase inhibitor of HSV replication. The chemical structure and mechanism of action of pritelivir are completely unrelated to acyclovir-related drugs. Therefore, it is possible that combinations of pritelivir and acyclovir-related drugs may be more effective than either drug alone. Initial clinical trial results suggest pritelivir would be vastly superior to acyclovir-based antiviral drugs in terms of its capacity to reduce herpes symptoms and the frequency of shedding of infectious HSV-2 virions (Wald, et al, 2014). However, it remains unclear when pritelivir will be available to the public. Side-by-side comparative studies will be needed to determine if, in fact, pritelivir is more effective for managing genital herpes than acyclovir-based drugs.

2-D. **Why Better Herpes Treatment Options Are Needed.** The current strategies medical professionals rely upon to diagnose, manage, and prevent herpetic disease are in many ways outdated. Recent advances in the understanding of the in vivo biology of HSV infections may be exploited to yield better solutions, as opposed to relying upon acyclovir-based antiviral drugs. Antiviral drugs may be improved upon, but the past 20 years of experience with acyclovir-related drugs suggest that antiviral drugs alone are insufficient to stop the epidemic spread of HSV infections from 4 billion carriers to >1 million uninfected persons every week. If antiviral drugs
were effective at preventing the spread of HSV infections, this should have been obvious by 2005. However, to date, antiviral drugs have not curbed the rate of HSV-1 or HSV-2 transmission from HSV latently infected carriers to naïve individuals.

At RVx, we believe better herpes solutions are possible today, and recommend the following changes, which might improve the management and prevention of genital herpes:

1. **Accurate Diagnosis and Prophylactic Vaccines for Discordant Couples.** The host immune response always serves as “the brakes” that restricts the spread of HSV. If genital herpes patients are accurately diagnosed with HSV-1 versus HSV-2 genital herpes, then patients with HSV-1 genital herpes may reduce the risk of sexual transmission by entering into a relationship with the >50% of the population who already carry HSV-1. Alternatively, an effective prophylactic HSV-1 or HSV-2 vaccine offered to a seronegative partner would greatly reduce the risk of transmission of herpetic disease.

2. **Proper management of genital herpes.** Many doctors have been misled to believe that management of genital herpes should focus exclusively on HSV (the virus). This approach does not adequately consider the in vivo biology of HSV infections, which indicates that latent HSV infections exist in an equilibrium that is controlled both by a gas pedal (the virus) and a braking system (the host immune response). If an antiviral drug is effective, this will interfere with the virus replication (amplification) required for a HSV reactivation event to progress to a recurrent herpes lesion. While this is sometimes helpful, ongoing, subclinical HSV reactivation events may be required to keep the adaptive immune system (antibodies and T-cells) adequately engaged in the active control of HSV replication. Hence, patients often observe that while antiviral drugs may initially help control their symptoms for 3 to 6 months, HSV-antibody levels (and likely HSV-specific T-cells) are not maintained when patients take antiviral drugs every day. If the host immune response becomes ineffective (no brakes), herpes sufferers note that the antiviral drugs “lose their potency” and their recurrent herpes symptoms return. Learn more about how daily antiviral drug suppression often erodes HSV antibody levels in patients.

3. **Therapeutic HSV-2 vaccines: an underexplored treatment modality.** The immune system explains why (1) 80% of HSV infections are asymptomatic; (2) HSV infections are devastating in newborns whose immune systems are under-developed; and why (3) HSV infections progress to fatal outcomes in interferon-deficient individuals. The possibility that the adaptive immune system may be “mismatching” (tolerized) in recurrent herpes sufferers has not been carefully investigated. Clonal exhaustion of T cells is known to occur when foreign antigens, like HSV proteins, are chronically present (Wherry and Kurachi, 2015). The underlying cause of recurrent genital herpes in many sufferers may reduce to “tolerization” of the adaptive immune system to HSV’s foreign proteins, which would severely compromise immune control of latent HSV infections.

Therapeutic HSV-2 vaccines, such as the Agenus HerpV or Genocea GEN-003 vaccines, are being considered as a new treatment modality to break this potential stalemate of “tolerance to HSV-2 immunogens.” However, like many failed HSV-2 subunit vaccines, the GEN-003 and HerpV therapeutic HSV-2 vaccines only expose recipients to 2% of HSV-2’s potential immunogens. At RVx, we believe that the TheravaxHSV-2 vaccine is far more likely to yield an effective therapeutic HSV-2 vaccine because it encodes up to 99.3% of HSV-2’s potential antigens. Clinical trials to test this concept are imminent.
2-E. Why genital herpes is most likely a vaccine-preventable disease. In recent years, biomedical researchers have attempted to develop “subunit vaccines” to prevent genital herpes, AIDS, and other infectious diseases. Subunit vaccines typically contain less than 2% of HSV-2’s antigens, and are based on the premise that one small piece of HSV-2 may serve as an effective vaccine. To date, all HSV-2 subunit vaccines tested in clinical trials have failed to prevent genital herpes.

RVx believes that our different approach, which uses rationally-engineered live vaccines that retain 99% of HSV’s potential antigens, will be sufficient to end the herpes epidemic. Live viral vaccines re-create every facet of a microbe’s life cycle, and fully prepare the human immune system to do battle with the natural pathogen. Live viral vaccines have been used to prevent the viral diseases of (1) smallpox, (2) yellow fever, (3) polio, (4) mumps, (5) measles, (6) rubella, and (7) chickenpox. Never once, in the history of medicine, has a live-and-appropriately-attenuated viral vaccine failed to stop the spread of its corresponding disease in the human population. RVx’s Profavax^{HSV} vaccines offer a similar opportunity to eradicate all forms of herpetic disease.