

## **IUSTI–E Scientific Advisory Council**

### **Topic Report 2016      Herpes**

#### **Rapporteur: Dr. Raj Patel, Prof Marco Cusini**

Herpes simplex virus infections due to HSV-1 or HSV-2 are characterized by initial primary infections of variable severity followed by a period of neuronal latency, which is interrupted by reactivation. Data from recent shedding and biopsy studies challenge traditional models of latency and reactivation, and suggest that disease at the neuronal level is probably much more recurrent than previously thought. In addition that much of the control of disease occurs at the neuronal – dermal junction. Such a model explains the limits of antiviral therapy for herpes, in particular the lack of success that antiviral suppression for herpes has had on the control of HIV acquisition or transmission. Additionally, it may also explain the somewhat complex interactions of HSV-1 and HSV-2 when they are acquired in the same or different locations and also the general trends of decline in HSV-2 infection in the recent NHANES studies in white males and females, where HSV-1 as a genital pathogen is gaining increasing significance.

Both the acquisition illness and the recurrent disease may become complicated.

Although many individuals with genital herpes are relatively problem free, HSV infections can cause a wide range of problems, which may benefit from clinical and therapeutic interventions. The IUSTI 2011 guideline has looked carefully at the evidence around management and produce guidance on the use of diagnostics, antiviral therapy and the management of complications

For many patients suppressive therapy remains the most effective means of managing their problems. Not only will continuous therapy control lesions and prodromal symptoms it can also be a highly effective for managing the psychosexual problems that plague many patients.

Antiviral therapy also has a role in managing transmission anxiety. With the recognition of the important role of asymptomatic shedding for onward HSV transmission, many patients feel powerless in managing transmission risk. A number of strategies used to limit the spread of other STIs have been recommended to control GH transmission – patient education, counselling, and behavioral interventions including the promotion of barrier use. The evidence for the effectiveness of all of these interventions is both divided and limited.

A large placebo controlled study of antiviral therapy has shown that continuous suppressive therapy once daily reduces rates of disease transmission to just below 50% compared to placebo. Although useful in managing short term anxiety in relation to HSV transmission the place of this strategy in controlling HSV transmission in general is yet to be defined. Although head to head comparative studies of individual agents to prevent transmission has not been done it highly likely that the effects seen with valacyclovir will also be present with acyclovir.

Transmission studies are difficult to perform and to date we only have data on the impact of suppressive therapy on limited populations. The use of this data for the management of other populations such as pregnant women, homosexual men or those with HIV co-infection remains a major challenge where accumulating evidence suggests a different transmission dynamic. The recent demonstration that standard doses of antivirals do not prevent transmission in couples discordant for both HIV and HSV reiterates the need for extreme caution in extrapolating the limited trial evidence to wider practice.

The management of HSV infection in pregnancy is a challenge. Third trimester new infections are

vertical transmission are highly variable between countries, although we suspect that in Europe the rate lies well below that seen in the USA. Where countries have a robust system for case reporting and see a very low rate it is justifiable to advocate a conservative approach to management in women with established disease at term. In other situations a more interventionist approach may be warranted; for instance in the USA, recurrences at term have been associated with neonatal disease (up to 3 % transmission) and can result in substantial anxiety. The demonstration that effective antiviral therapy from 36 weeks onwards can limit the need for emergency C/S in this group allows a managed approach for most women.

The control of both symptomatic and asymptomatic HSV infection has recently been shown to be possible using therapeutic vaccination. The effect in well controlled studies appears to last to at least one year, and the reduction in asymptomatic shedding is in the order of 50%. This raises the tantalizing prospect of early vaccination as a standard adjunct to conventional management to allow patients and clinicians to be more proactive in disease management.

## **Advances in the field 2015-16**

### **1. Reliability of HSV-2 Serology**

**Most clinicians are aware of the limited value of non western blot technologies for diagnosing HSV2 in low prevalence populations. Work published in 2016 shows that a large number of people lose antibodies to HSV2 and may have negative tests despite recurrent disease**

- 2. Levels of HSV-2 have for some time plateaued in non-Hispanic white populations in North America. Studies in Europe (Germany) show a similar trend**
- 3. A number of therapeutic vaccine studies over short follow up periods are showing measurable effects on disease and on viral shedding.**
- 4. Dose ranging trials for helicase primases and therapeutic vaccines have been conducted using shedding as a primary marker for impact on diseases – both cross over and parallel arm studies have shown the utility of this methodology**
- 5. Good data on the timing of transmission for neonatal infection**

## **5 Most Important Recent Publications**

1. van Rooijen MS, Roest W, Hansen G, Kwa D, de Vries HJ. False-negative type-specific glycoprotein G antibody responses in STI clinic patients with recurrent HSV-1 or HSV-2 DNA positive genital herpes, *Sex Transm Infect.* 2016 Jun;92(4):257-60. doi: 10.1136/sextrans-2015-052213. Epub 2016 Jan 11.
2. Wald A, Corey L, Timmler B, Margaret A, Warren T, Tyring S, Johnston C, Kriesel J, Fife K, Galitz L, Stoelben S, Huang ML, Selke S, Stobernack HP, Ruebsamen-Schaeff H, Birkmann A. Helicase-primase inhibitor pritelivir for HSV-2 infection. *N Engl J Med.* 2014 Jan 16;370(3):201-10. doi: 10.1056/NEJMoa1301150
3. GEN-001/002 studies available in abstract form
4. Esber A, et al. Risk of Bacterial Vaginosis among Women with Herpes Simplex Virus Type 2 Infection: A Systematic Review and Meta-analysis. *J Infect Dis.* 2015 Jul 1;212(1):8-17
5. Cantey JB, et al. Herpes Simplex Virus DNAemia . Preceding Neonatal Disease. *J Pediatr.* 2015 May;166(5):1308-9

## **Potential Speakers**

- 1. MS van Rooijen Amsterdam**
- 2. Emily Clarke UK**
- 3. David Koelle Seattle**
- 4. Anna Wald Seattle**

### **Questions to be answered by future Research**

1. The effectiveness of therapeutic and prophylactic vaccines
2. Management of IRIS related HSV
3. Best management for recurrent HSV meningitis
4. Why is Neonatal HSV rising
5. Simple algorithms for using HSV serology
6. Managing patients with non-resistant recurrent disease who are unresponsive to acyclovir
7. The mechanisms of latency and reactivation
8. Can resistance be predicted through genotypic analysis

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