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A PEER-REVIEWED ARTICLE

Are HSV infections more prevalent in older HIV+ patients?

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Herpes infection is a worldwide problem and represents a significant public health issue. There are numerous reports in relation to the seroprevalence of HSV infection (HSV-1 and HSV-2) in elderly patients with a peak of HSV-2 seroprevalence in elderly male patients (Bunzi *et al.*, 2004). Other studies have identified HSV-1 and HSV-2 seropositivity in association with increasing age, female gender, and history of sexually transmitted infections. HSV-2 seropositivity has also been associated with genital herpes, coinfection with HIV infection, and coinfection with hepatitis C (Singh *et al.,* 2005).

The frequency of HSV-2 seroprevalence varies according to the study and population. In the case of HIV-infected patients, it may range from 45% to 90% as age increases (Rode *et al.*, 2008), (Bunzii *et al.*, 2004), (Nagot *et al.*, 2008), (McMahon *et al.*, 2008), (Dolar *et al.*, 2006). Compared to non-HIV-infected populations, HIV-positive patients have a higher HSV type 2 seroprevalence (45.8% vs. 8.7 %) (Rode *et al.*, 2008). In fact, a significant predictor of increased HSV seroprevalence is aging (Rode *et al.,* 2008). Data on seroprevalence of HSV type 1 and/or type 2 among elderly HIV-positive patients is scarce.

The interplay between HIV and HSV viruses has been described in different studies. HSV-2 reactivations, both clinical and subclinical, may play a role in increasing the rate of HIV-1 replication. (Nagot *et al.*, 2008). The connection between these two viruses may also occur at a biological level as shown by studies demonstrating that HSV-2 proteins are capable of activating the HIV long terminal repeat which may result in increased HIV gene expression (McMahon *et al.*, 2008) (Jayasuriya *et al.*, 2008).

Some studies have shown a potential suppression of HIV-1 RNA levels with therapy directed to HSV suppression (Nagot *et al.*, 2008), (McMahon *et al.*, 2008). This benefit has been translated in reduced general plasma HIV-RNA levels in HSV and HIV co-infected women. Even though initial results of HSV suppression on HIV viral loads may show promise, other studies have shown no benefit in relation to suppression of HIV-RNA levels (McMahon *et al.*, 2008)

The impending epidemic of elderly HIV-infected patients has been described in numerous studies; most report epidemiologic changes in the population infected with HIV and the influence of antiretrovirals, T cell count, and other co-morbidities in morbidity and mortality of this group of patients. (Grabar *et al.*, 2006), (Navarro *et al.*, 2008), (Nogueras *et al.*, 2006), (Gebo *et al.*, 2006), (Walston *et al.*, 2006). These studies have shown that the effectiveness of the immune response after the start of antiretrovirals may not be optimal in elderly HIV-infected patients. (Gebo *et al.*, 2009), (Gebo *et al.*, 2006)

To our knowledge, there are no studies describing the seroprevalence of HSV-1 and HSV-2 in elderly (>50) HIV-infected populations and their impact on HIV control, morbidity and mortality outcomes. In our clinic, 151 patients >60 years of age were identified as of September 2009. A total of 28 cases (18.5% of total population) of clinically-based herpes infection were identified in this group. Forty-three percent of these patients received episode-based treatment, 32% were on chronic suppressive therapy, and 25% were either not on treatment or documented treatment was not found in their records. Number of HSV episodes was not documented, neither was HSV seroprevalance.

We suggest the possibility that the seroprevalence of HSV infections (type 1 and 2) is high in elderly HIV-infected populations and, as a result, these patients may need screening for subclinical infection. High seropositivity may call for an early suppressive therapy upon diagnosis to avoid long term interactions between HIV and HSV infections, especially in elderly patients.

This article will review the literature on HSV-1 and HSV-2 infection seroprevalence in elderly HIV-infected patients and the potential use of early HSV suppressive therapy in these vulnerable populations.

HSV-1 and HSV-2 seroprevalence in HIV-infected patients

Rode *et al.* (2008) estimated the HSV-2 seroprevalence and its association with age, sex, human herpesvirus type 8, and HIV infection. The authors studied a cohort of 166 HIV-infected patients and 219 blood donors. Antibodies against HSV-2 were determined by enzyme immunoassay. The researchers found a seroprevalence of 45.8% in HIV-infected patients; independent predictors of HSV-2 included HIV infection, female gender, older age, and HHV-8 seropositivity.

Santos *et al.* (2006), in a retrospective review of 150 HIV-infected patients, determined the seroprevalence of HSV-2 and its association with age, sex, and other demographic and behavioral factors in Brazil. ELISA was used to examine serum samples. A total of 83 patients were male (average age 38.8) and 67 were female (average age 35.4). The authors found a prevalence of HSV-2 of 52% and higher among men (53%) compared to woman (50.7%). There was no stratification by age group. Clinical genital herpes was reported in only 21.2% of the HSV-2 positive patients. Subclinical infection was a common finding in this study.

Devi *et al.* (2008) conducted a study of coinfected women (HSV-2 and HIV) with reproductive tract infections. The sample included 92 patients with reproductive tract infections of whom 18 (19.6%) and 9 (9.8%) were positive for HSV and HIV infections respectively. Coinfection rate (HSV-2 and HIV) was 16.7%. None of the patients had clinical herpes genitalis; all were subclinical cases. The authors recommended that any reproductive tract infection, whether ulcerative or not, must be thoroughly evaluated and HSV serology must be included in the diagnosis protocol due to the potential interactions between HSV and HIV.

In a study by Anuradha *et al.* (2008), the seroprevalence of HSV-2 infection in HIV-infected patients was compared to the general population. One hundred HIV-positive patients (age range 20-54 years), irrespective of past or current history of genital herpes, and 50 healthy control volunteers were studied. Twenty-two patients in the HIV-infected group had a history of genital herpes. The authors found an HSV seroprevalence of 49% and 22% among HIV-positive patients and controls respectively, a difference found to be of statistical significance.

Freedman *et al.* (2004) reviewed the epidemiology of HSV and HIV coinfection. These authors found a relative risk of 2.1 of acquiring HIV infection in patients previously infected with HSV-2. At the same time they found a 52% risk of sexual transmission that could be attributed to HSV-2. The researchers hypothesized that in populations where HSV-2 prevalence is 80% or more, almost half of the sexually acquired HIV can be attributed to HSV-2.

HSV seroprevalence in two groups of HIV-infected patients in France was described by Andreoletti *et al* (2005). In the first group, 223 of 434 subjects (51%) demonstrated positive HSV-2 serology with 66% positivity in the second group. The authors found that almost 70% of patients had no clinical history of herpes infection. The researchers recommended testing for HSV-specific serology to detect asymptomatic subclinical disease as a potential strategy to diagnose HSV and help in the control of HIV with suppressive therapy.

Allan and Das (2003), in a study of HSV seroprevalence in 96 HIV-infected patients, found a striking 86% and 97% of HSV-1 seroprevalence among men and women respectively. HSV-2 seroprevalence was 50% and 94% among men and women respectively.

In a review of HSV-suppressive therapy, Nagot *et al.* (2008) studied coinfected women (HIV and HSV-2) enrolled in a randomized placebo-controlled trial of therapy to suppress reactivation of HSV-2 infection. Cervicovaginal lavage specimens were obtained over a period of 12 weeks to detect and quantify the HIV-RNA and HSV-2 DNA loads.

Interestingly, the authors found the association of HSV-2 reactivation on HIV-1 replication tended to be stronger in patients with high CD4 cell counts (>500 cells). Finally, the authors found a positive correlation between clinical and subclinical HSV-2 reactivations and HIV-1 replication. Therefore, HSV-suppressive therapy may be a promising tool for HIV control (Nagot *et al.*, 2008).

The seroprevalence of HIV-1 and HSV-2 infections in elderly patients has not been reported adequately in this population. The thought is that the seroprevalence is quite high regardless of acute or history of genital herpes infections. If this turns out to be true, then this population might be exposed to a significant coinfection between HIV and HSV. The latter could complicate the already complex case of elderly patients with HIV infection (comorbidities, medication interactions, and aging effects).

HSV suppressive therapy and its implication on HIV viral load in HIV-positive populations

Deko *et al* (2009) retrospectively reviewed 69 (age range 19-62 years) cases of HSV-suppressive therapy for recurrent genital herpes infections between the years of 2000 and 2007 in a university hospital setting in England. Immuno-suppression was found in 11.8% of cases (HIV cases or steroid concomitant therapy). The authors compared the results with the British guidelines for sexually transmitted diseases and HIV treatment. They found that 82% of patients had the infection for at least 12 months at start of therapy and 78.2% had at least six recurrences per year before the start of treatment. Prophylaxis with acyclovir or valacyclovir was continued for seven years without untoward effects. Unfortunately there was no information regarding age groups or the seroprevalence and results of elderly patients.

Conant *et al.* (2002) evaluated the use of valacyclovir versus acyclovir in HIV-infected patients for HSV infections. These patients were studied using two controlled trials; the first group with 1062 patients received valacyclovir or acyclovir for one year and were assessed monthly. The second group consisted of 467 patients who were treated episodically (> or 5 days) and assessed daily. The authors found no differences between acyclovir and valacyclovir for suppression or acute treatment of herpes infections in HIV-infected patients.

Therapy to suppress HSV-2 reduces the frequency of reactivation of HSV-2 as well as HIV-1 levels, suggesting that suppression of HSV-2 may reduce the risk of transmission of HIV-1. In a recent study, Celum *et al* (2010) performed a randomized placebo-controlled trial of suppressive HSV-2 therapy in couples in which only one of the partners had both HIV and HSV-2 and was not taking antiretroviral therapy. The primary end point was transmission of HIV to the non-infected partner. Despite the fact that HSV-2 suppressive therapy decreased HIV viral load by 0.25 logs and had a 73% reduction of genital ulcers due to HSV-2, the authors found no reduction in the risk of HIV transmission with daily suppressive therapy with acyclovir.

Reynolds (2009) discussed the role of HSV-2 suppresive therapy for HIV prevention. This author mentioned studies conducted in several parts of the world. One in Tanzania enrolled 821 patients treated with acyclovir and followed them for 12 months; this study failed to show a decrease in HIV transmission. The same outcome occurred in two other studies in Peru and the United States (1814 men who have sex with men). Another study in Zambia and Zimbabwe failed to show any benefit in relation to HIV transmission when patients are exposed to HSV-2 suppressive therapy. This author calls for better prevention strategies, better understanding of the dynamics of HIV-HSV coinfection and potential development of a vaccine for better control of HSV and HIV infections. This view is shared by Baggaley *et al* (2009) in a study of HSV-2 suppressive therapy. The authors found that HSV-2 suppressive therapy may avert relatively few HIV-1 transmission events per person-year of treatment, however, more research is needed into the effect of HSV-2 suppressive therapy on T cell count decline and the impact of higher dosing schedules.

Baeten *et al.* (2008) described a randomized cross-over trial of HSV-2 suppressive therapy with valacyclovir conducted in 20 Peruvian women coinfected with HIV and not

on antiretroviral therapy. In this study, plasma and endocervical swab specimens were collected for HIV-1 RNA polymerase. The authors found that suppressive HSV-2 therapy has the potential to reduce HIV-1 infectiousness and possibly reduce HIV progression.

White *et al.* (2008), in a study conducted in Africa on the impact of HSV-2 suppressive therapy on population-level incidence of HIV, found a reduction in population HIV incidence by >20% in the long term. This study was performed in female sexual workers who were treated with long term HSV-2 suppressive therapy. The researchers stated that in order to get a substantial impact, HSV-2 suppressive therapy requires high coverage in the general population and long duration, or very high symptom recognition and treatment-seeking behavior.

The above mentioned studies emphasized the potential benefit of HSV suppressive therapy in HIV-infected patients. In relation to the general population, this benefit may be shown in terms of HIV acquisition but results of studies are mixed. Except in a few reports, no studies have analyzed the case of elderly HIV-infected patients and the potential benefit of HSV-1 and HSV-2 suppressive therapy.

Implications for elderly HIV-infected patients

Elderly patients infected with HIV have significant problems. Comorbidities, potential medication interactions, and psychosocial issues are main areas to be tackled. In our clinic, 151 patients > 60 years were identified as of September 2009. The median age of this group was 61.8 and their baseline CD4 count was 404 with approximately 28% of patients having CD4 counts <200 /mm3. Comorbidities of hypertension, diabetes, dyslipidemia, hepatitis C, and depression were the most common (Spizale *et al.*, 2009). In this study we found that diabetes and mobility problems were statistically significant issues in patients > 60 years. HSV seroprevalance appears to be high in this group and an active study is being undertaken to determine the exact seroprevalence.

In a recent multicentric cross-section study conducted in Spain, Mothe *et al* (2009) described clinic characteristics of patients with HIV infection >70 years old. The majority of them were male (76%) with low CD4 counts at diagnosis (52%) compared to low CD4 counts in younger populations at time of diagnosis (34%). Dyslipidemia, hypertension, diabetes, cardiovascular disease, chronic renal failure, malignancies, and cognitive dysfunction were the most common co-morbidities found. The authors found an average use of 2.97 drugs besides antiretrovirals.

Gebo *et al.*, (2009), in a study of patients >50 years old, suggested that even though virological response might be equal or better in the older group of HIV patients compared to younger groups, the effectiveness of the immune response might not be the same. This author in another paper (2008) mentions that comorbidities and interactions among medications taken by elderly patients with HIV might have a significant impact in the care of these patients. The need for early treatment and best regimens are also advocated by these authors.

Elderly groups may present to HIV care with more taboos and less social resources than younger groups. A great percentage of elderly HIV patients are already retired, living alone most of the time, with no structured social networks appropriate for their age. Meyer *et al.* (2005) reviewed the psychological impact of serological herpes simplex type 2 testing in HIV-positive patients in an urban setting. The authors concluded that even though an impact is expected, the benefit of knowing patients' serological HSV status and taking appropriate measures would be higher compared to the potential psychological harm. Therefore, elderly patients might have some psychological burden if they are aware of their HSV status, but the benefits may outweigh the problem.

Interactions between antiretrovirals and medications used for other comorbidities in elderly patients have been major concerns. Even though there are some studies on the subject, there are no clear guidelines in relation to preferred antiretrovirals and their pharmacokinetic and pharmacodynamic properties in elderly HIV-infected patients. In relation to adherence, it appears that elderly groups have better adherence to antiretrovirals (Cox, 2009), (Grabar *et al.*, 2006), (Rhee *et al.*, 2008), (Effros *et al.*, 2008),

(Branas *et al.*, 2008). Some of the previously mentioned studies have referred to the safety of acyclovir and valacyclovir in HIV-infected patients in long-term trials even though there are no studies in HIV-infected elderly patients. Therefore, even though medication interactions might occur, the benefits of HSV-1 and HIV-2 suppression may overcome this potential problem.

Interactions between HSV and HIV viruses need to be studied in depth in this population. This group suffers from significant comorbidities, medication interactions, and apparent reduced immune response to HIV antiretroviral therapy. These patients may have subclinical HSV infection which can go undetected. HSV seroprevalence data in elderly HIV-positive patients is not widely available. Reports from our clinic indicate that 68% of patients with acute or history of HSV infection (based on clinical grounds) were not treated or received episode-based treatment, even though patients might have recurrent episodes not documented in their records or might not recall previous episodes. Potential benefits in terms of prevention (decreased genital ulcer disease, decreased HIV transmission, decreased HIV genital viral loads, HSV and HIV virus interactions) might be obtained if seroprevalence in this population were known.

Conclusions

Herpes simplex infections represent a significant problem in HIV-infected patients. The seroprevalence reports in different studies vary from 50% to 80% for men and women respectively. The few studies in elderly patients indicate that aging is a risk factor for increased seroprevalence. Therefore, it is plausible to think that elderly HIV-infected patients may have a high HSV seroprevalence.

This review raised many questions. The exact prevalence of HSV infections/seroprevalence in elderly HIV-infected patients is not well defined, since the majority of studies are not based on seroprevalence and most of them have been conducted in younger subjects.

There are significant interactions between HSV and HIV viruses and reports have shown an increased rate of HIV acquisition in HSV-2 infected patients. The core of these interactions has not been studied in depth.

HSV-1 and HSV-2 suppressive therapy have been studied in numerous trials and the results of benefits of HSV suppression on HIV infection are mixed. Elderly patients (>50 years) have not been included in these trials. Another point that needs more research is whether HSV suppression actually decreases HIV viral load in serum and HIV genital viral shedding in elderly HIV-positive patients.

We suggest that the elderly HIV-infected group (>50 years) may suffer from a very high HSV seroprevalence and as a result this population might be exposed to significant interactions between HSV and HIV. It is also well known that immune reconstitution after start of antiretrovirals is slower in elderly HIV-positive patients. All these factors combined may place this group at a higher risk for complications.

More data is needed to determine whether universal screening should be considered for HIV-infected patients >50 years in order to determine the seroprevalence and benefit of starting HSV-suppressive therapy, even in the absence of clinical herpes infections. This cohort of patients needs to be followed to determine morbidity and mortality outcomes, HSV-1 and HSV-2 complications, response to antiretrovirals, and development of non-AIDS-related complications.❖

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