

# Psychosocial impact of serological diagnosis of herpes simplex virus type 2: a qualitative assessment

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**Objectives:** To assess the emotional and psychosocial responses to a serological diagnosis of HSV-2 infection in individuals without previous history of genital herpes.

**Methods:** 24 individuals who had a positive HSV-2 serology by western blot and no clinical history of disease were recruited from four clinics (sexually transmitted disease, maternal and infant care, family medicine, and virology research) over a 10 month period. In-depth qualitative interviews were conducted to elicit an individual's responses to the HSV-2 diagnosis.

**Results:** Three categories of themes were identified from the interviews. Short term emotional responses included surprise, denial, confusion, distress, sadness, disappointment, and relief to know. Short term psychosocial responses included fear of telling sex partners, anger at the source partner, guilt about acquiring or transmitting, and concern about transmitting to a child. Perceived ongoing responses included fear of telling future partners, concern about transmitting to a sex partner, feeling sexually undesirable, feeling socially stigmatised, feeling like "damaged goods," sex avoidance due to social responsibility, fear of transmitting to a newborn, and relationship concerns relating to the diagnosis.

**Conclusions:** Individuals exhibit strong emotional and psychosocial responses to a serological diagnosis of HSV-2 infection. Many of the negative responses may be time limited and influenced by factors that are potentially amenable to counselling.

Herpes simplex virus type 2 (HSV-2) is the most common cause of genital herpes, a chronic sexually transmitted infection. Most people with HSV-2 do not have a history of genital herpes and remain undiagnosed unless they transmit the infection to a partner who becomes symptomatic. In the past few years, HSV-2 type specific antibody assays have become available, and clinicians can use these tests to identify asymptomatic HSV-2 infected individuals.<sup>1,2</sup> Longitudinal data suggest that such individuals have substantial reactivation rates but mild clinical disease.<sup>3</sup> The effect of a serological diagnosis of HSV-2 infection on the emotional and psychosocial state of patients has not been described. Although previous research has identified psychosocial morbidity associated with HSV-2, it has focused specifically on individuals with symptomatic recurrences.<sup>4–6</sup> Only one published quantitative study has explored the psychosocial impact of HSV-2 diagnosis in asymptomatic individuals.<sup>7</sup>

The current study was designed to assess qualitatively emotional and psychosocial responses to a diagnosis of HSV-2 infection based on results of a serological test in asymptomatic individuals and to provide a framework for counselling delivered in clinical settings.

## METHODS

### Subjects and setting

From August 2000 to the end of May 2001, individuals without a history of genital herpes were recruited from four University of Washington clinics (sexually transmitted disease (STD), maternal and infant care (MICC), family medicine (FM), and virology research (VR)) located in Seattle, Washington. Individuals who had HSV-2 infection determined by western blot<sup>8</sup> but no history of genital herpes, were age 14 years or older, and able to communicate in English, were invited to participate in a 1 hour long interview scheduled at their convenience. Recruitment procedures varied by site. At the STD clinic, free HSV serological testing was

offered to clinic patients; of the 18 invited to participate, 13 agreed. At the MICC, where HSV antibody testing is included in the routine panel of tests provided to prenatal patients,<sup>9</sup> seven of eight invited women agreed to participate. At the FM and VR clinics, participants in previous research studies were contacted and four of 10 agreed to participate. Of these, three had been serologically tested for HSV-2 after their partners presented with initial symptoms of HSV-2 infection. All consecutive individuals identified who met the inclusion criteria listed above were offered an interview; there was a 67% acceptance rate.

### Interview instrument

Based on published studies,<sup>10–13</sup> a set of questions to guide a semistructured interview was developed. Study inquiries included factors that may be common among individuals with genital infections—for example, fear of telling new or current sex partners about infection, fear of transmitting genital herpes to partners or to a fetus, or diminished sexual desire.<sup>4,5</sup> Participants were asked to recall their responses at several points in time (1 week, 1 month, and 1 year following diagnosis). We employed this approach because a recent report suggested that psychosocial morbidity associated with genital herpes may be most significant immediately following diagnosis, with the effects dissipating over time.<sup>14</sup>

### Data collection

Institutional review boards at both the University of Washington and the Centers for Disease Control and Prevention (CDC) approved the study protocol. After written informed consent, participants were interviewed for approximately an hour in a private room at one of the four clinical sites by one of three trained interviewers (DD, JM, and SS). Interviews were audiotaped and transcribed verbatim by a single individual.

**Table 1** Selected demographic and clinical characteristics of study participants

	Women (n=14)	Men (n=10)
Age, median (range)	34 (19–51)	36 (27–55)
Race		
White	10	8
African-American	2	1
Asian	0	1
Hispanic	2	0
Pregnant	7	NA
Sex of sex partner		
Opposite sex	13	8
Same sex	0	2
Both	1	0
Recall previous symptoms	4	2
Clinic recruited from		
Sexually transmitted disease	3	10
Maternal and infant care	7	0
Family medicine	2	0
Virology research	2	0

### Data analysis

Analyses utilised constant comparative analysis following the grounded theory method, which employs both deductive and inductive approaches to identify patterns or themes.<sup>15</sup> The interviews were coded using both themes drawn from previous research<sup>16–28</sup> and themes that emerged from initial review of the transcripts. The codes were readjusted and refined in a series of iterative cycles to test and build theoretical models.<sup>29</sup> Consensus on the coding of each interview was reached and codes for all 24 interviews were entered into the qualitative computer software CDC EZ-Text.<sup>30</sup> For quality assurance, six interviews were selected at random and recoded by one of the authors. The agreement was 88% between these interviews and the initially coded interviews.

Themes, defined as a group of similar responses provided by at least three participants,<sup>31</sup> were quantified using CDC EZ-Text. These response themes were organised into categories, which were then used in developing a hypothesised model illustrating potential emotional and psychosocial responses to an HSV-2 serological diagnosis. In this model, the factors influencing these responses have been grouped into moderators and mediators. Moderators are existing factors that act as buffers to emotional and psychosocial responses; these factors, present before diagnosis, potentially have an effect on the subsequent responses. Mediators are intervening factors that can mitigate the severity and durations of responses; these factors are a result of receiving the diagnosis and they may influence the level of response to having HSV-2.

## RESULTS

### Participants

Of the 24 participants, 58% were women and 42% were men (table 1). The mean age was 35 years (range 19–55). Seven of 14 women were pregnant and were diagnosed with HSV-2 infection during their current pregnancy. Seventy five per cent of the participants were white and 25% identified with other racial/ethnic groups. Most (88%) participants reported opposite sex partners. Six (25%) participants were interviewed less than 1 month, 14 (58%) were interviewed 1–5 months, and four (17%) were interviewed more than 1 year after serological diagnosis of HSV-2 infection. After learning that they have genital herpes, 25% of participants recalled symptoms consistent with an HSV-2 outbreak, while 75% denied recall of any symptoms consistent with an outbreak. Of the four participants interviewed more than 1 year after their diagnosis, two had remained asymptomatic and two were symptomatic.

**Table 2** Emotional and psychosocial responses to HSV-2 serological diagnosis (n = 24)

Response	No	%
<b>Short term emotional</b>		
Surprise	12	50.0
Denial	9	37.5
Confusion	8	33.3
Distress	6	25.0
Relief to know	5	20.8
Sadness	4	16.7
Disappointment	4	16.7
Self blame	3	12.5
“Why me?”	3	12.5
<b>Short term psychosocial</b>		
Fear of telling current partner	11	45.8
Anger at source partner	6	25.0
Guilt about acquiring or transmitting	5	20.8
Concern about transmitting to child	4	16.7
Fear of telling past partner(s)	4	16.7
Decreased libido	3	12.5
<b>Perceived ongoing</b>		
Acceptance	14	58.3
Fear of telling future partner(s)	12	50.0
Concern about transmitting to partner	11	45.8
Feeling sexually undesirable	10	41.7
Feeling socially stigmatised	8	33.3
Feeling like “damaged goods”	8	33.3
Sex avoidance due to social responsibility	8	33.3
Relationship problems after diagnosis	8	33.3
Concern of transmitting to newborn	7	29.0
Increased commitment to current partner	3	12.5
Relieved to discover both have HSV-2	3	12.5
Reluctance towards future relationships	3	12.5

### Themes

Three categories of themes were identified: short term emotional, short term psychosocial, and perceived ongoing responses. Short term emotional responses were defined as affective responses (for example, anger, fear, guilt) to the diagnosis. Similarly, short term psychosocial responses were also affective responses, but pertained to potential social interactions (for example, anger at the person who caused the infection, fear of telling sexual partner about diagnosis, guilt over possibly infecting a partner). Ongoing concerns and feelings raised by the chronic nature of HSV-2 infection represented the third category.

### Short term emotional responses

Nine themes that described short term emotional reactions to a serological HSV-2 diagnosis were identified in interviews with three or more participants (table 2). Surprise, the most common theme, was often associated with not having had symptoms and, therefore, not anticipating a positive test. One pregnant woman (41, MICC) said, “I was kind of surprised. I wasn’t tested the first time I was pregnant. I’ve never had symptoms, so I was just surprised.”

Denial was another common theme, with participants reporting doubt after being told of their diagnosis. One man (37, STD) said, “Yeah, I was just having the test to see if I’ve ever been exposed to it. I’d never had symptoms and so when the test came back positive, it was just like, could this test be wrong? Exactly is what I thought. Because I’ve never had an outbreak.”

Denial was often found in conjunction with surprise: “I was a little freaked out. It was such a surprise. I thought, ‘Are you sure?’ To my knowledge . . . I never had any symptoms that I took to be symptoms of genital herpes.” (Female, 40, MICC)

Confusion about the meaning and implications of the diagnosis was frequently expressed. For many, confusion was linked to lack of symptoms. One woman (38, STD) stated, “So that was what was confusing for me when I got my results.

Because I said, 'Well how could I have not known? Never known?'" Another woman (27, MICC), who was pregnant, said, "When she (the physician) tells me that I have it (HSV-2) and really do not have it (symptoms), I don't understand. Am I ever going to have outbreaks? I don't even know how to recognise the signs. She says I may never have an outbreak but I may also get outbreaks. If I catch a fever, I'm thinking to myself . . . because I know that's one of the signs because I read through it, (am I) having an outbreak now . . . it's just questions."

Distress, which included feelings of being hurt, stressed, upset or miserable, was reported by participants. One man (52, STD) stated, "I felt miserable. I don't like the fact that I've contracted a disease." Distress was often accompanied by not understanding how or when the virus was acquired: "I was upset, puzzled. Didn't know how or where it came from. I had no symptoms so I didn't know. I just came just for a basic check up so it kind of did blow me away. There's no cure for it. It would be one thing if you gave me pills or a shot." (Male, 32, STD)

Some participants were disappointed or sad, blaming themselves for the infection or viewing acquiring the infection as unfair. The sense of unfairness often stemmed from participants considering themselves to be sexually or socially responsible. One woman (51, FM) said, "It was just disheartening because I've been good for so long. I've been responsible and reliable—gone to work, paid the bills, bought a house and paid taxes. It just struck me as . . . This is not fair! This is worse than not fair! I keep coming back to there's no real way to deal with it."

Some participants expressed a sense of relief at knowing that they were HSV-2 seropositive. Although the participants in this study did not have a clinical history of genital herpes, some began to recall symptoms that previously they had not attributed to herpes. Therefore, the HSV-2 diagnosis provided an explanation for their previously unexplained symptoms. For example, one woman (46, FM) stated, "It made me aware that I had had herpes outbreaks for a decade only I didn't know that's what it was. And when I would have an outbreak, I would just assume it had to do with, I don't know, a tampon string that irritated (me)...and it was just a little discomfort in that area for several days and then it would go away. So I guess in a little bit of a way finding out I had herpes was a little bit of a relief. Like, 'Oh that's what that is!'"

### Short term psychosocial responses

Short term psychosocial responses to a serological HSV-2 diagnosis were described by six themes (table 2). Fear of telling a current partner was a frequent psychosocial response associated often with fear of rejection, present even for participants who knew that their current sex partner had herpes. One man (32, STD) said, "I thought she was going to freak out and run away from me. Scared that she was going to run off and leave me forever." Another man (37, STD) reported that his initial thought was, "Oh my gosh I'm positive and if I tell him he probably you know, might reject me for this. Then I thought, oh no he's had herpes so he's certainly not going to do this to me. But there's always the possibility. So there was this little thinking that went on subconsciously...I waited a couple of days and then told him, because I think I had to go through my own little process of dealing with that."

Concern over telling previous sexual partners was linked to being viewed negatively or not wanting to cause emotional harm. One woman (32, STD) expressed reluctance to tell past partners: "I don't know how long ago I got it, so why go back and tell four or five different men from the past ten years who may not have anything? And then (they have) this bad image of me." One man (27, STD), when asked about

the potential disclosure to past partner(s), stated, "Well it's the fear of having hurt somebody—I don't want to damage people I care about. So on the one hand, I want to tell them before they can do more damage, or whatever, I guess if you want to call it that. But on the other hand, I realise that I'll probably damage them somewhat just by telling them. At least to cause them to have some apprehension like what I had."

Anger at the person whom they believed had given them herpes was occasionally expressed. One man (32, STD) said, "I look at it, you know, as I should have been protecting myself. So it's more my fault than it is the person who gave it to me. I'm not upset no more. I mean I was at first. I wanted to kill the girl actually—figure of speech you know. But I was that mad."

Five participants, including all three who were believed to have transmitted the infection to their partner, expressed feelings of guilt. The other two participants mentioned guilt either because of the possibly having infected a past partner or because of "bringing a disease into the house" (female, 27, MICC). One woman (28, STD) revealed, "I just felt very guilty. I felt very badly that I didn't know and that I affected somebody else's life that way."

For some women, daily interactions with their children were affected by their concerns. One woman (27, MICC) said, "Like if I give them a kiss, am I going to give it to them? It's in the back of your mind. Even if you know it's not true, you still kind of worry about it. That's about the only thing that's changed in my relationship with my babies." Another woman (21, MICC), worried that she had transmitted herpes to her child, stated: "Sometimes I put my daughter in the tub with me, so I was like, 'Should I stop putting her in the tub with me? Do I need to bring her in to get checked?'"

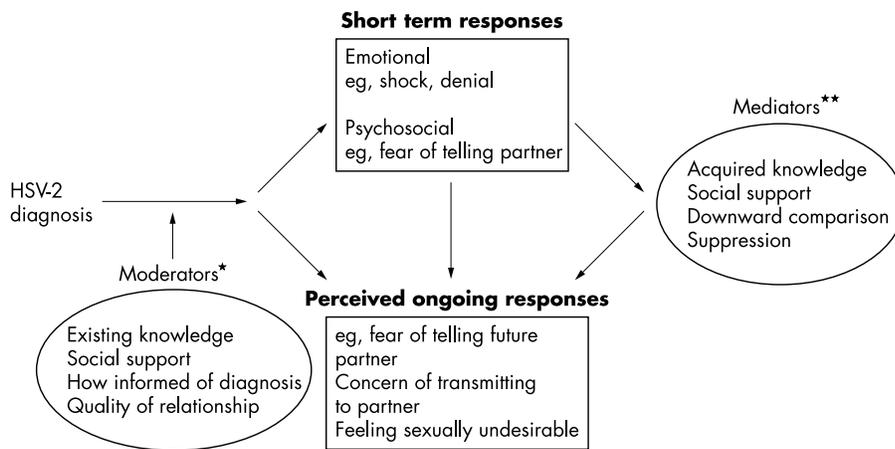
Some participants' sex drives were affected by their knowledge of having herpes. One man (32, STD) disclosed, "It didn't change too much of my daily routine but as far as like, being sexual and things like that, I kind of lost interest," whereas another woman (27, MICC) said, "It just died. There's no desire!"

### Long term responses

Psychosocial responses that participants experienced or perceived as ongoing could be summarised in 12 themes (table 2). Fear of telling future partners or reluctance to engage in future relationships were expressed by many participants. One woman (37, STD) stated, "It's just hard when I think about if I'm ever with someone else again. You know if my (current) relationship doesn't last, it makes me think, you know, I don't want to be with anyone else again. I don't want to have to go through telling them this and have them freak out and walk away. That's probably the hardest part for me."

Participants who had a current partner with an unknown or HSV-2 seronegative status had an ongoing concern of transmitting herpes to that partner. In fact, some felt a sense of social responsibility to their partners and were avoiding sex as a preventive measure: "You feel like you're this walking disease, and if you get intimate with your husband, it's just going to feel as though you are giving him something that you shouldn't be giving him. It's in the back of your mind, so you really can't concentrate on being intimate." (Female, 27, MICC) This theme, fear of transmitting, was expressed more frequently by women.

Three themes, social stigma, feeling sexually undesirable, and feeling like "damaged goods," highlighted participants' perceptions of the social implications of having herpes. One woman (32, STD) explained, "You feel like you're not as good anymore, I guess. And because it's such a, you know, associated with such stigma. It's not just a little black mark, it's



**Figure 1** Model of psychosocial responses to a serological HSV-2 diagnosis. \*Moderators are factors that act as buffers to emotional and psychosocial responses; these factors are present before diagnosis and potentially have an effect on the subsequent responses. \*\*Mediators are intervening factors that mitigate the severity and durations of responses; these factors are a result of receiving the diagnosis and then influence the level of response to having HSV-2.

like a big black check mark against you.” One man (55, STD), who works in the health field, indicated that a lot of his own patients remark, “Now I’m damaged goods. Who’s going to want me?”

Both pregnant and non-pregnant women expressed concern over transmission to newborns. For women who were currently pregnant, preventing transmission to newborns was a main concern they felt would continue through their pregnancy. As one woman (19, MICC) said, “Well, I’m pregnant. I just don’t want nothing to happen to the baby.” Another woman (37, VR), who was not pregnant, indicated her fear about transmitting her HSV-2 infection to a newborn in a future pregnancy, “Well the one other thing I was upset about when I first found out he had it was is this going to affect my ability to have children or is this going to affect a baby?...That was my first big fear that somehow it would affect a baby.” In contrast, men did not express concern about transmission to children or newborns, but were fearful of disclosing or transmitting their HSV-2 infection to current and future partners.

Two themes that were viewed by some participants as positive outcomes included increased commitment to the current partner and relief to discover both partners had the same serostatus. For several participants, this increased commitment seemed to be related to their fear of telling future partners. This was articulated by one woman (28, STD), “So now we both have it, it’s like okay, we don’t really have to worry about that anymore. (But) if we ever break up we know we’ll have to deal with it and explaining it to our next partner. (It) has made us feel like, well gosh this is something to make you think more carefully about ever breaking up.” Participants who already knew that their partners were infected with HSV-2 and had previously been concerned about acquiring the virus themselves now expressed a sense of increased commitment to each other given that both of them were HSV-2 seropositive. As expressed by one woman (44, VR), “Oh—this is good...For me it just levelled out the playing field. We’ve both got it. Great! That seemed like a lot of freedom to me.”

At least partial acceptance of the diagnosis of HSV-2 infection was reported by 14 (58%) of the participants; however, these individuals still had to contend with ongoing issues. For some individuals, acceptance of HSV-2 infection appeared to be associated with the amount of time that had passed since diagnosis. For example, all individuals diagnosed more than a year ago accepted their diagnosis, whereas only eight of 20 diagnosed within the past 5 months expressed at least partial acceptance.

### Response model

Our hypothesised model of psychosocial responses to a serological HSV-2 diagnosis is displayed in figure 1. This model

suggests that short term responses and perceived ongoing responses may be buffered by moderators and influenced by mediators. Additionally, the psychological short term responses may have direct and indirect effects on the perceived ongoing responses.

Moderators included existing knowledge, social support, how a person was informed of test results, and the quality of the relationship with sex partner(s). Several individuals identified that having basic knowledge about herpes before testing helped them cope with their diagnosis. Many participants’ responses suggested that perception of support from family and friends was an important element in helping them to cope with the diagnosis. Another important moderator was how individuals were informed of their HSV-2 positive serostatus, with several individuals expressing anger regarding this part of their clinical experience. Finally, quality of relationships with sex partner(s) was an important moderator. Many participants remarked that having an open and honest intimate relationship helped them to deal with the diagnosis. Conversely, poor communication exacerbated negative responses to serological diagnosis.

Mediators included the amount of knowledge acquired about herpes after diagnosis, level of perceived social support regarding diagnosis, tendency of participants to put their diagnosis into a larger perspective (“downward comparison”), and suppression of responses associated with diagnosis. Acquiring knowledge about herpes, either as the result of counselling or through personally seeking out information, helped to normalise the disease, lessen the perceived stigma, and relieve participants’ feelings of isolation. One woman (46, FM) stated, “I think one of the pieces of information I was given when the herpes was diagnosed was just how many people have it. And I think that because it wasn’t something that was going to kill me, and I could control it and not spread it, the fact that I wasn’t the only person in Seattle with herpes, I think that helped me accept it.” Another woman (51, FM) stated, “I think probably the most comforting news [was] hearing that approximately 25% of the people who came in to family medicine [clinic] have it and only half of them knew it.” Social support was also identified as a mediator, with many people remarking how important it was to gain the acceptance and understanding of their sex partners and friends. Alternatively, a lack of support regarding the diagnosis was identified as a source of ongoing stress; however, both men and women, regardless of sexual orientation, employed downward comparison, often contrasting their HSV diagnosis with a HIV diagnosis. For example, one man (39, STD) said, “As far as being comfortable with it, you know ten years ago I wouldn’t have been. But with HIV being out there, I can live with herpes.” Finally, several women, using suppression as a coping mechanism, stated that they chose not to think about their diagnosis or their subsequent feelings.

## DISCUSSION

The availability of accurate serological testing techniques for HSV-2 coupled with high prevalence rates of HSV-2 within the general population necessitate clinical strategies to deal with the psychosocial aspects of this disease. This qualitative study examined the emotional and the psychosocial responses to receiving a HSV-2 seropositive diagnosis among 24 participants with no history of genital herpes. We found that initial emotional reactions range from distress to denial. Fears of telling current and future partners were consistent responses for most participants. Persistent concerns included fear of transmitting to current or future partners, a reluctance to engage in future relationships, and for women, transmission to a newborn or child. Moderating factors that influenced responses included the manner in which individuals were informed of their diagnosis and prior knowledge regarding herpes. Mediating factors that mitigated the severity of ongoing responses include the acquisition of information pertaining to prevalence rates and medical aspects of herpes, the quality of current relationships, and social support.

An interesting finding that has not been identified previously in the literature is that some participants are “glad to know” that they have herpes, as receiving a herpes diagnosis provided an explanation for physical symptoms that previously had lacked an explanation. Finding out their HSV-2 seropositive status may provide individuals with the information necessary to prevent future transmission.<sup>32</sup> In addition, we found that more than half of the participants reached a level of acceptance regarding their diagnosis and that time was a key factor.

Our study suggests that existing or acquired knowledge about HSV-2 infection protects against potentially severe emotional and psychosocial responses following serological diagnosis, partly a normalising effect. Although the technology of rapid testing for HSV-2 is now available,<sup>1</sup> our findings clearly suggest that time should be allocated for counselling. At a minimum, counselling should be designed to address the inherently confusing nature of “asymptomatic” HSV-2 infection, such as the discrepancies in infection, transmissibility, symptoms, and recurrences. Counselling should also focus on the difficulties associated with telling sex partners or with feeling guilt about possible transmission to others. Understanding that HSV-2 is a common infection is also likely to be an important counselling message that may assist individuals in their coping as suggested by studies of patients with recurrent genital herpes.<sup>33,34</sup> Time limitations for clinicians must be recognised, however, and innovative alternatives, such as integrating the efforts of health educators into clinical practice or interactive computer software,<sup>35</sup> warrant further investigation.

While the emotional and psychosocial burden of recurrent genital herpes has been documented previously,<sup>11–14</sup> the impact of a serological, compared to clinical, diagnosis of genital herpes has been examined only recently. Smith and colleagues found an absence of change on a number of psychological measures completed by 11 individuals before and 6 months after serological HSV-2 positive diagnosis.<sup>7</sup> Wilkinson *et al* reported that they found no significant difference in anxiety and depressive symptoms between 25 HSV-2 seropositive individuals without a history of genital herpes and 26 HSV-2 seropositive individuals with a history of genital herpes.<sup>36</sup> While encouraging, both quantitative studies had small numbers of participants. Our qualitative approach allowed us to capture meanings and feelings that may have been overlooked in the context of quantitative survey methodology. Our findings parallel observations made in qualitative research on the impact of a sexually transmitted infection diagnosis, such as *Chlamydia trachomatis*,<sup>37</sup> and on other more chronic forms of loss, such as receiving a diagnosis of HIV<sup>38</sup> or other chronic disease.<sup>39</sup> In this study, the loss is of sexual health.

A limitation of qualitative studies is the lack of generalisability. The diverse nature of our sample, combined with the identification of similar themes across the participants, provided initial evidence that yielded the hypothesised response model. The findings may be tempered by potential bias from participants—for example, recall bias or social desirability bias, or by any interpretative bias held by the authors. Further studies could include following patients longitudinally and conducting interviews at fixed intervals to better understand the process of adjustment to HSV-2 diagnosis.

In conclusion, our qualitative findings suggest that many negative responses to the diagnosis of HSV-2 may be time limited and influenced by factors that are potentially amenable to counselling. Negative responses to diagnosis may also be mitigated by knowledge gained through counselling, and some responses may be constructive, potentially serving a preventive function for partners of HSV-2 seropositive individuals.

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## CONTRIBUTORS

JM, conceptualisation of research issues, qualitative interviews, data analysis, development of the manuscript, and synthesis of the relevant literature; SS, qualitative interviews, data analysis, development of the manuscript, and synthesis of the relevant literature; RC, conceptualisation of research issues, data analysis, development of the manuscript, and synthesis of the relevant literature; LS, conceptualisation of existent research issues, data analysis, development of the manuscript, and synthesis of the relevant literature; WW, conceptualisation of research issues, development of the manuscript, and synthesis of the relevant literature; DD-S, qualitative interviews and development of the manuscript; RDic, conceptualisation of research issues, development of the manuscript, and synthesis of the relevant literature; AW, conceptualisation of research issues, development of the manuscript, and synthesis of the relevant literature.

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