Health-related quality of life of young people and adults with primary or recurrent episodes of genital herpes: a mixed methods systematic review protocol

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Review question: The review questions are:
- What is it like to live with primary or recurrent episodes of genital herpes?
- What interventions improve the health-related quality of life (HRQOL) of young people and adults with primary or recurrent episodes of genital herpes?

The specific objectives are:
- To identify and explore the perceptions and experiences of young people and adults with symptomatic primary or recurrent genital herpes regarding the impact of genital herpes on their HRQOL.
- To determine the effectiveness of interventions for improving the HRQOL of young people and adults with primary or recurrent genital herpes.

This mixed methods review seeks to develop an aggregated synthesis of quantitative and qualitative data on the HRQOL implications of genital herpes for the individual in order to derive conclusions and recommendations for clinical practice and policy decision making.

Keywords antiviral treatment; genital herpes; health-related quality of life; psychological interventions; young people


Introduction

Genital herpes is caused by type 1 and type 2 herpes simplex virus (HSV-1 and HSV-2). Internationally both HSV-1 and HSV-2 contribute to the prevalence of genital herpes, although HSV-1 is primarily associated with oral-oral transmission of orolabial herpes (or “cold sores”) and HSV-2 is almost entirely sexually transmitted through skin-to-skin contact.1 Global prevalence of genital herpes is increasing with approximately 140 million people aged 15–49 years infected with genital HSV-1 infection and an estimated 417 million infected with HSV-2 internationally.1

Transmission is usually via direct contact with an infected person who is shedding virus from secretions on oral, genital or anal mucosal surfaces, although genital herpes can also be acquired from contact with lesions at other anatomical sites including the mouth, eyes and other non-mucosal surfaces.2 Up to 70% of all genital HSV-2 infections are transmitted during asymptomatic viral shedding3 with at least 80% of people with proven HSV unaware that they have been infected.4

A primary episode of genital herpes can be distressing for the individual since it frequently presents with multiple painful lesions on the external genitalia, the cervix, rectum, thighs and buttocks, which burst to leave erosions and ulcers.5 Individuals may also experience dysuria, vaginal or urethral discharge, and systemic symptoms such as fever and malaise. A primary episode may persist for up to 20 days.6 Recurrent genital herpes is caused by reactivation of the dormant HSV in the nerve roots of the sacral plexus,7 which may cause painful lesions, while systemic symptoms are less common in recurrent episodes and episodes are usually shorter, lasting between five to 10 days.6
episodes are managed with oral antiviral therapy in addition to self-care measures. These self-care measures can include regular bathing to prevent secondary infection; measures to decrease the pain of micturition including the application of Vaseline or a topical anesthetic such as lidocaine 5%; increasing fluid intake to dilute urine and urinating in a bath or shower to reduce stinging; wearing loose fitting clothing to reduce irritation of lesions; oral analgesia such as paracetamol; and infection control measures such as avoiding sharing towels and abstinence from penetrative, non-penetrative and orogenital sex until lesions have cleared.8

Three systematic reviews have examined the effectiveness of antiviral treatment on the duration of symptoms9,10 and time to recurrence9-11 in people with a primary episode of genital herpes. These have all identified that oral antiviral treatments decrease symptoms in people with primary episodes of genital herpes and that daily maintenance treatment with oral antiviral agents effectively reduces frequency of recurrences and improves quality of life. There is insufficient evidence to establish which type of oral antiviral drug is the most effective in reducing the duration of symptoms,10,11 with one review showing that there was low quality evidence both for and against the effectiveness of oral aciclovir in reducing the duration of symptoms for genital herpes.9

Recurrent episodes of genital herpes may require the self-care measures outlined above as well as the avoidance of any identified triggers such as ultraviolet light and excessive alcohol consumption.8 In addition, episodic antiviral treatment and suppressive antiviral therapy may be considered. One systematic review10 showed that if herpes is recurrent, aciclovir, famciclovir and valaciclovir when taken at the start of recurrence are all equally beneficial in reducing duration of symptoms, and reducing lesion healing time and viral shedding.

A diagnosis of genital herpes can lead to considerable psychosocial distress for the individual.12 Frequently, genital herpes is associated with depression,12-14 diminished self-concept,15 withdrawal from intimate relationships16 and diminished quality of life.1,17,18 Other emotional responses include shame and anxiety about having an outbreak or transmitting herpes to someone else.12 It has also been identified that genital herpes can negatively affect sexual wellbeing,19 particularly when individuals perceive that they are stigmatized by others.17,20

A number of interventions have been developed that seek to improve the quality of life of people who experience both primary and recurrent genital herpes. These include suppressive antiviral therapies,14,18 psychological support21 and social support.17,22,23 Antiviral therapies include, for example, suppressive valacyclovir therapy and long-term aciclovir suppression.8

Psychological support may include educational counselling at diagnosis24 and at follow-up,25 psychotherapy,26 cognitive behavioral therapy,27 cognitive restructuring28 and experiential counselling interventions.29 Social support preferences vary but may take the form of virtual support groups, friends, sexual partners, religious/spiritual figures and health providers.17 There is a growing body of qualitative and quantitative evidence that suggests the impact of primary and recurrent genital herpes on the quality of life of young people and adults can be ameliorated by such interventions within primary care and genito-urinary medicine settings.

A search for systematic reviews in several sources specializing in systematic review publications, including the JBI Database of Systematic Reviews and Implementation Reports, the Cochrane Database of Systematic Reviews and the PROSPERO international prospective register, identified no published systematic review on this topic. The previous reviews that have been conducted have focused on screening,30,31 pharmacological treatment,9,11,31-35 transmission10 and psychological factors in recurrent genital herpes.36 Therefore, the impact of this aspect of genital herpes on the health of patients remains unclear.

In this proposed mixed methods review, both the quantitative and qualitative components will explore health-related quality of life (HRQOL) of young people and adults with primary or recurrent episodes of genital herpes. For the purposes of this review, HRQOL is defined as “those aspects of self-perceived wellbeing that are related to or affected by the presence of disease or treatment”.37(p.1384) Combining both quantitative and qualitative studies in the same review will provide a more detailed understanding of both the experiences of living with genital herpes and associated interventions, which will subsequently inform recommendations for clinical practice and policy decision making.
Inclusion criteria

Participants

For both objectives, this review will consider studies that include community dwelling participants, aged 15 years and over, who have been diagnosed with genital herpes. Participants of any gender, ethnic background and geographical location will be considered.

Exclusion criteria will be:
- Patients who are HSV-1 or HSV-2 serologically positive but asymptomatic.
- Carers, family members, partners and healthcare professionals of people who have symptomatic genital herpes but do not have symptomatic genital herpes themselves.

Phenomena of interest

The qualitative component of this review will consider studies that identify and explore the perceptions and experiences of young people and adults with primary or recurrent genital herpes regarding the impact of the virus on their HRQOL.

Intervention

The quantitative component of this review will consider studies that evaluate:
- Antiviral suppression therapies, for example: suppressive oral valaciclovir, aciclovir and famciclovir.
- Psychological interventions, for example: educational counselling, psychotherapy, cognitive behavioral therapy, cognitive restructuring and experiential counselling interventions.
- Self-care measures, for example: stress reduction and self-managed episodic antiviral therapy.
- Social support, for example: virtual support groups, friends, sexual partners, religious/spiritual figures and health providers.
- A combination of the above interventions.

There will be no limits to dosage, frequency, duration and intensity of interventions. Other interventions as identified by the literature will also be included.

Comparator

This review will compare interventions against usual care or placebo, where applicable. In addition, our review will compare the efficacy of the above interventions against one another.

Outcomes

For the first objective, studies will be considered that identify or describe the perceptions and experiences of young people and adults who have had one episode or repeated episodes of genital herpes regarding the impact of the virus on their HRQOL.

For the second objective, in order to investigate the impact of antiviral therapies, psychological interventions, self-care measures and social support, the primary outcome of interest will be HRQOL. Studies will be included if they have objectively measured HRQOL using disease specific HRQOL scales for primary or recurrent genital herpes or generic HRQOL scales. Disease specific quality of life scales are:
- Recurrent Genital Herpes Quality of Life scale
- Quality of Life with Herpes Scale
- Genital Herpes Questionnaire
- Herpes Research Center Questionnaire.

Generic health related quality of life scales are:
- 36-item Short-Form Health Survey
- Health Related Quality of Life Scale
- General Health Questionnaire.

Secondary outcomes will be stress, anxiety, depression or self-esteem. For the first objective, studies will be included if they have addressed these outcomes thematically or objectively using validated instruments. For the second objective, studies will be included if these outcomes have been measured objectively. Such scales may include: the State-Trait Anxiety Inventory, Beck Depression Inventory and the Rosenberg Self Esteem Scale.

Context

The review will seek to investigate the impact of genital herpes on individuals’ HRQOL in the primary care and genito-urinary medicine settings.

Types of studies

This review will consider both experimental and quasi-experimental study designs including randomized controlled trials, non-randomized controlled trials, before and after studies and interrupted time-series studies. In addition, analytical observational studies including prospective and retrospective cohort studies, case-control studies and analytical cross-sectional studies will be considered for inclusion. This review will also consider descriptive observational study designs including case series, individual case reports and descriptive...
cross-sectional studies for inclusion. The qualitative component of the review will consider studies that focus on qualitative data including, but not limited to, designs such as phenomenology, grounded theory and ethnography, action research and feminist research.

Methods
Search strategy
The search strategy will aim to find both published and unpublished studies. An initial limited search of MEDLINE and CINAHL has been undertaken (Genital Herpes OR herpes genitalis AND Antiviral suppression therapies OR Psychological interventions OR Self-care measures OR Social support AND “quality of life” OR QOL OR HRQOL OR stress OR anxiety OR depression OR Self-esteem) followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe the article.

This informed the development of a search strategy which will be tailored for each information source. A full search strategy for MEDLINE is detailed in Appendix I. The reference list of all included studies will be screened for additional studies.

The search will include studies published in the English language, from 1980, as the initial search of the literature in the subject area did not identify any relevant research prior to this date. In addition, the contribution of any research prior to 1980 would be limited in its applicability to current interventions.

Information sources
The databases to be searched include: CINAHL, MEDLINE (Ovid), British Nursing Index, Embase, PsycINFO and Web of Science.

The trial registers to be searched include Cochrane Central Register of Controlled Trials.

The search for unpublished studies will include:
- British Library Thesis Index (EThOS)
- World Health Organization’s library database (WHOLIS)
- The System for Information on Grey Literature in Europe (SIGLE)
- ProQuest Digital Dissertations
- OpenGrey
- The Conference Papers Index
- Direct contact with individual researchers, national and international research institutes/centers and organizations (including non-governmental organizations) working in the field of sexual health.

Study selection
Following the search, all identified citations will be collated and uploaded into Endnote and duplicates removed. Titles and abstracts will then be screened by two independent reviewers for assessment against the inclusion criteria for the review. Studies that meet or could potentially meet the inclusion criteria will be retrieved in full and their details imported into Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information (JBI SUMARI). The full text of selected studies will be retrieved and assessed in detail against the inclusion criteria. Full text studies that do not meet the inclusion criteria will be excluded and reasons for exclusion will be provided in an appendix in the final systematic review report. Included studies will undergo a process of critical appraisal. The results of the search will be reported in full in the final report and presented in a PRISMA flow diagram. Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer.

Assessment of methodological quality
Quantitative papers selected for retrieval will be assessed by two independent reviewers for methodological validity prior to inclusion in the review using the standardized critical appraisal instruments from the Joanna Briggs Institute for the following study types: randomized controlled trials, quasi-experimental studies, case control studies, cohort studies, cases series, case reports and analytical cross sectional studies. Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer.

Qualitative papers will be assessed by two independent reviewers for methodological validity prior to inclusion in the review using the JBI Critical Appraisal Checklist for Qualitative Research. Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer. The results of critical appraisal will be reported in narrative form and in a table.

Data extraction
Quantitative data will be extracted from papers included in the review using the standardized data
extraction tool available from JBI SUMARI\textsuperscript{42} by two independent reviewers. These data extracted will include specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives. Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer. Authors of included papers will be contacted to request missing or additional data where required.

Qualitative data will be extracted from papers included in the review using the standardized data extraction tool from JBI SUMARI\textsuperscript{42} by two independent reviewers. The data extracted will include specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives. Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer. Authors of included papers will be contacted to request missing or additional data where required.

\textbf{Data synthesis}

Papers will, where possible, be pooled in statistical meta-analysis using JBI SUMARI.\textsuperscript{42} Effect sizes will be expressed as either odds ratios (for dichotomous data) or weighted (or standardized) mean differences (for continuous data) and their 95\% confidence intervals will be calculated for analysis of measured outcomes based on patients’ scores in the scales used.

Heterogeneity will be assessed statistically using the standard chi-squared and I\textsuperscript{2} tests. The choice of model (random or fixed effects) and method for meta-analysis will be based on the guidance by Tufanaru \textit{et al.} 2015.\textsuperscript{43} Where statistical pooling is not possible the findings will be presented in narrative form including tables and figures to aid in data presentation where appropriate.

A funnel plot will be generated to assess publication bias if there are 10 or more studies included in a meta-analysis. Statistical tests for funnel plot asymmetry (Egger test, Begg test, Harbord test) will be performed where appropriate.

Qualitative research findings will, where possible be pooled using JBI SUMARI,\textsuperscript{42} with the meta-aggregation approach.\textsuperscript{44} This will involve the aggregation or synthesis of findings to generate a set of statements that represent that aggregation through coding a thematic description to all quantitative data, assembling all of the resulting themes from quantitative and qualitative syntheses, and configuring these themes to produce a set of synthesized findings in the form of a set of recommendations or conclusions.

\textbf{Assessing certainty in the findings}

For quantitative data a Summary of Findings will be created using GRADEPro GDT software.\textsuperscript{45} The GRADE approach for grading the quality of evidence will be followed. The Summary of Findings will present the number of studies and number of participants; the confidence in effect estimates (quality of evidence) and the best estimates of relative and absolute effects.\textsuperscript{46,47} The Summary of Findings will be based upon the primary outcome HRQOL and for secondary outcomes where there is sufficient homogeneity across outcome measures.

For qualitative data the final synthesized findings will be graded according to the ConQual approach for establishing confidence in the output of qualitative research synthesis and presented in a Summary of Findings.\textsuperscript{48} The Summary of Findings will include the major elements of the review and detail how the ConQual score is developed. Included in the table is the title, population, phenomena of interest and context for the specific review. Each synthesized finding from the review is then presented along with the type of research informing it, a score for dependability, credibility, and the overall ConQual score.

\textbf{References}

1. World Health Organization. Globally, an estimated two-thirds of the population under 50 are infected with herpes simplex virus type 1. News release. 2015 [Internet]. [cited


### Appendix I: Initial search strategy for MEDLINE

<table>
<thead>
<tr>
<th>Question part</th>
<th>Question term</th>
<th>Search terms</th>
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<tr>
<td><strong>Population</strong></td>
<td>People who have had genital herpes</td>
<td>(&quot;genital herpes&quot; OR &quot;herpes simplex virus&quot; OR &quot;herpes genitalis&quot; OR HSV OR HSV-1 OR HSV-2 OR &quot;HSV type 1&quot; OR &quot;HSV type 2&quot;) Keywords in title and Abstract OR (Herpes Genitalis/ OR Herpesvirus 2, Human/) (MESH terms)</td>
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<tr>
<td><strong>Interventions</strong></td>
<td>Antiviral suppression therapies</td>
<td>(&quot;Antiviral suppression therapy&quot; OR &quot;antiviral therapy&quot; OR &quot;oral valaciclovir&quot; OR &quot;acyclovir&quot; OR &quot;famciclovir&quot;) Keywords in title and Abstract OR (Antiviral Agents/ OR Acyclovir/) MESH terms OR (Psychological OR counseling OR psychotherapy OR &quot;cognitive behavioral therapy&quot; OR CBT OR &quot;cognitive restructuring&quot;) Keywords in title and Abstract OR (Adaptation, Psychological/ OR Counseling/ OR Cognitive Therapy/) MESH terms OR (&quot;stress reduction&quot; and &quot;self-care&quot; OR self management&quot;) Keywords in title and Abstract OR Self Care/ MESH terms OR (&quot;Social support&quot; OR &quot;support group&quot; OR coping OR adjustment OR &quot;self-help group&quot;) Keywords in title and Abstract OR Social Support/ MESH terms</td>
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<tr>
<td>Phenomena of interest</td>
<td>Health related quality of life</td>
<td>(&quot;quality of life&quot; OR QOL OR HRQOL or stress OR mood OR anxiety OR depression OR, shame OR stigma OR hopelessness OR self-esteem OR &quot;sexual identity&quot; OR “body-image” OR “self-concept”) Keywords in title and Abstract OR (&quot;Quality of Life&quot;/ OR Stress, Psychological/ OR Depression/ OR Anxiety/ OR Shame OR Social Stigma/ OR Self Concept/ OR Body Image) MESH terms</td>
</tr>
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