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Viral DNA Load and Recurrence Frequency in Herpes Simplex Infection: A Three-Group Comparative Study

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Abstract

Background Recurrent herpes simplex infection markedly reduces patients' quality of life. How closely viral replicative activity tracks the severity of the course has not been sufficiently measured. We set out to compare viral DNA load in patients with differing recurrence frequency and to describe it alongside clinical, immunological, and epidemiological indicators.

Materials and Methods 240 participants aged 18 to 68 years were allocated to three groups: a main group (n = 140, frequently recurring course), a comparison group (n = 60, infrequently recurring course), and a control group (n = 40, apparently healthy individuals). Viral DNA load was measured by real-time PCR, serum IFN-γ, IL-4, and total IgE by enzyme-linked immunosorbent assay, and the CD4/CD8 ratio by flow cytometry. Epidemiological data were collected by questionnaire and review of medical records.

Results Viral DNA load rose stepwise across the groups: undetectable in the control group, 2.4 ± 0.2 in the comparison group, and 4.1 ± 0.3 $\log_{10}$ copies/mL in the main group ($p < 0.001$). In parallel, the annual number of recurrences in the main group was 2.7-fold higher than in the comparison group (5.8 ± 0.3 vs 2.1 ± 0.2) and remission was 2.9-fold shorter (2.3 ± 0.2 vs 6.7 ± 0.5 months; $p < 0.001$). Immunological indicators in the main group differed from control: IFN-γ and the CD4/CD8 ratio were lower, IL-4 and total IgE higher ($p < 0.001$). Hypothermia (62.1%) and stress (55.7%) were the triggers most often reported, and 65.7% of recurrences occurred in autumn and winter.

Conclusion A recurring course was associated with disturbed immunological balance, higher viral DNA load, and a set of epidemiological factors. A stepwise relationship was found between viral DNA load and recurrence frequency. Establishing the prognostic value of this indicator will require a prospective study with baseline measurement followed by observation.

Keywords: Herpes simplex, interferon-gamma, polymerase chain reaction, recurrence, risk factors, viral load, virus shedding.

Introduction

Infections caused by herpes simplex virus (HSV) are among the most widespread viral diseases in the human population. According to World Health Organization estimates for 2020, 3.8 billion people under 50 years of age, or 64% of the population, carry HSV-1, while 520 million people aged 15 to 49 years (13%) carry HSV-2. Roughly one in ten HSV-1 infections, some 376 million cases, is genital.[1,2] In the same year, 205 million people aged 15 to 49 (5.3%) had clinical signs of genital herpes at least once, and HSV-2 was responsible in 92% of them.[1] A systematic analysis for the United States put adult HSV-1 seroprevalence at 63.5% (95% CI 61.3–65.7). In that setting HSV-1 accounted for 15.4% of genital herpes, and this share has been rising by a factor of 1.02 per year.[3]

After primary infection the virus persists for life in sensory nerve ganglia. Its reactivation is linked to triggers such as fever, sun exposure, menstruation, injury, emotional stress, and surgery.[1,4] During reactivation the mucosal antiviral response is governed by the cytokine system: type I and type II interferons reinforce local antiviral activity, while a rise in IL-4 and total IgE reflects a shift of the response toward its humoral arm.[5]

The state of the interferon system in herpesvirus infection has attracted particular attention in recent years.[14,16] Work on herpetic keratitis has shown that the epithelial selectivity of interferon-λ and polymorphisms at the IFNL3/IFNL4 locus are among the factors that determine disease severity and the frequency of recurrence.[6] Secondary immune deficiency is regularly documented in recurrent herpetic disease, and the ability of the virus to synthesize proteins that block class I and II HLA receptors disrupts the signalling cascade of the specific immune response.[7] Even so, how closely these indicators track a recurring course, particularly in regional cohorts, remains insufficiently measured.

In routine practice, treatment usually begins once lesions have appeared, whereas the greatest benefit from suppressive therapy is obtained immediately before reactivation.[4,8] Justifying such an approach first requires measuring, in a single cohort, which clinical, immunological, virological, and epidemiological features accompany a recurring course. In local material these indicators have usually been examined separately, which provided the rationale for the present study.

The current state of the problem can be summarized under four headings:

(1) A shift in immunological balance. Recurrence proceeds with a deviation of the Th1/Th2 response toward Th2. Reduced IFN-γ production weakens cell-mediated antiviral defence, while rising IL-4 and total IgE indicate predominance of the humoral component. The virus is thereby given the opportunity to escape immune control and to move from latency into active replication.[5,7]

(2) Indicators of cellular immunity. A fall in the CD4/CD8 ratio reflects weakening of the effector arm of the T-cell response and is associated with a more severe and more frequently recurring course in persistent viral infections.[6,7]

(3) Viral DNA load. Real-time PCR permits quantitative measurement of viral replicative activity and is specified in the clinical protocols of Uzbekistan as the principal laboratory method of diagnosis.[8] How closely the level of viral load corresponds to clinical severity has barely been studied in local material.[4]

(4) Epidemiological triggers. Hypothermia, insolation, emotional stress, intercurrent respiratory infections, and hormonal change are the provoking factors most often cited in relation to recurrence.[1,9] Their combination with immunological disturbance raises the likelihood of recurrence, yet the separate contribution of each factor has not been quantified in regional material.

Objective

To compare viral DNA load in patients with differing recurrence frequency and to describe it alongside clinical, immunological, and epidemiological indicators. Because infection was laboratory-confirmed in both the main and comparison groups, the difference between them relates specifically to the type of course, while the control group serves to establish background values. As the design is cross-sectional, the findings describe association rather than the ability to predict a future recurrence.

Materials and Methods

Study design and participants

The study was conducted between 2024 and 2027 at the Bukhara Regional Branch of the Republican Specialized Scientific and Practical Medical Center of Dermatovenereology and Cosmetology and at the Bukhara Regional Infectious Diseases Hospital, using a prospective observational design, with the epidemiological component carried out in a retrospective–prospective manner. A total of 240 participants aged 18 to 68 years were enrolled: 140 formed the main group with clinically active recurrent RHSI, 60 formed the comparison group with a mild-to-moderate, infrequently recurring course, and 40 formed the control group of apparently healthy individuals without clinical signs of HSV infection. Diagnosis was confirmed in the laboratory by PCR and serological methods.

Inclusion and exclusion criteria

Inclusion criteria: age 18 to 68 years and written consent to participate. For the main and comparison groups, laboratory confirmation of HSV-1/HSV-2 infection (PCR or serology) was additionally required. The control group comprised apparently healthy individuals with no history of clinically manifest herpetic eruptions.

Exclusion criteria: acute infectious diseases, decompensated chronic somatic diseases, autoimmune and oncological diseases, HIV infection, pregnancy and lactation, and receipt of immunomodulators or systemic corticosteroids within the preceding 3 months.

Clinical assessment

Clinical data (annual frequency of recurrences, duration of a single recurrence, length of remission, severity of the course, and localization of lesions) were collected from all participants using a standardized questionnaire and cross-checked against outpatient records and dispensary follow-up registers.

Immunological and virological assays

Serum IL-4, IFN-γ, and total IgE were determined by enzyme-linked immunosorbent assay. Indicators of cellular immunity, including $CD4^+$ and $CD8^+$ T-lymphocyte subpopulations and their ratio, were assessed by flow cytometry. Viral DNA load was quantified by real-time polymerase chain reaction and expressed as $\log_{10}$ copies/mL. All laboratory tests were performed in strict accordance with the manufacturers' instructions for the reagents used. Blood samples were obtained during remission, at least 14 days after resolution of the most recent recurrence.

Epidemiological assessment

The following epidemiological indicators were assessed in every participant: age and sex distribution, permanent place of residence (urban/rural), type of occupation and working conditions, seasonal distribution of recurrences, spectrum of provoking factors (hypothermia, insolation, respiratory infections, stress, hormonal changes, immunosuppressive states), presence of chronic comorbidities, and a history of herpes infection in family members or sexual partners.

Statistical analysis

Data were processed using Microsoft Office Excel and IBM SPSS Statistics under Windows 10. The arithmetic mean (M), standard error of the mean (m), and relative values (%) were calculated. Continuous variables are reported as M ± m. Student's t-test and the χ^2 test were used to assess the significance of intergroup differences. Because no herpetic recurrences occurred in the control group, no between-group comparison of trigger factors was made; these factors are described as frequencies within the main group.

A Bonferroni correction was applied across the four primary immunological comparisons (IFN-γ, IL-4, total IgE, CD4/CD8), setting the significance threshold at $p < 0.0125$. A p value below 0.001 was taken as high significance, below 0.01 as moderate, below 0.05 as borderline, and above 0.05 as not significant.

Reporting standard

The manuscript was prepared in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement for observational studies.[10] Selection of participants and their allocation to groups is shown in Fig. 1.

Results

Participant flow

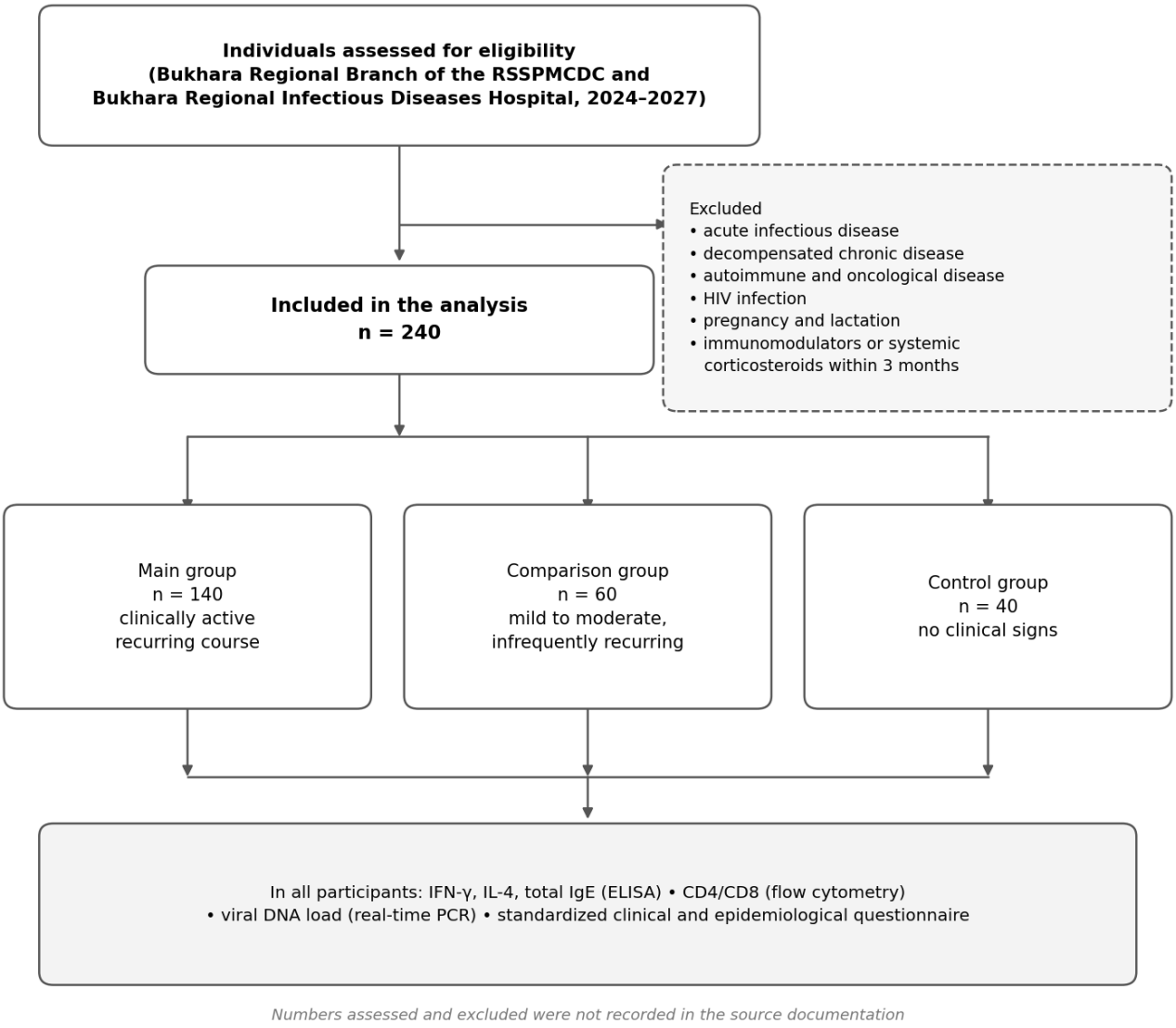

Fig. 1 Selection of participants and allocation to groups (STROBE flow diagram). The numbers assessed for eligibility and excluded were not recorded in the source documentation, so the upper part of the diagram is shown with a dashed outline.

Demographic comparability of the groups

Analysis of the age distribution showed that individuals aged 18 to 29 and 30 to 44 years predominated in all three groups (Table 1). The mean age was 35.6 ± 0.9 years in the main group and 34.2 ± 1.4 years in the control group. Overall comparison of the age distribution across the three groups showed that the intergroup difference was not statistically significant ($\chi^2 = 1.27$; degrees of freedom = 4; $p = 0.866$), that is, no appreciable difference in age structure was detected between the groups. Women predominated in all groups (61.4% in the main group, 58.3% in the comparison group, and 52.5% in the control group), but the intergroup difference was not significant ($p > 0.05$).

Table 1 Distribution of participants by age and sex

Indicator	Control, n = 40	Comparison, n = 60	Main, n = 140	χ^2	p
18–29 years	14 (35.0%)	26 (43.3%)	58 (41.4%)		
30–44 years	19 (47.5%)	23 (38.3%)	61 (43.6%)	1.27	0.866
45–68 years	7 (17.5%)	11 (18.3%)	21 (15.0%)		
Women	21 (52.5%)	35 (58.3%)	86 (61.4%)		> 0.05
Men	19 (47.5%)	25 (41.7%)	54 (38.6%)		> 0.05
Mean age, years	34.2 ± 1.4	—	35.6 ± 0.9		> 0.05

Note: data are presented as absolute numbers (%) and as M ± m. The χ^2 test for age distribution was calculated on a 3 × 3 table. The mean age of the comparison group was not recorded in the source documentation and is therefore not given.

Clinical characteristics of recurrences

A marked difference in the annual frequency and duration of recurrences was recorded between the main and comparison groups (Table 2). The mean annual number of recurrences in the main group was 5.8 ± 0.3, which was 2.7-fold higher than the 2.1 ± 0.2 in the comparison group ($p < 0.001$). The duration of a single recurrence was 8.4 ± 0.4 days in the main group, significantly longer than the 5.6 ± 0.3 days in the comparison group ($p < 0.01$). The gap in remission duration was wider still. It lasted only 2.3 ± 0.2 months in the main group against 6.7 ± 0.5 months in the comparison group, a 2.9-fold difference ($p < 0.001$).

Table 2 Clinical indicators of recurrence in the main and comparison groups

Indicator	Main group, n = 140	Comparison group, n = 60	p
Annual number of recurrences	5.8 ± 0.3	2.1 ± 0.2	< 0.001
Duration of a single recurrence, days	8.4 ± 0.4	5.6 ± 0.3	< 0.01
Duration of remission, months	2.3 ± 0.2	6.7 ± 0.5	< 0.001

Note: data are M ± m, where m is the standard error of the mean. p denotes significance relative to the comparison group.

Viral DNA load

Viral DNA load rose stepwise across the three groups (Fig. 2). It was undetectable in every participant in the control group. In the comparison group, with an infrequently recurring course, the mean load was 2.4 ± 0.2 $\log_{10}$ copies/mL, rising to 4.1 ± 0.3 $\log_{10}$ copies/mL in the main group with frequent recurrences ($p < 0.001$). This comparison is the principal finding of the study, because infection was laboratory-confirmed in both the main and comparison groups and they differ from one another only in the type of course. The 1.7 $\log_{10}$ difference observed therefore relates to recurrence frequency rather than to the presence of infection as such.

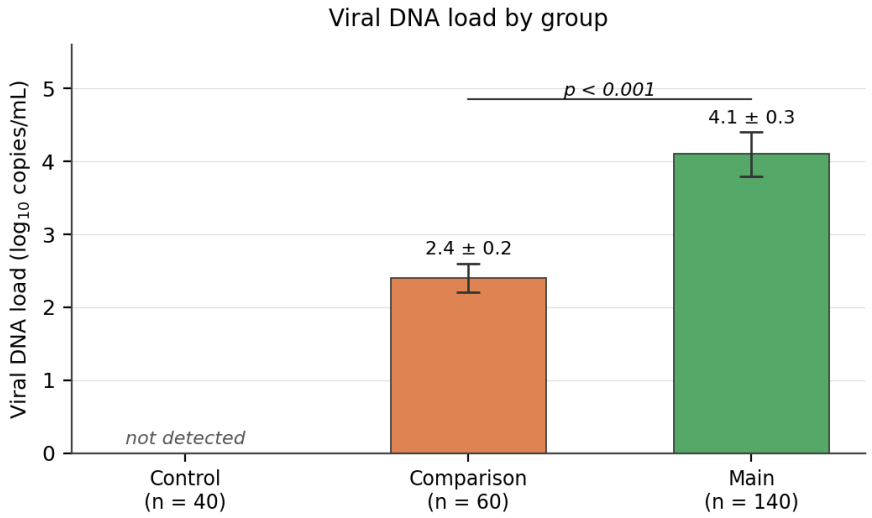

Fig. 2 Distribution of viral DNA load by group. HSV DNA quantified by real-time PCR (log_{10} copies/mL). Data are presented as M ± m.

Immunological indicators

Immunological indicators were analysed to assess what immune state might underlie the difference in virological activity (Table 3, Fig. 3). This analysis was made between the main and control groups, since immunological results are not available for the comparison group. IFN-γ fell from 38.4 ± 1.8 pg/mL in the control group to 16.9 ± 1.1 pg/mL in the main group. IL-4 rose from 9.2 ± 0.6 to 22.3 ± 1.0 pg/mL and total IgE from 58.1 ± 3.2 to 142.7 ± 6.3 IU/mL. The CD4/CD8 ratio fell from 1.82 ± 0.05 to 1.21 ± 0.04. The difference was statistically significant in all four comparisons ($p < 0.001$).

This trend indicates a shift of the Th1/Th2 balance toward Th2, and the reduced CD4/CD8 ratio reflects weakening of the effector function of cellular immunity. These changes are considered as a possible mechanism underlying the virological activity described above. Since the comparison was made against healthy individuals, however, they may equally relate to the presence of infection rather than to recurrence frequency.

Table 3 Immunological indicators in the control and main groups

Indicator	Control group, n = 40	Main group, n = 140	p
IFN-γ, pg/mL	38.4 ± 1.8	16.9 ± 1.1	< 0.001
IL-4, pg/mL	9.2 ± 0.6	22.3 ± 1.0	< 0.001
Total IgE, IU/mL	58.1 ± 3.2	142.7 ± 6.3	< 0.001
CD4/CD8 ratio	1.82 ± 0.05	1.21 ± 0.04	< 0.001

Note: data are M ± m, where m is the standard error of the mean. Immunological values for the comparison group are not yet available; testing is ongoing.

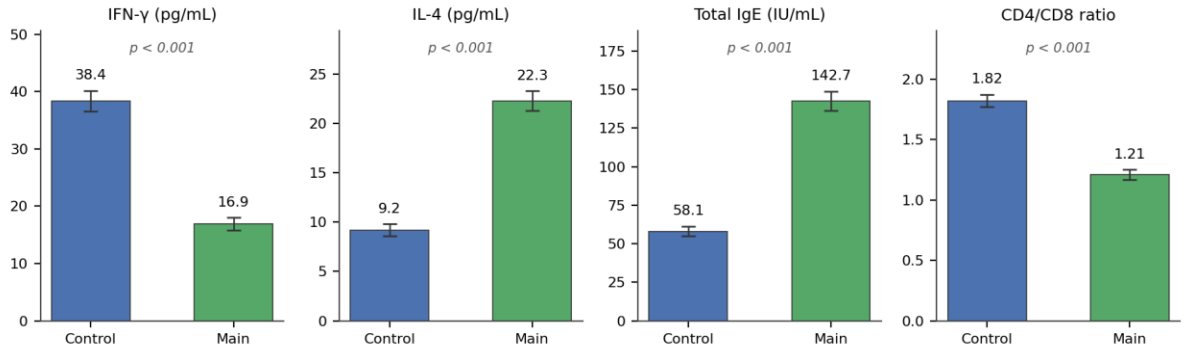

Fig. 3 Immunological indicators in the control and main groups. The grouped bar chart shows IFN-γ, IL-4, total IgE, and the CD4/CD8 ratio in the control and main groups. Only two groups are shown because immunological testing in the comparison group is still ongoing. Data are presented as M ± m.

Epidemiological risk factors

Analysis of the seasonal distribution of recurrences revealed an important epidemiological pattern: in the main group, most recurrences occurred in autumn and winter (34.3% and 31.4%, respectively), while the proportion fell appreciably in spring and summer (Table 4). The mean duration of a recurrence was also longest in autumn (8.6 ± 0.4 days) and winter (8.1 ± 0.4 days). This pattern confirms the role of hypothermia and intercurrent respiratory infections in provoking recurrence.

Table 4 Seasonal distribution of recurrences in the main group

Season	Proportion of recurrences, %	Mean duration, days	p (duration)
Winter	31.4	8.1 ± 0.4	< 0.001
Spring	16.4	6.3 ± 0.3	< 0.05
Summer	17.9	5.8 ± 0.3	> 0.05
Autumn	34.3	8.6 ± 0.4	< 0.001

Note: p denotes significance relative to summer. Data are M ± m.

Patients in the main group most often named hypothermia as a trigger of recurrence — 87 patients (62.1%) (Table 5). Stress followed (78 patients; 55.7%), then intercurrent respiratory infections (68 patients; 48.6%). Among women, an association with hormonal change was recorded in more than two-thirds (58 of 86; 67.4%). Insolation (35.0%) and exacerbation of chronic comorbidity (30.7%) were reported less often. Most patients named several factors at once.

The social and occupational profile of the main group was as follows: rural residents accounted for 54.3% and urban residents for 45.7%. Individuals engaged in physical labour or working in cold or damp conditions made up 38.6% of patients. A history of herpes infection in a sexual partner was recorded in 44.3% of patients, and a family history of herpetic eruptions in more than a third.

Table 5 Frequency of factors reported as triggering a recurrence in the main group

Trigger factor	Patients (n = 140)	Proportion, %
Hypothermia	87	62.1
Stress	78	55.7
Intercurrent respiratory infections	68	48.6
Hormonal changes (women, n = 86)	58	67.4
Insolation	49	35.0
Exacerbation of chronic comorbidity	43	30.7

Note: proportions sum to more than 100% because a patient could report several factors at once. Data were collected retrospectively by questionnaire. No between-group comparison of trigger factors was made, since no herpetic recurrences occurred in the control group.

Proposed follow-up planning scheme

To help translate the observed differences into routine follow-up, a five-step scheme is proposed (Fig. 4). It distinguishes three types of course according to recurrence frequency and duration of remission and sets out a follow-up plan for each. No threshold values or scoring system are used: establishing exact boundaries between the categories would require prospective material. The scheme was not tested here and should not be taken as a ready clinical recommendation.

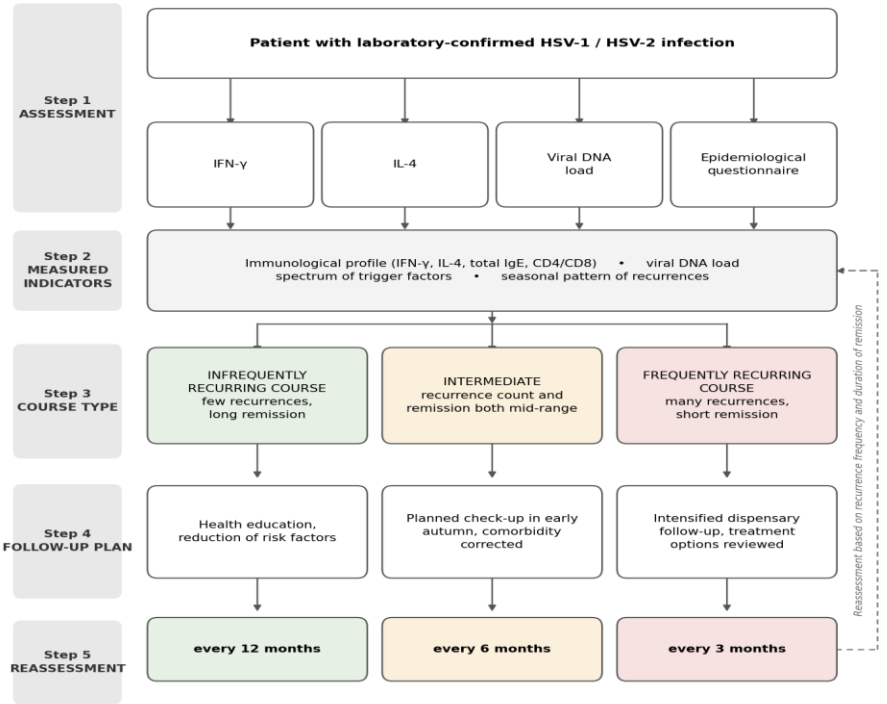

Fig. 4 Proposed follow-up planning scheme. The patient is assessed, clinical, immunological, virological, and epidemiological indicators are measured, the type of course is determined from recurrence frequency, and a corresponding follow-up plan is set. The dashed line denotes reassessment. The scheme is proposed on the basis of the study findings and has not been tested prospectively.

Practical implications

The differences observed show that immunological balance and virological activity are appreciably altered in patients with frequent recurrences. The clearest practical implication comes from the epidemiological part: the clustering of recurrences in autumn and winter, together with hypothermia showing the strongest association, suggests that preventive counselling and a planned check-up are best arranged before the season begins.

Discussion

The principal finding of this study is that viral DNA load rises stepwise with recurrence frequency: it was undetectable in the control group, 2.4 ± 0.2 in patients with infrequent recurrences, and 4.1 ± 0.3 $\log_{10}$ copies/mL in those with frequent recurrences ($p < 0.001$). The value of this gradient lies in the fact that infection was laboratory-confirmed in both the main and comparison groups, which differ from one another only in the type of course. The difference observed therefore reflects the level of viral replicative activity rather than the presence of infection.

The picture obtained agrees with data describing the role of cytokines and chemokines in mucosal immunity: when the local antiviral action of type I and type II interferons is weakened, spread of the virus in the epithelium is no longer adequately contained.[5] The regular documentation of secondary immune deficiency in herpesvirus infection[7] and the finding that the strength of the interferon response determines disease severity in herpetic keratitis[6] lend further support to our results.

The 1.7 $\log_{10}$ difference observed, roughly fiftyfold, gives a quantitative expression to the relationship between recurrence frequency and the level of viral replication. Asymptomatic viral shedding is known to continue between recurrences and to occur even in carriers without clinical signs,[15,20,21] which makes DNA load a convenient measure of disease activity. Since PCR is already designated in the clinical protocols of Uzbekistan as the principal laboratory method of diagnosis,[8] using this indicator in practice is also straightforward in organizational terms.

The epidemiological component revealed a clear seasonal and occupational pattern in the local setting. More than two-thirds of recurrences (65.7%) fell in autumn and winter, and hypothermia was the trigger most often reported by patients (62.1%). These findings fit the list of triggers cited by WHO[1] and observations of recurrent herpetic disease in the region,[9] and they argue for planning preventive measures before the autumn season begins.

The differences found by place of residence and occupation confirm that risk factors are not purely individual in nature. The predominance of rural residents in the main group (54.3%) and the share of patients working in cold or damp conditions (38.6%) call for occupational hygiene and organizational measures to be built into the preventive plan alongside medical ones.

The between-group difference ran in the same direction and was statistically significant for every immunological indicator. Relying on a single indicator would nonetheless be unwise, since the groups may overlap partly in their ranges of values.

Comparison of the present findings with international data clarifies the regional specificity of the study. The recurrence rate in our cohort (5.8 ± 0.3 recurrences per year in the main group) exceeded the figures reported in meta-analyses and global estimates,[4,18,19] which may reflect delayed initial presentation and incomplete dispensary coverage. The predominance of women (61.4%) is consistent with global modelling data showing a persistently high incidence among women of reproductive age.[2,3] That hypothermia showed the strongest association is consistent with the trigger factors listed in official guidelines[8,13] and lends additional support to the external validity of the observed patterns.

In the available literature, immunological and epidemiological criteria are typically applied separately. The efficacy of suppressive therapy in reducing recurrence frequency is established in randomized trials and official guidelines,[12,13] yet the question of whom to treat and when remains open.[17] The contribution of the present work is that immunological, virological, and epidemiological indicators were measured in the same cohort and their association with a recurring course was compared within a single methodological framework. The epidemiological factors require no laboratory base and can be assessed even at a rural physician's post, while the immunological indicators help explain the biological mechanism behind the

difference. Determining which of these two layers is more useful in practice is a task for the next stage.

Certain features of the study design are worth bearing in mind when interpreting the results. As the design is cross-sectional, the differences observed describe the association between the indicators and the type of course; assessing causation or the ability to identify a future recurrence in advance would require prospective follow-up. Trigger factors were recorded from patient history, so recall may play a part in how they are interpreted. Blood samples were taken at least 14 days after the most recent recurrence, and immunological indicators were measured once, during remission; repeated measurements are planned to capture their behaviour in the run-up to a recurrence.

A few points about how the data are presented should also be noted. Dispersion was recorded in the source documentation as the standard error of the mean, and the analysis is reported in that form. Recurrence frequency, duration of a recurrence, and duration of remission were each recorded independently, from patient history. The immunological and virological comparison was made between the main and control groups; a comparison between the main and comparison groups would be more informative about the tendency to recur, and that work is currently ongoing and will be reported separately. Trigger factors are described within the main group, since herpetic recurrences do not occur in the control group. Formal testing of normality and nonparametric analysis would have added information, and detailed specifications of the laboratory kits would make replication in another laboratory more straightforward. The study was carried out in a single region, cases caused by HSV-1 and HSV-2 were not analysed separately, and the cytokine panel was limited to IFN-γ, IL-4, and total IgE — adding IL-10, TNF-α, and IL-2 would round out the picture. As the study protocol runs to 2027, these results represent an interim analysis, and the directions listed above will be addressed in the next stages of the work.

Taken together, measuring clinical, immunological, virological, and epidemiological indicators in a single cohort revealed the multi-layered nature of a recurring course. The next stage envisages measuring these same indicators at baseline and then following patients up, so that their true prognostic value can be assessed.[11]

Conclusion

This study shows that viral DNA load rises stepwise with recurrence frequency: undetectable in the control group, 2.4 ± 0.2 in patients with infrequent recurrences, and 4.1 ± 0.3 $\log_{10}$ copies/mL in those with frequent recurrences. Because infection was laboratory-confirmed in both groups compared, this difference relates to the type of course rather than to infection itself. The immunological changes recorded (lower IFN-γ and CD4/CD8 ratio, higher IL-4 and total IgE) were noted as a background that may help explain this virological activity. Hypothermia, intercurrent respiratory infections, and stress showed the strongest association with a recurring course. The clustering of recurrences in autumn and winter suggests that preventive measures are best planned before the season begins. A follow-up planning scheme is proposed on this basis. It was not tested in the present study, so validation in an independent sample and an interventional trial would be needed before any conclusion could be drawn about its effect on recurrence frequency or duration of remission.

Data Availability Statement

The aggregate figures underlying the conclusions presented here are given in full in the text and tables. Patient-level data are not publicly available because of personal data protection requirements; reasonable requests will be considered by the corresponding author.

Authors' Contributions

H.N.Q. developed the study concept, collected the data, and wrote the manuscript. M.M.R. supervised the study and critically reviewed the manuscript. Q.O.Sh. performed the epidemiological analysis and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

Compliance with Ethical Principles

The study was reviewed and approved by the Local Ethics Committee of the Bukhara State Medical Institute (Protocol No. 12069, 18 June 2026, Bukhara). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patients' Consent

Written informed consent to participate and to the publication of anonymized data was obtained from every person included in the prospective component. The retrospective review of medical records was carried out under the protocol approved by the ethics committee, using de-identified data.

Funding and Sponsorship

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Declaration on the Use of Artificial Intelligence

An artificial intelligence tool was used in preparing the manuscript for text editing, structural organization, and language refinement. The study concept, the collection and analysis of the primary data, the interpretation of the results, and all scientific conclusions are the authors' own. The authors have reviewed and approved the final version of the manuscript and take full responsibility for its content.

Conflict of Interest

None declared.

Acknowledgments

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