




BMJ Open Effect of acyclovir therapy on the outcome of mechanically ventilated patients with lower respiratory tract infection and detection of herpes simplex virus in bronchoalveolar lavage: protocol for a multicentre, randomised controlled trial (HerpMV)

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ABSTRACT

Introduction Herpes simplex virus (HSV) is frequently detected in the respiratory tract of mechanically ventilated patients and is associated with a worse outcome. The aim of this study is to determine whether antiviral therapy in HSV-positive patients improves outcome.

Methods and analysis Prospective, multicentre, open-label, randomised, controlled trial in parallel-group design. Adult, mechanically ventilated patients with pneumonia and HSV type 1 detected in bronchoalveolar lavage ($\geq 10^5$ copies/mL) are eligible for participation and will be randomly allocated (1:1) to receive acyclovir (10 mg/kg body weight every 8 hours) for 10 days (or until discharge from the intensive care unit if earlier) or no intervention (control group). The primary outcome is mortality measured at day 30 after randomisation (primary endpoint) and will be analysed with Cox mixed-effects model. Secondary endpoints include ventilator-free and vasopressor-free days up to day 30. A total of 710 patients will be included in the trial.

Ethics and dissemination The trial was approved by the responsible ethics committee and by Germany's Federal Institute for Drugs and Medical Devices. The clinical trial application was submitted under the new *Clinical Trials Regulation* through CTIS (The Clinical Trials Information System). In this process, only one ethics committee, whose name is unknown to the applicant, and Germany's Federal Institute for Drugs and Medical Devices are involved throughout the entire approval process. Results will be published in a journal indexed in MEDLINE and CTIS. With publication, de-identified, individual participant data will be made available to researchers.

Trial registration number NCT06134492.

INTRODUCTION

Herpes-simplex virus (HSV), in majority HSV type 1, can be detected frequently in the

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The study is the first multicentre, randomised controlled trial to answer the study question.
- ⇒ As a pragmatic trial, it will be performed in real-life situations and the outcomes can be instantly applied in daily practice.
- ⇒ A limitation is the non-blinding of treating physicians.

respiratory tract of mechanically ventilated patients with lower respiratory tract infection (LRTI). The detection frequency of HSV type 1 ranges between 5% and 64%, depending on the study population and the disease severity.^{1–5} However, there is ongoing discussion whether these HSV detections represent only a harmless viral shedding, as a consequence of reactivation reflecting the severity of the underlying disease and immunoparalysis, or a clinically relevant infection requiring antiviral therapy.⁶ Study results on this issue are conflicting. The challenge of rendering a confident clinical diagnosis of HSV pneumonia in these patients further complicates the decision of whether to initiate an antiviral therapy. The gold standard for diagnosing HSV pneumonia is a lung biopsy. However, this procedure is not routinely feasible for patients on mechanical ventilation. Furthermore, cytological changes typical for HSV infection are admittedly specific but suffer from poor sensitivity.⁷ Above all, the clinical symptoms of HSV pneumonia are non-specific

and often mimic those of bacterial pneumonia. This also applies to radiological imaging. So far, only retrospective studies have examined the benefits of antiviral therapy in HSV-positive patients with mechanical ventilation and LRTI. A meta-analysis of these studies⁸ found that antiviral treatment was associated with reduced hospital mortality (risk ratio (RR) 0.74, 95% CI 0.64 to 0.85) and 30-day mortality (RR 0.75, 95% CI 0.59 to 0.94). However, all studies had a high risk of bias and overall evidence is low. Therefore, the aim of this multicentre, randomised controlled trial is to prospectively determine whether acyclovir therapy improves outcomes in mechanically ventilated patients with pneumonia and HSV-1 detection in bronchoalveolar lavage (BAL).

METHODS AND ANALYSIS

Overview of trial design

The trial is an investigator-initiated, prospective, multicentre, open-label, randomised, controlled trial in a parallel-group design. Mechanically ventilated patients in the intensive care unit with pneumonia and HSV-1 detected in BAL are eligible for participation and will be randomly allocated to receive acyclovir (intervention group) for 10 days (or until discharge from intensive care unit (ICU) if earlier) or no intervention (control group). Approval has been obtained from the ethics committee and the Federal Institute for Drugs and Medical Devices (EU-CT: 2023-504322-19-00). The trial will be conducted at approximately 28 study sites in Germany.

Primary objective

The primary study objective is to ascertain whether acyclovir therapy provides a survival benefit for mechanically ventilated patients with pneumonia who exhibit HSV-1 presence in their BAL. The primary outcome is mortality measured at day 30 after randomisation (primary endpoint).

Secondary objectives

The secondary objective of the study is to determine whether therapy with acyclovir has an impact on disease progression. Secondary endpoints include:

- ▶ Ventilation-free days up to day 30 (days without invasive ventilation via endotracheal tube, including tracheostoma) are counted.
- ▶ Vasopressor-free days up to day 30 (counting days without continuous vasopressor administration >1 hour/day).
- ▶ Delta Sequential Organ Failure Assessment Score (SOFA) (baseline—day 10 or end of therapy (EOT)).
- ▶ Delta SOFA subscore kidney (baseline—day 10 or EOT).
- ▶ Delta estimated glomerular filtration rate (eGFR) value (baseline—day 10 or EOT).
- ▶ Length of stay in ICU and hospital stay until day 30.
- ▶ Cost of intervention (ICU and hospitalisation days+acyclovir).

- ▶ Days without delirium/coma (based on confusion assessment method for the intensive care unit/ Richmond Agitation-Sedation Scale (CAM-ICU/RASS) until day 10/EOT).
- ▶ Microbiological cure (EOT)—HSV eradication for blood and respiratory tract, respectively.
- ▶ 90 days mortality.
- ▶ 180 days mortality.
- ▶ Quality of life (EuroQol 5-Dimension 5-level (EQ-5D-5L) questionnaire) day 10 or EOT, day 30, day 90 and day 180.
- ▶ Incidence of serious adverse events (SAEs).

Inclusion criteria

Individuals who meet all of the following inclusion criteria may be included in this study:

- ▶ ≥18 years.
- ▶ Invasive mechanical ventilation is expected for ≥48 hours from the time of randomisation.
- ▶ PCR HSV-1 in BAL ≥10⁵ copies/mL.
- ▶ Pneumonia (community or nosocomial acquired, including ventilator-associated).
- ▶ Written declaration of consent of the patient or legal representative.

Schuieler *et al*⁹ show that the HSV viral load in patients with >10⁵ HSV copies/mL did not differ significantly between a sample taken by BAL and a sample taken from tracheobronchial secretion. However, within the trial bronchial specimen collection (bronchial lavage/BAL) should preferably be performed to detect HSV-1. Invasive mechanical ventilation includes any form of positive pressure ventilation above expiratory pressure during inspiration delivered via an orotracheal or nasotracheal tube, or tracheostomy tube with or without positive end-expiratory pressure. The following criteria should be present for the diagnosis of pneumonia: New, persistent, or progressive infiltrate in combination with two of three other criteria: (1) Leucocytes >10 000 or <4000/μL, (2) fever ≥38.3°C, (3) purulent secretion. Pathogen detection (eg, bacteria) is not mandatory. The initial diagnosis of pneumonia should not be more than 96 hours ago. Given the infrequent detection of HSV-2, our study focuses solely on HSV-1. For instance, in the investigation conducted by Schuieler *et al*,⁹ PCR testing was employed to analyse respiratory secretions from 425 ICU patients for HSV-1/2 replication. Among these patients, 126 (29.6%) exhibited a minimum of 10³ copies/mL of HSV-1. Notably, only one patient showed additional evidence of HSV-2 replication.

Exclusion criteria

Subjects who meet any of the following exclusion criteria will not be included in the study:

- ▶ History of hypersensitivity to acyclovir or valacyclovir or other components of the investigational product.
- ▶ Pregnancy/lactation.
- ▶ Simultaneous participation in another interventional clinical trial.
- ▶ Decision to withhold life-sustaining therapies.

- ▶ Use of a virostatic agent (intravenously or orally) with activity against herpes simplex (valacyclovir, famciclovir/penciclovir, brivudine, cidofovir, foscarnet) for therapeutic or prophylactic reasons at the time of randomisation.
- ▶ History of solid organ transplantation, stem cell transplantation.
- ▶ Absolute neutrophil count $<1500/\mu\text{L}$ ($<1.5 \times 10^9/\text{L}$).
- ▶ Previous study participation.

Study procedures

Patients in the intervention group receive acyclovir intravenously at doses of 10 mg/kg body weight every 8 hours, corresponding to a total daily dose of 30 mg/kg body weight, provided renal function is not impaired. In patients with renal impairment and patients with renal replacement therapy the acyclovir dose is adjusted according to the manufacturer's recommendation. For patients with a body mass index (BMI) of $\leq 25 \text{ kg/m}^2$, the dose calculation is based on the actual current body weight. For patients with a BMI $>25 \text{ kg/m}^2$, the adjusted body weight (=adjusted ideal weight in kg) is used for dosage calculation. The required dose of acyclovir must be administered by slow intravenous infusion over a period of at least 2 hours. Rapid or bolus injections must be avoided. When used in an infusion bag, the reconstituted acyclovir solution must be diluted, taking care not to exceed the maximum concentration of 5 mg/mL acyclovir per bag. The investigational medicinal product is provided by the local hospital pharmacy of the study site within the framework of regular medical care. The time interval between randomisation and the start of treatment should be kept as short as possible. The duration of therapy is 10 days or until discharge from ICU if earlier.

Patients allocated to the control group will receive no intervention. Blinding of the treating physicians and patients is not intended. The reason for this is that the primary endpoint is not influenced by the open study design, but the effort of a placebo-controlled study is enormous.

Acyclovir dose justification

Randomised controlled trials have not yet been conducted to assess the efficacy of acyclovir in treating pneumonia with HSV detected in both immunocompromised and immunocompetent patients. Consequently, the optimal dosage of acyclovir remains unknown. Furthermore, it is worth noting that no randomised controlled trial of acyclovir has been performed for other non-meningitis HSV-associated infections, such as hepatitis, or oesophagitis. In muco-cutaneous HSV infections 15 mg/kg acyclovir is given daily. However, in immunocompetent patients these infections are self-limiting infections and acyclovir is given to shorten symptom duration and not to reduce mortality. In contrast, in ventilated ICU patients with pneumonia and HSV in BAL the majority of clinicians administer a daily dosage of 30 mg/kg, which was associated with better outcomes compared with patients

without HSV-specific therapy.⁸ With this in mind, in the HerpMV study, acyclovir will be administered at a dose of 10 mg/kg body weight 8-hourly. This approach is also supported by observations within the PTH study (Pre-emptive Treatment for Herpesviridae).¹⁰ Although a lower number of patients who received preemptive acyclovir treatment (15 mg/kg daily for 14 days) developed HSV bronchopneumonitis compared with those who received a placebo, a significant proportion of patients still developed HSV bronchopneumonitis, which was defined by clinical symptoms suggestive of pneumonia and the presence of HSV $\geq 10^5$ copies in the BAL (40% vs 72%, $p=0.003$). Thus, while pre-emptive administration of acyclovir was able to reduce the incidence of HSV pneumonia, there were still HSV breakthrough infections using low-dose acyclovir. This observation supports the administration of high-dose acyclovir in the HerpMV study.

Randomisation

The randomisation list (1:1) will be generated by the Center for Clinical Studies Jena (ZKS) with a computer-based algorithm (SAS V.9.4). Thereafter, the list will be implemented in an internet-based system. The list will be stratified only by centre.

Concomitant medication, therapy and concomitant diseases

There are no restrictions regarding concomitant medication within the scope of the study. If the treating physician deems it necessary to administer a virostatic agent with activity against herpes simplex (such as valacyclovir, famciclovir, penciclovir, brivudine, cidofovir, foscarnet, ganciclovir, valganciclovir) for therapeutic purposes (eg, HSV tracheobronchitis) or as a prophylactic measure (eg, in cases of new-onset neutropenia) within 10 days after randomisation, such administration is permitted in subjects belonging to the control group. This must be noted in the patient's file and in the electronic case report form (eCRF). The patients will be considered accordingly in the statistical evaluation. Patients in the intervention group may also switch to another antiviral with activity against herpes simplex (such as valacyclovir, famciclovir, penciclovir, brivudine, cidofovir, foscarnet, ganciclovir, valganciclovir) within 10 days after randomisation, if the treating physician deems it necessary for therapeutic (eg, Cytomegalovirus (CMV) disease) or prophylactic reasons in order to broaden the spectrum of activity, for instance, against CMV. This must be noted in the patient's file and in the eCRF.

Statistical analysis

Data will be reported according to the Consolidated Standards of Reporting Trials guidelines for reporting randomised trials. Group-specific baseline data and endpoints will be described by appropriate statistical measures (mean, SD, 25th, 50th, 75th percentile, IQR, absolute and relative frequencies). For the confirmatory analysis of the primary endpoint, the Cox mixed-effects model will be applied to the mITT population (modified

intention-to-treat population). This population will contain all patients included in the study who will be randomly assigned to the control group and all patients in the therapy group who have received at least one dose of the investigational product. Here, study centres will be included in the model as random effects (to account for possible centre effects) and treatment arm, age, baseline SOFA score and sepsis at baseline (yes/no) as fixed effects. The confirmatory test will be two-sided at a significance level $\alpha=0.05$ for the fixed effect of the treatment arm. The estimator for the effect is the HR with 95% CI for the comparison between treatment arms. In sensitivity analyses, (1) the associated mixed-effects logistic model is applied (binary: deceased yes/no) (2) the per-protocol population is examined (3) to examine the influence of missing values, the Cox model is furthermore applied with replacement of missing values by multiple imputation by fully conditional specifications. In case the planned number of cases cannot be reached at the end of the study, an additional Bayesian analysis of the primary endpoint is planned.

Ventilation-free days, vasopressor-free days (each from baseline to day 30) and days without delirium/coma (from baseline to day 10/EOT) are each analysed with mixed-effects cumulative logistic regression. Thereby, in all three models, endpoints are scored as '-1' for patients who died during the corresponding period. Centres are random effects in each case, and treatment arm, age and sex are fixed effects. Hospital length of stay, as well as ICU length of stay, are each examined with a mixed-effects Cox model, with the centres as random effects and the treatment arm as fixed effects, with censoring after day 30, considering only those patients who survived to that point. The delta of the SOFA score between baseline and EOT is examined with a mixed linear model (with the treatment arm as the effect). Here, the centres are random effects. The same applies to the SOFA subscore for the kidney, as well as the eGFR value. Both 90-day and 180-day mortality will be examined using a mixed-effects Cox model, with centres as random effects and treatment arm, age, baseline SOFA score and sepsis at baseline (yes/no) as fixed effects. The cost of the intervention and the proportion of patients with microbiological cure will be examined descriptively. The EQ-5D-5L questionnaire will be analysed descriptively for days 10/EOT, 30, 90 and 180 after baseline, separately by treatment arm. The tests of the secondary parameters are exploratory in nature and represent sensitivity analyses for the primary analysis. Therefore, an alpha correction for multiple testing is omitted. The number of all SAEs is analysed descriptively. The population for safety analysis (safety population) contains all patients of mITT. All patients will be analysed according to their treatment received. In particular, AEs in patients in the control group who receive acyclovir during the course are counted up to the time of the first acyclovir administration in the control group and all AEs after this time in the 'control acyclovir switcher' group.

Exploratory subgroup analyses are planned for the primary endpoint according to severity (using SOFA (<10 vs ≥ 10) and Acute Physiology And Chronic Health Evaluation (APACHE)-II score (<25 vs ≥ 25)), Acute Respiratory Distress Syndrome (ARDS) (no ARDS/mild/moderate/severe), HSV viral load detection in the blood (yes/no), immune status and extended-CardioVasc-SOFA subscore (<3 vs ≥ 3) (each at baseline), and adequate antibiotic therapy (yes/no; according to resistogram S,I over a period of at least 48 hours within the first 72 hours after randomisation). If necessary, further analyses will be performed depending on the current state of knowledge.

Proposed sample size/power calculations

The sample size estimate for the primary endpoint (30-day mortality) is based on the Kaplan-Meier estimator. Based on the results of the meta-analysis,⁸ we assume an event rate of 0.4 in the control group and an RR of 0.75 (ie, fewer events with acyclovir therapy). This results in an event rate of 0.3 in the acyclovir group, corresponding to an absolute risk reduction (ARR) of 10%. We expect a dropout rate of ~1%. To demonstrate an ARR above 10% at 1 month with a power of 0.8, a sample of 710 (2×355) patients is needed, under these assumptions, with a two-sided significance test at the 5% significance level. The case number planning was performed with R V.4.0.3 and specifically the R package npurvSS V.1.0.1.

Data entry and storage

Data collection will be conducted by trained staff at each study site, and data will be entered into a web-based clinical trial database system. Information to be collected via the case report form includes demographic data, patient characteristics, trial characteristics, comorbidities and risk factors, infection parameters, antibiotic data, clinical observations and microbiological data and outcome data. The database will contain validation ranges to minimise the chance of data entry errors.

Safety monitoring plan

A Data Safety Monitoring Board (DSMB) will be established, comprising two independent pulmonary and critical care physicians and one independent statistician. The DSMB receives information about the trial progress, amendments and listings of safety-relevant items including SAEs and suspected unexpected serious adverse reactions (SUSARs). After examining the available data, the DSMB makes recommendations regarding continuation, modification or discontinuation of the clinical trial.

Quality assurance and safety

The information entered into the eCRF at the trial site is regularly systematically checked for completeness, consistency and plausibility by routines implemented in data capture software and by centralised monitoring. Agreement of study data with source data and compliance with the informed consent process are verified by external monitors (Center for Clinical Studies). Safety of the study medication is assessed by reporting of adverse

events, SAEs and SUSARs. According to German regulations, safety reports are forwarded to the authorities and ethics boards. A DSMB will receive a descriptive analysis regularly to assess the safety of the study intervention.

Stopping rules

The entire trial can be terminated prematurely by the sponsor at any time for medical and ethical reasons (ie, recommendation by the DSMB). The sponsor may terminate participation of a study site if inadequate protocol adherence is repeatedly observed, the quality of the data is deficient or the recruitment is insufficient. The study can be terminated for individual patients if the patient or the representative withdraws informed consent, severe side effects of the study medication are observed or the treating physician assesses the trial participation as being detrimental for the patient.

Description of laboratory and other investigations

To investigate the influence of the immune status on the response to therapy or the course of the disease, blood samples will be taken from all subjects on day 0, day 3 and day 10 (or on the last day of therapy with acyclovir in the intervention group or transfer from intensive care in patients in the control group if this occurs before day 10). In addition, it will be investigated whether viraemia with herpes viruses is present and, if so, whether this has been eliminated by therapy with acyclovir. At day 10, respectively EOT, a respiratory specimen for detection of HSV-1 viral load will be collected. See online supplemental table S1 for details of the clinical trial schedule/visit plan.

Schedule and duration of the clinical trial

The recruitment phase will be approximately 30 months. For the individual patient, the intervention duration will be a maximum of 10 days, the primary endpoint will be collected at day 30 and follow-up will be at day 90 and 180.

Patient and public involvement statement

The German Self-Help Group 'Deutsche Sepsis-Hilfe e.V' (DSH) will aid support for the study, including providing input during protocol development, types of data collected and methods of communication with participants. Several studies could show that reactivation of latent viruses is common with prolonged sepsis, with frequencies similar to those occurring in transplant patients on immunosuppressive therapy. Therefore, patients with sepsis will represent a large proportion of enrolled patients. On request, patients will be informed of the study results after publication of the study.

ETHICS

All trial participants will conduct the study in accordance with local laws and International Conference on Harmonisation guidelines for Good Clinical Practice. The trial was approved by the ethics committee and by Germany's Federal Institute for Drugs and Medical Devices (EU-CT: 2023-504322-19-00). The clinical trial

application was *submitted* under the new *Clinical Trials Regulation* through *CTIS*. (The Clinical Trials Information System; <https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trials-information-system>). In this process, only one ethics committee, whose name is unknown to the applicant and Germany's Federal Institute for Drugs and Medical Devices are involved throughout the entire approval process. Written informed consent will be obtained from all patients or their representative by study physicians. All study participants are insured according to the requirements of the Medicinal Products Act (https://www.gesetze-im-internet.de/englisch_amg/englisch_amg.html#p0389).

The trial design takes several patient safety considerations into account. First, the decision on the prescription of the trial drug and premature termination, if the patient's safety is compromised, is at the discretion of the treating physician. Furthermore, if the treating physician deems it necessary to commence a virostatic agent within 10 days after randomisation in control group patients, for example, newly diagnosed HSV-tracheobronchitis, such actions are always permitted. In addition, acyclovir has been used unchanged since 1982 for the treatment of herpes infections and there is a longstanding experience with this substance. Acyclovir is generally well tolerated. With peripheral intravenous administration, phlebitis (at the infusion site), transient serum creatinine elevation (due to crystallisation of acyclovir in the renal tubules, which can be avoided by slow infusion of a sufficiently diluted solution), skin rash, or urticaria are possible. Data from randomised controlled trials and studies with a control group show that the incidence of acyclovir-induced impairment of renal function is low and reversible.¹¹ Central nervous effects with intravenous administration of higher doses occur in about 1% of cases. To further minimise the risk of nephrotoxicity and neurotoxicity for study participants and to account for the fact that there are few and conflicting (in obese) or no (in critically ill patients) pharmacokinetic studies for special patient groups, a conservative dosing approach will be used in the study.¹² Thus, considering both, the safety profile of acyclovir and current data on the study question, there are scientific reasons to expect that subject participation in the trial may result in a direct clinically relevant benefit to the subject that achieves demonstrable health-related improvement.

Dissemination plan

Results will be published in a journal indexed in MEDLINE; there are no publication restrictions. In addition, results will be posted in CTIS as required. After publication, de-identified, individual participant data that underlie this trial, along with a data dictionary describing variables in the data set, will be made available to researchers whose proposed purpose of use is approved by the Trial Management Team.

Trial status

The HerpMV trial will randomise its first patient in Q1/2024. Protocol version V4_20230929.

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Contributors SH drafted the work and study protocol and gave substantial contributions to the conception and design of the work, NB, SF and PF drafted the study protocol and gave substantial contributions to the conception and design of the work. SD, MD, CE, MH, MAW, AZ and MWP gave substantial contributions to the conception and design of the work and revised it critically for important intellectual content. All authors gave final approval of the version to be published.

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Table S1. Clinical trial schedule/visit plan

Day	Pre-screening	Baseline T 0	1	2	3	4	5	6	7	8	9	10 or EOT	30	90	180
Check inclusion and exclusion criteria	X (check)	x													
Clarification, obtaining the declaration of consent		X													
Pregnancy test if necessary ¹		X													
Randomization		X													
Demographics ²		X													
SOFA score		X			X		X		X			X			
APACHE/CFS		X													
Extended-CardioVasc-SOFA-Sub-Score		X	X	X	X	X	X	X	X	X	X	X			
Concomitant diseases		X													
Concomitant medication ³							X								
Microbiological results						X									
Physiological parameters ⁴		X													
Serology herpes viruses ⁵		X													
Renal replacement procedures		X	X	X	X	X	X	X	X	X	X	X			
Immune status		X													
Laboratory values ⁶		X			X		X		X			X			
Acyclovir administration (intervention group only).							X								
Delirium/Coma (CAM-ICU / RASS)		X	X	X	X	X	X	X	X	X	X	X			
Vasopressor		X	X	X	X	X	X	X	X	X	X	X	X		
Ventilation		X	X	X	X	X	X	X	X	X	X	X	X		
Length of stay Hospital/ICU													X	X	X
Whereabouts													X	X	X
Survival status													X	X	X
EQ5D-5L												X	X (±48h)	X (±48h)	X (±48h)
Questionnaire ethical aspects (once) ⁷												X	X	X	X
HSV-1 PCR blood		X										X			
HSV-1 PCR respiratory ⁸												X			
(S)AEs ⁹							X								
Study protocol deviations															X

¹ Blood or urine (only in women with childbearing potential)

² Age, gender, height, weight

³ Interferon, intrathecal methotrexate, theophylline, zidovudine, ciclosporin, nephrotoxic agents, probenecid, valacyclovir, famciclovir/penciclovir, brivudine, cidofovir, foscarnet, ganciclovir, valganciclovir, other viral agents.

⁴ Blood pressure, heart rate, body temperature, urine output

⁵ Herpes simplex 1 (HSV-1) IgG/IgM, Varicella Zoster (VZV) IgG/IgM, Cytomegalovirus (CMV) IgG/IgM

⁶ on **day 0 and 3**: sodium, potassium, creatinine, GFR - according to Cockcroft -Gault, bilirubin, ALAT (GPT), lactate, CRP, PCT, hematocrit, leukocytes, platelets, ferritin, IL6, **day 5 and 7**: Sodium, potassium, creatinine, GFR - according to Cockcroft -Gault, bilirubin, ALAT (GPT), lactate, CRP, PCT, hematocrit, leukocytes, platelets and **on day 10**: creatinine, GFR - according to Cockcroft -Gault, bilirubin, ALAT (GPT), lactate, CRP, PCT, leukocytes, platelets, ferritin.

⁷ One time between day 10/EOT and day 180 (depending on when the patient can adequately respond).

⁸ or tracheobronchial secretion or pharyngeal lavage water (depending on clinical diagnostics)

⁹ If the patient is discharged from the ICU before day 10, then the (S)AE recording ends with this day.