Revisiting acyclovir dosing for adult viral encephalitis using a full Bayesian LeiCNS PBPK modeling approach

Sun, M.; Manson, M.L.; Märtson, A..; Bodilsen, J.; Lange, E.C.M. de; Guo, T.

Clinical Pharmacokinetics (2025) 64:1413–1423
https://doi.org/10.1007/s40262-025-01545-w

ORIGINAL RESEARCH ARTICLE

Revisiting Acyclovir Dosing for Adult Viral Encephalitis Using a Full Bayesian LeiCNS PBPK Modeling Approach

Ming Sun[1,4] · Martijn L. Manson[1] · Anne-Grete Märtson[1] · Jacob Bodilsen[2,3,4] · Elizabeth C. M. de Lange[1] · Tingjie Guo[1,4]

Accepted: 27 June 2025 / Published online: 13 July 2025

Abstract

Background and Objective Acyclovir is a primary treatment for central nervous system (CNS) infections caused by herpes simplex virus (HSV) and varicella-zoster virus (VZV). However, patient outcomes remain suboptimal, despite acyclovir treatment. Given the lack of alternative therapies, there is a pressing clinical need to revisit acyclovir dosing for viral encephalitis. This study aimed to evaluate current and alternative acyclovir dosing regimens using a Bayesian CNS physiologically based pharmacokinetic (PBPK) modeling approach.

Method A full Bayesian analysis was performed using LeiCNS3.0 model to describe acyclovir's CNS distribution. Simulations were performed for standard dosing (10 mg/kg TID) and various alternative dosing regimens. Drug efficacy was evaluated using 50%fT > IC_{50} (50% of the dosing interval with drug concentration above IC_{50}) and C_{min} > IC_{50} (minimum concentration of the drug exceeding IC_{50}). A toxicity threshold of 25 mg/L for plasma peak concentration was applied.

Results The standard regimen (10 mg/kg TID) achieved the 50%fT > IC_{50} target but failed to consistently meet the C_{min} > IC_{50} target, particularly for VZV. Alternative regimens of increasing the dosing frequency to QID or extending infusion durations to 1.5 h or 2 h improved efficacy while maintaining safety. Prolonged infusion durations reduced peak plasma concentration thus lowered toxicity risks

Conclusions The Bayesian CNS PBPK modeling approach demonstrated robust predictive capacity for CNS PK. Current acyclovir dosing regimens may be inadequate for treating HSV and VZV encephalitis. Alternative dosing strategies involving increased frequency or extended infusion durations appear more effective and safer. Future efforts should focus on refining the PK/pharmacodynamic (PD) relationship between acyclovir exposure and antiviral efficacy to improve therapeutic outcomes.

1 Introduction

Viral encephalitis is a severe inflammation of the central nervous system (CNS) caused by viral infections, often involving herpes simplex virus (HSV) and varicella-zoster virus (VZV). The disease is rare but may be fatal and survivors are often faced with severe neurological impairment despite antiviral treatment [1]. Acyclovir is the primary antiviral for treating viral encephalitis, with a standard dosing regimen of 10 mg/kg intravenously three times daily (TID) for HSV and up to 15 mg/kg for VZV [2]. While standard regimen reduces mortality, morbidity and mortality rates remain concerningly high [3]. Early initiation of acyclovir improves outcomes [4–6], yet significant mortality and neurological issues persist despite timely treatment [7, 8]. The current dosing of acyclovir for HSV encephalitis was established from limited 1980s trials [9, 10] based on plasma pharmacokinetics (PK) after a single infusion [11], and no PK studies exist in patients with VZV-mediated encephalitis. Importantly, there has been limited investigations into the PK of acyclovir within the CNS. While previous studies have shown that average steady-state CSF acyclovir concentrations typically represent 13–50% of plasma acyclovir

✉ Tingjie Guo
t.guo@lacdr.leidenuniv.nl

1 Systems Pharmacology and Pharmacy, Leiden Academic Centre for Drug Research (LACDR), Leiden University, Leiden, The Netherlands

2 Department of Infectious Diseases, Aalborg University Hospital, Aalborg, Denmark

3 Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

4 ESCMID Study Group for Infectious Diseases of the Brain (ESGIB), Basel, Switzerland

Key Points

Acyclovir dosing needs to be studied since current dosing regimens are associated with poor clinical outcomes. Given the limited data on CNS acyclovir distribution in humans, we propose combining Bayesian analysis with a comprehensive CNS physiologically based pharmacokinetic (PBPK) model (LeiCNS3.0) to robustly simulate CNS acyclovir concentrations.

Compared with the standard acyclovir dosing (10 mg/kg every 8 h via a 1-h IV infusion), which fails to maintain trough concentrations above IC_{50} in key CNS compartments such as brain extracellular fluid (ECF) and subarachnoid space (SAS), alternative regimens, such as 9–17 mg/kg every 6 h via at least a 1-h infusion for herpes simplex virus (HSV) and 15–20 mg/kg every 6 h over 1.5 or 2 h infusion for varicella-zoster virus (VZV), may improve CNS drug exposure while staying within safety limits.

Current plasma-based dosing may not achieve effective therapeutic levels in the brain ECF. Emphasizing CNS-specific PK/PD targets is critical for optimizing acyclovir treatment for viral encephalitis and improving patient outcomes.

concentrations [12], a sufficient understanding of the drug PK profile within the CNS, the target site of action in treating viral encephalitis, remains lacking. This knowledge gap raises concerns about whether the current dosing regimen effectively ensures sufficient CNS exposure to achieve optimal therapeutic outcomes for viral encephalitis.

Several model-based approaches using pharmacodynamic (PD) targets, such as maintaining acyclovir concentrations above the IC_{50} for 50% of the dosing interval ($50\%fT > IC_{50}$) or ensuring the trough concentration (C_{min}) exceeds the IC_{50} ($C_{min} > IC_{50}$), have been developed for systemic viral infections [13–15]. However, these methods, which rely heavily on drug exposure data to facilitate model construction, may not be entirely applicable to describe the complexities of drug CNS PK due to the limited information on acyclovir CNS exposure. This limitation highlights the need for reassessment and optimization of acyclovir dosing regimens specifically for CNS viral infections, potentially through alternative modeling approaches that better account for the unique PK properties of the CNS.

The use of physiologically based pharmacokinetic (PBPK) modeling, particularly when combined with Bayesian methods, offers a promising approach to better understand drug distribution within the CNS and address the limitations posed by sparse data [16]. Compared with the empirical PK modeling approaches, PBPK models include system-specific and drug-specific parameters to allow for scaling and translation of the model prediction across species (such as from preclinical to clinical) and disease conditions [17]. Additionally, due to a knowledge-driven nature of model building procedure, PBPK modeling has the advantage of analyzing scarce PK data while possessing a complete predictive capability. Due to practical issues and sometimes ethical limitations, PK data from human brain samples is sparsely available and PBPK modeling can therefore be a suitable alternative approach to predict PK within different CNS regions. PBPK modeling allows for the mechanistic description of the physiology and therefore can provide an informative insight into the drug distribution in the CNS [18]. In addition, the Bayesian method has been lately proposed as an addition to the PBPK modeling to allow for integration of existing knowledge into the analysis to further optimize the predictive capability of the model [16]. In a Bayesian analysis, prior knowledge, e.g., from existing literature, can be included as an extra source of data for the model fitting to allow for the characterization of the parameters' uncertainty, which allows us to better understand the real-world variability.

In this study, we set out to study acyclovir CNS PK on the basis of a previously developed comprehensive human version of the CNS PBPK model framework LeiCNS3.0 [19] using a full Bayesian approach. Facilitated by the developed model, we also aimed to evaluate the current and alternative acyclovir dosing regimens for the optimal treatment of CNS viral infection.

2 Methods

In this study, we performed the modeling on the basis of the existing CNS PBPK model framework LeiCNS3.0 [19] and used published literature data on acyclovir, followed by a full Bayesian approach. The developed model was used to simulate the CNS PK profiles in brain extracellular fluid (ECF) and the lumbar site (subarachnoid space, SAS) for the current standard acyclovir dosing regimen as well as three alternative dosing regimens. On the basis of the predefined therapeutic target and toxicity threshold, we evaluated the suitability of these acyclovir dosing regimens for treating viral encephalitis (Fig. 1).

2.1 PK Data and LeiCNS3.0 Model Framework

The LeiCNS3.0 model adequately predicted PK of a series of drugs in nine physiological CNS compartments including

brain microvessels, brain ECF, brain intracellular fluid (ICF), lysosomes, lateral ventricles, third and fourth ventricles, cisterna magna, and SAS [19]. The model consisted of parameters of drug-specific properties and system-specific properties collected from various sources of data such as published literature data or in-house microdialysis studies (Table S1). For the analysis, we used human acyclovir concentration data from both plasma and the lumbar site, identified from two studies [20, 21]. We excluded data from populations with chronic kidney disease (CKD), including only individuals with normal renal function [20]. Additionally, data from patients with multiple sclerosis (MS) were used in another referenced study [21].

2.2 Bayesian Analysis

The general workflow involves three key steps: (1) sensitivity analysis of model parameters, (2) defining the prior distributions of the LeiCNS3.0 model physiological parameters, and (3) estimating the posterior distribution of these parameters (Fig. 1).

2.2.1 Identifying Sensitive Parameters

A sensitivity analysis (SA) was first performed to identify physiological (systems) parameters to which the model is sensitive. A 0.1-fold to tenfold change was applied to all systems-specific parameters and the corresponding change in

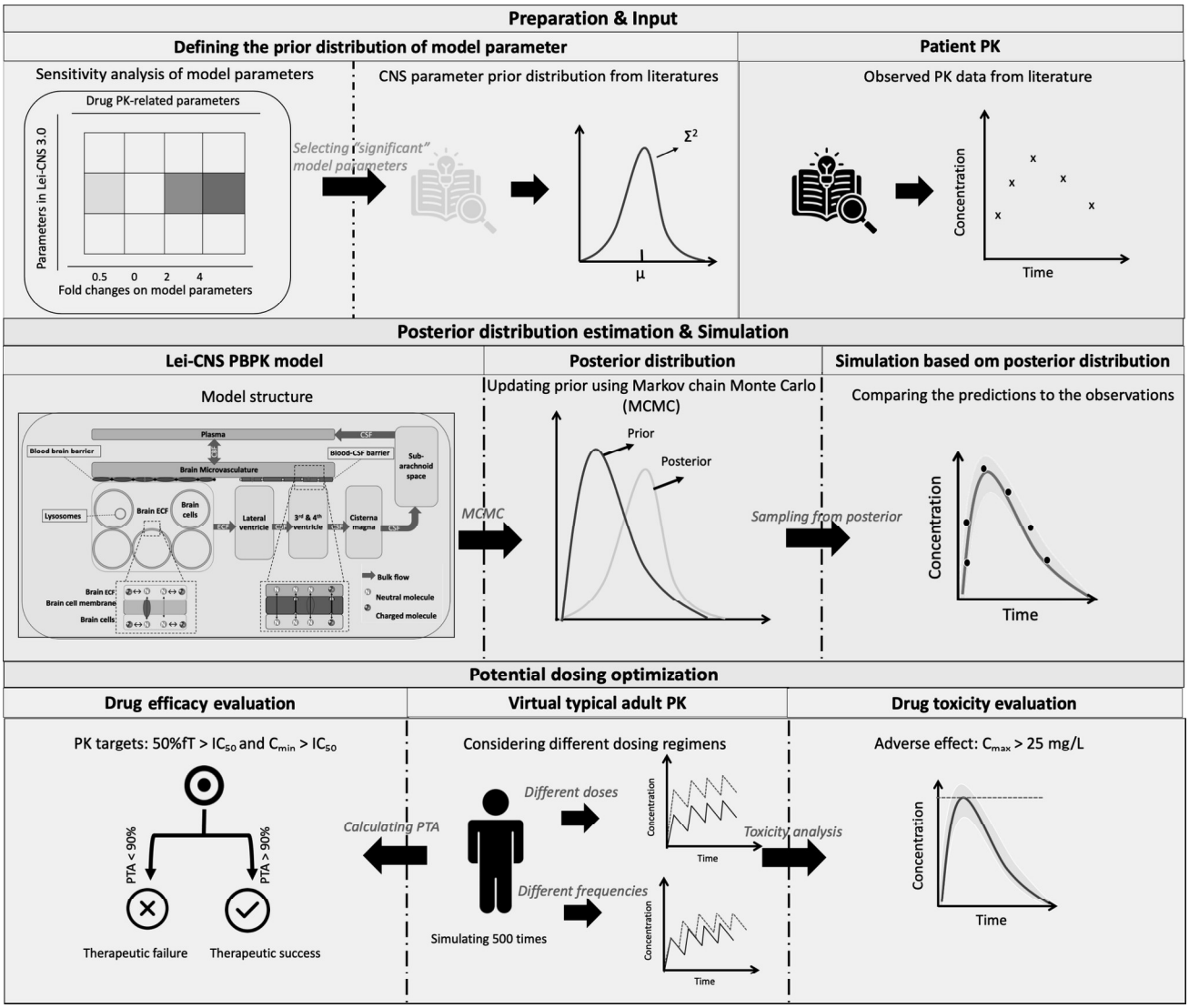

Fig. 1 Overview of the approaches. μ and Σ^2, the mean and the variance of the selected parameter; 50%$fT > IC_{50}$, drug concentrations at the steady state > IC_{50} for 12 h during 24 h treatment; $C_{min} > IC_{50}$, drug trough concentration at the steady state during the whole treatment; MCMC, Markov chain Monte Carlo; PTA, probability of drug target attainment.

the model-predicted acyclovir concentrations was examined. The selection of the system parameters for further Bayesian analysis was based on whether the impact of the parameter in question on the predicted area under the concentration–time curve (AUC) exceeded 15% in any model compartment. The identified sensitive parameters were set free for estimation in the Bayesian analysis and the remaining parameters were fixed at the reported value (Table S1).

2.2.2 Defining Prior Distribution

For the identified sensitive systems parameters, we set a prior using log-normal distributions according to literature data (Table S2). Parameters specifically affected by pathological CNS changes were adjusted to represent conditions observed in CNS infections (Table S2). Likelihood functions for plasma and SAS observations were modeled assuming a log-normal distribution and the prior for the variance of the residuals was set using a half-Cauchy distribution [16].

2.2.3 Estimating Posterior Distribution

The Markov chain Monte Carlo (MCMC) method with the No-U-turn sampler (NUTS) was used to estimate the posterior distributions of model parameters on the basis of an acceptance rate of 0.8 [22]. Four Markov chains were deployed in parallel with 1000 iterations each, including 500 iterations of warmup. The Gelman–Rubin statistic $\hat{R}$ and normalized effective sample size (Neff/N) were calculated to evaluate the convergence and efficiency of MCMC sampling process, respectively. Additionally, MCMC sampling trace plots and posterior distributions were used to visually examine the convergence and robustness of the analysis. Finally, posterior predictive checks (PPC) were consulted to assess the predictive performance of the model [23].

2.3 Dose Regimen Evaluation

2.3.1 Efficacy

Effective concentrations of acyclovir for treating CNS viral infections were defined using two PD targets: (1) maintaining acyclovir concentrations above the half-maximal inhibitory concentration (IC_{50}) for at least 50% of each 24-h dosing interval, denoted as $50\%fT > IC_{50}$ [13, 14], and (2) ensuring trough concentrations (C_{min}) to exceed the IC_{50} [15]. For this study, IC_{50} values used as clinical break points were set at 0.56 mg/L for HSV and 1.125 mg/L for VZV [14].

To evaluate the adequacy of different dosing regimens in achieving these effective concentrations, we conducted a probability of target attainment (PTA) analysis. The PTA was calculated as the percentage of simulations where the defined PD targets were achieved (Eq. 1).

$$\mathrm{PTA}\% = \frac{\text{The number of simulations achieving PK target}}{\text{total simulations}} \times 100\%. \quad (1)$$

We considered these two distinct PD targets, $50\%fT > IC_{50}$ and $C_{min} > IC_{50}$, where a 90% threshold was set to ensure a high likelihood of achieving therapeutic efficacy while minimizing the risk of resistance development [13–15]. Using the Bayesian LeiCNS3.0 model, we simulated acyclovir concentrations in plasma, brain ECF, and SAS on the basis of 500 posterior samples, i.e., resulting in 500 times simulation.

2.3.2 Toxicity

A previous study suggested that plasma peak toxicity thresholds for acyclovir are 25 mg/L and 50 mg/L, with levels above 25 mg/L linked to moderate adverse effects such as nausea, abdominal pain, vomiting, renal failure, and neutropenia, and levels above 50 mg/L associated with severe neurotoxicity [15]. As such, we evaluated predicted acyclovir concentrations in plasma for 15 mg/kg and 20 mg/kg (three times daily, TID, or four times daily, QID) against these two toxicity thresholds. Plasma peak concentrations surpassing this threshold were considered to represent a higher risk of toxicity.

2.3.3 Dosing Regimens

A range of dose regimens were considered in the simulation, including the current standard dosing regimen (10 mg/kg/8 h) and alternative regimens of 10 mg/kg, 15 mg/kg, and 20 mg/kg administered either three times daily (TID) or four times daily (QID). Additionally, to investigate the impact of infusion duration on potential toxicity associated with acyclovir dosing, extended infusion durations of 1.5 and 2 h were simulated. Once optimal regimens were identified, we further explored the surrounding dose range to refine the dose recommendations. To ensure clinical feasibility, only integer dose levels were considered using the same efficacy and toxicity criteria.

2.4 Software and Data Analysis

The acyclovir concentration data were extracted using WebPlotDigitizer (version 4.2). The PBPK modeling and Bayesian analysis were performed using Stan (version 2.27.0) and its R interface CmdStanR (version 0.61), facilitated by Torsten (version 0.89). Data visualization was performed using R (version 4.3.3), R packages ggplot2 (version 3.4.4), and bayesplot (version 1.10.0).

3 Results

3.1 Model Development and Evaluation

We identified eight sensitive parameters that were carried forward to the Bayesian analysis (Fig. S1, Table S2). We successfully estimated the posterior distribution for all the selected model parameters (Table S3). The numerical results showed that all $\hat{R}$ values were close to 1, indicating a successful convergence of the parameter estimations. All Neff/N values exceeded 0.5, suggesting that the model parameters were reliably estimated (Fig. S2). Trace plots showed robust mixing of posterior samples indicated by their "fuzzy caterpillar" appearance. The overlaid density plots from all chains demonstrated convergence to a consistent distribution (Fig. S3A). Compared with the prior, the posterior distribution of parameters became more condensed and informative, indicating improved precision and reliability in the model parameters (Fig. S3B). The posterior predictive check showed that the model was able to adequately predict the observed data, with most observations falling within the 95% prediction interval (Fig. 2).

3.2 PK Profiles of Acyclovir Under the Standard Dosing Regimen

The PK data of acyclovir identified in the literature were based on oral administration of valacyclovir, a prodrug of acyclovir. We therefore corrected the valacyclovir–acyclovir conversion in the model, eliminating absorption and biotransformation for any simulation-based process. We simulated acyclovir concentrations in plasma, brain ECF, and SAS under the standard intravenous (IV) dosing regimen (10 mg/kg, TID). The pharmacokinetic (PK) profiles (Fig. 3) indicate distinct differences among these compartments.

In the plasma compartment, the highest drug exposure was observed, with an area under the concentration–time curve (AUC) over 8 h, which measures the total drug exposure over the dosing interval, reaching 26.1 mg h/L. The median peak concentration at steady state ($C_{ss,max}$) was 11.2 mg/L, and the drug was rapidly eliminated, as indicated by a median half-life ($t_{1/2}$) of 2.3 h. In contrast, both brain ECF and SAS showed lower AUC and $C_{ss,max}$ (Fig. 3). The SAS compartment exhibited the lowest drug exposure with a median AUC of 5.9 mg h/L and a $C_{ss,max}$ of 1 mg/L, while having the highest median trough concentrations ($C_{ss,min}$) of 0.5 mg/L and a much longer median half-life of 4.5 h.

3.3 PTA of Acyclovir Based on Plasma and CNS Concentrations

3.3.1 Efficacy

The efficacy of acyclovir was first assessed using the PD target of 50%$fT > IC_{50}$ (Fig. 4A). The standard dosing regimen of 10 mg/kg TID achieved a PTA exceeding 90% for HSV infection across all compartments, including plasma, brain ECF, and SAS. However, for VZV infection, this threshold was not met in the SAS compartment until the dosage was increased to 15 mg/kg. Increasing the dosing frequency to QID improved PTA outcomes on VZV infection for the 50%$fT > IC_{50}$ target, with the 10 mg/kg QID regimen approaching the 90% PTA threshold in the SAS compartment.

When using the PD target of $C_{min} > IC_{50}$, the PTA for the standard 10 mg/kg TID regimen was below 25% across all compartments, indicating suboptimal treatment for both

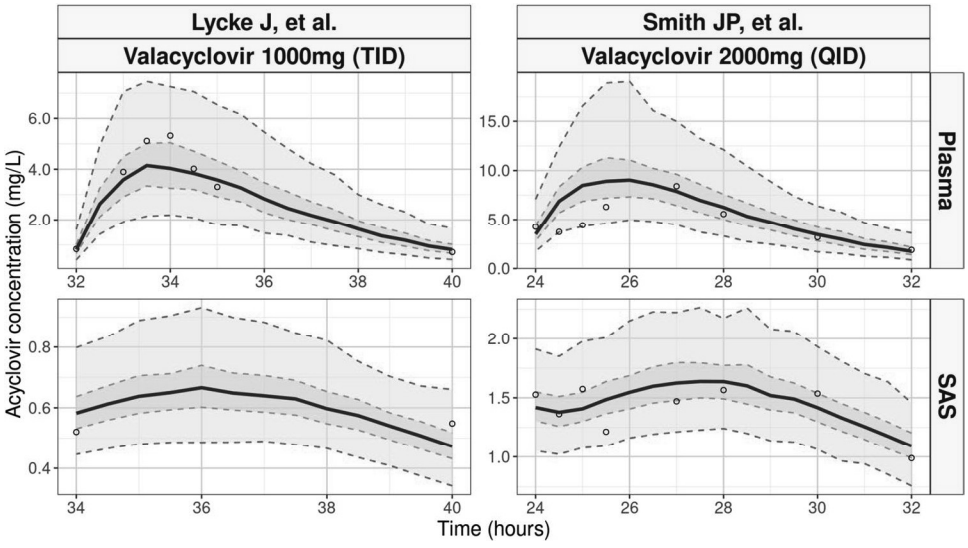

Fig 2 Posterior predictive check (PPC) for the Bayesian LeiCNS3.0 model. Simulated acyclovir data over time in plasma and brain subarachnoid space (SAS) are shown (line, median; middle band color, 50% interval; outer band, 95% interval) against the observations (dots, mean values).

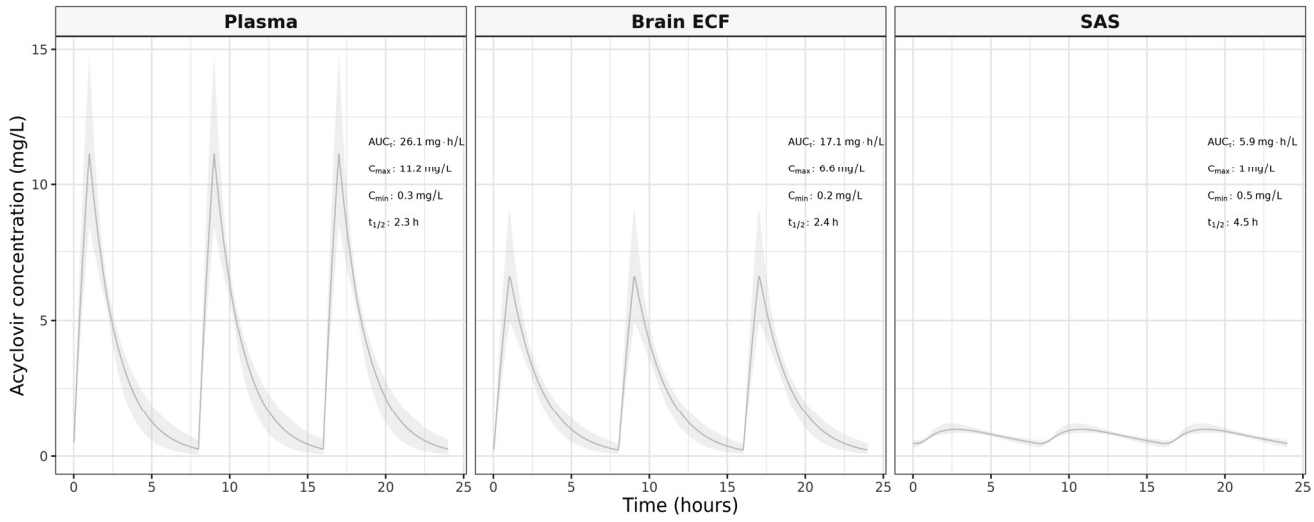

Fig. 3 Simulated acyclovir concentrations over time in different compartments [plasma, brain extracellular fluid (ECF), and subarachnoid space (SAS)] for the standard dosing regimen of 10 mg/kg administered three times daily (TID). The solid lines represent median predicted concentrations, with the shaded areas indicating the 95% confidence intervals. The area under the curve over 8 h (AUC_τ), the median maximum concentration at the steady state (C_{ssmax}), the median trough concentration (C_{ssmin}), and the median half-life ($t_{1/2}$) were calculated on the basis of predicted concentrations in each compartment.

HSV and VZV (Fig. 4A). For HSV, only the higher doses of 15 mg/kg and 20 mg/kg TID reached a PTA of 90% only in the CNS SAS, but not in brain ECF. For VZV, the PTA remained below 25% across all compartments, even at the 20 mg/kg TID dose. Increasing the dosing frequency to QID enhanced PTA outcomes for the $C_{min} > IC_{50}$ target. For HSV, all doses from 10 to 20 mg/kg surpassed the 90% PTA threshold in all compartments. In the case of VZV, only 20 mg/kg QID regimens achieved a PTA of 90% across each compartment, whereas the 15 mg/kg QID dose resulted in a suboptimal PTA below 75% in brain ECF. The 10 mg/kg QID dose failed to meet this target in any compartment, highlighting a continued suboptimal response in achieving adequate trough concentrations.

3.3.2 Toxicity

The results showed that a dose of 20 mg/kg, whether administered TID or QID, resulted in acyclovir plasma concentrations exceeding the toxicity threshold of 25 mg/L but remained below 50 mg/L at peak concentration during steady state (Fig. 4B), suggesting a potential risk of adverse effects without necessarily causing neurotoxicity. Conversely, doses of 15 mg/kg or below, regardless of dosing frequency (TID or QID), were considered safe, as they did not surpass the defined toxicity threshold. As shown in Fig. 5B, for the 20 mg/kg dose administered either TID or QID, extending the infusion duration from the standard 1 h to 1.5 or 2 h effectively lowered peak plasma concentrations below the defined toxicity threshold (25 mg/L). Importantly, the PTA outcomes with extended infusion durations at 20 mg/kg remained comparable to those achieved with the standard 1-h infusion regimen (Fig. 5A).

3.3.3 Identifying Optimal Range of Dosing Regimens

On the basis of the results above, we identified 10 mg/kg infused over 1 h QID for HSV and 20 mg/kg infused over 1.5–2 h QID for VZV to balance efficacy and safety. We then explored adjacent dose levels around these two doses. For HSV, we evaluated a dosing range of 8, 9, 10,11, 12, 13, 14, 15, 16, and 17 mg/kg QID with infusion durations of 1, 1.5, and 2 h. For VZV, we evaluated a dosing range of 15, 16, 17, 18, 19, and 20 mg/kg QID with the same infusion durations. The results suggested a dosing range of 9–17 mg/kg infused over at least 1 h QID for HSV and 15–20 mg/kg infused over at least 1.5 h QID for VZV to meet both efficacy and toxicity criteria (Fig. S4).

4 Discussion

Acyclovir has been commonly used as a first-line treatment for HSV and VZV associated viral encephalitis. In this study, we performed a full Bayesian PBPK modeling for characterizing acyclovir CNS distribution for the first time, which allowed us to optimize acyclovir dosing.

We found that the PTA can differ significantly between the choice of PD targets. An appropriate PD target is probably dependent on both the specific antiviral agent and the

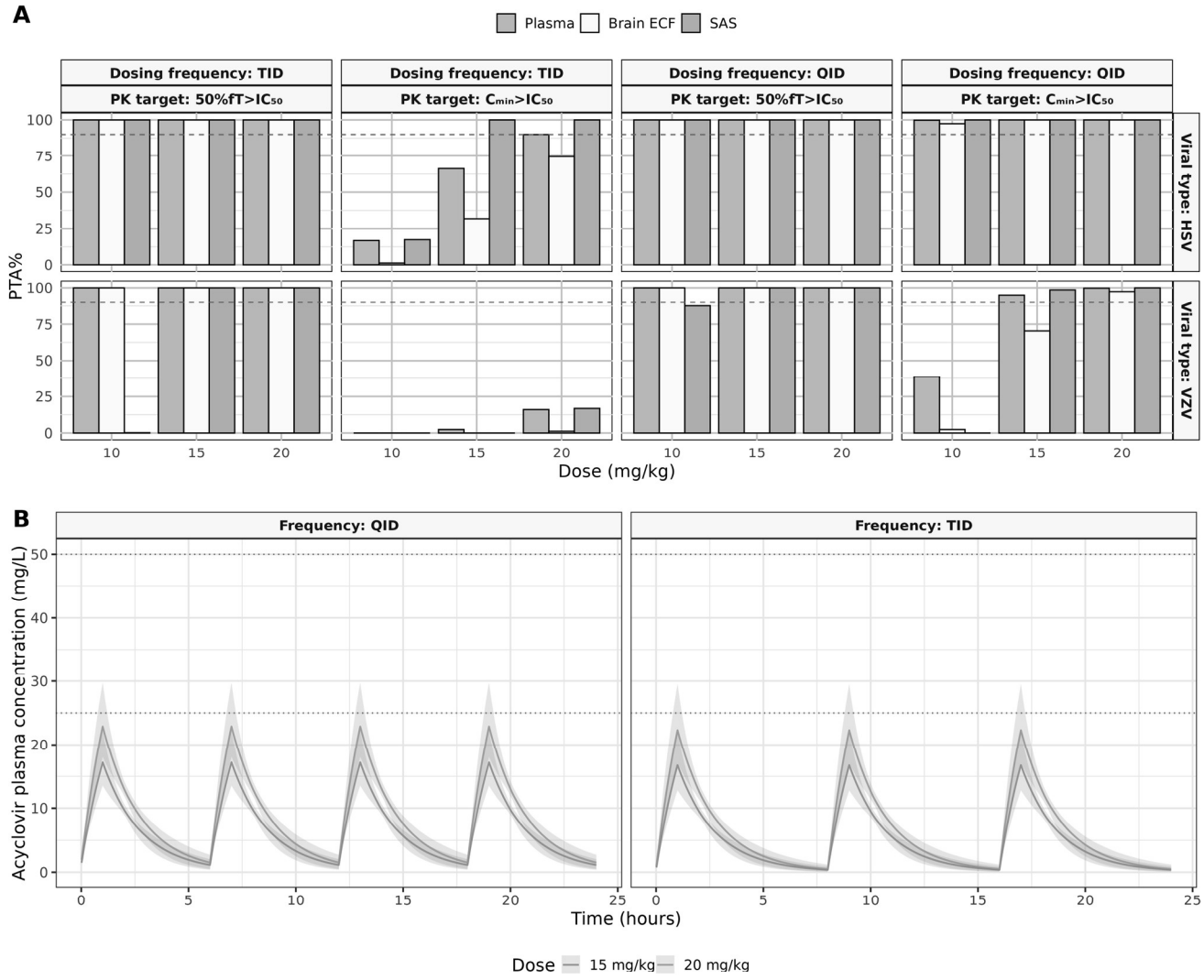

Fig. 4 **A** Probability of target attainment (PTA) of acyclovir in treating herpes simplex virus (HSV) and varicella-zoster virus (VZV) in plasma, brain extracellular fluid (ECF), and subarachnoid space (SAS) at different doses (10 mg/kg, 15 mg/kg, 20 mg/kg) and dosing frequencies (TID: three times per day; QID: four times per day). The red dashed line marks the PTA of 90%, the threshold defined to indicate adequate acyclovir dose regimens. **B** Simulated plasma concentrations of acyclovir over time for different dose regimens (15–20 mg/kg with TID or QID dosing). The solid line represents the median value of predicted concentration, with the shaded area representing the 95% confidence interval. The red dashed line represents the threshold concentration (25 mg/L or 50 mg/L) associated with side effects.

type of virus [24]. For HSV and VZV infection, the 50%$fT > IC_{50}$ target and the $C_{min} > IC_{50}$ target are both commonly employed in model-informed approaches for guiding acyclovir dosing [13–15]. Our results showed that with the current standard dosing regimen, the PD target 50%$fT > IC_{50}$ can be achieved in general, whereas $C_{min} > IC_{50}$ cannot be consistently met. This aligns with our expectation, as the $C_{min} > IC_{50}$ target is stricter by definition where drug concentration needs to be always above IC_{50} to be on target. However, both targets rely on in vitro IC_{50} values and assume that simply exceeding this threshold for a specified duration ensures efficacy, without capturing the actual relationship between drug exposure and changes in viral dynamics in the brain. To better understand and optimize antiviral treatment, a more

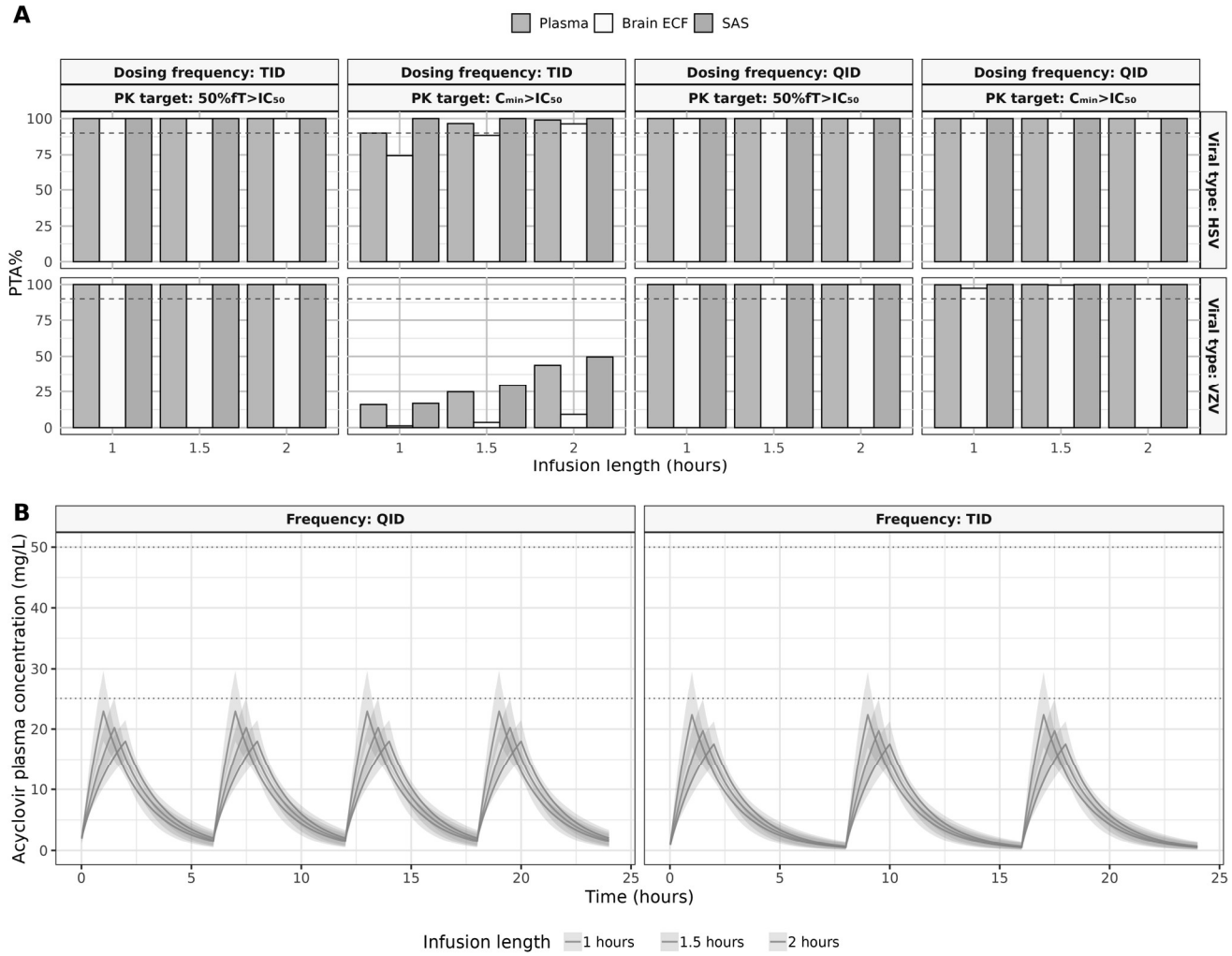

Fig. 5 **A** Probability of target attainment (PTA) for acyclovir against herpes simplex virus (HSV) and varicella-zoster virus (VZV) across plasma, brain extracellular fluid (ECF), and subarachnoid space (SAS), assessed at varying infusion durations (1, 1.5, and 2 h) and dosing frequencies (TID: three times daily; QID: four times per day) under the higher dose of 20 mg/kg. The horizontal red dashed line indicates a PTA threshold of 90%. **B** Simulated concentration–time profiles of acyclovir in plasma under different infusion durations (1, 1.5, and 2 h) and dosing frequencies (TID and QID) under the higher dose of 20 mg/kg. Solid lines represent median predicted concentrations, while shaded areas indicate the 95% confidence intervals of predictions. The horizontal red dashed line indicates the concentration threshold (25 mg/L or 50 mg/L) linked with adverse events

mechanistic PK/PD approach is needed beyond static PK/PD cutoffs toward mechanistic models that link drug concentrations to viral load reduction. Currently, PK/PD studies of acyclovir treatment for viral encephalitis remain scarce [25]. However, semi-mechanistic viral kinetic models are already commonly applied in antiviral fields such as hepatitis C and HIV [24, 26]. By linking viral dynamics with PK profiles, they integrate data on viral load and drug exposure to describe processes including infection of target cells, production and clearance of virus, loss of host cells, and shifts in drug effectiveness due to resistance. Applying a similar framework to herpesvirus infections, using in vitro viral load data along with PBPK-predicted brain ECF concentrations could help answer key questions. These include whether current acyclovir dosing contributes to resistance in HSV and VZV, how treatment delays affect outcomes, and how dosing can be adjusted to achieve full viral clearance rather than relying on empirical IC_{50} thresholds. Shifting from PK-based to PK/PD-based dose optimization would allow us to connect drug levels directly to antiviral effects in the brain and support more rational dosing decisions.

Conventionally, whether an acyclovir dose is sufficient is judged on the basis of the drug plasma concentration. However, since viral replication in encephalitis occurs within brain cells, the drug concentration in the brain ICF would ideally be considered. In practice, the available PK/PD index is based on the IC_{50} derived from extracellular fluid concentrations, and no IC_{50} values have been established for the

ICF. Therefore, brain ECF is likely more relevant for assessing acyclovir efficacy in the treatment of viral encephalitis. We found that compared with plasma and brain ECF, acyclovir in the SAS had lower median peak concentrations, but higher median trough concentrations were observed in SAS, possibly due to a slower elimination rate of acyclovir in the CSF compartment, which aligns with the previous observation that acyclovir can remain in CSF longer than plasma [12, 27]. Meanwhile, brain ECF had the lowest median trough concentrations. This difference yielded a lower PTA in the brain ECF than in plasma on the basis of the $C_{min} > IC_{50}$ target, suggesting that an underestimated dose may be derived on the basis of PTA in plasma. When using the $50\%fT > IC_{50}$ target, the current regimen appears sufficient in both plasma and brain ECF but not in SAS. These results highlight the importance of choosing the right target compartment to guide dosing. Although drug concentration in ECF can be hardly measured in patients, a PBPK modeling approach can be instrumental for us to understand the drug PK in its target site so that an optimal dose decision can be made accordingly.

Toxicity is an additional aspect we considered in the acyclovir dose evaluation, as acyclovir has been reported to cause neurotoxicity. 9-Carboxymethoxymethylguanine (CMMG), an acyclovir metabolite, has been reported to be responsible for possible acyclovir-related neurotoxicity [28, 29]. The conversion process of acyclovir into CMMG is mediated by alcohol dehydrogenase (ADH) and ADH2 enzymes [30]. These enzymes are expressed both systemically and in the brain [31, 32]; however, the lack of quantitative tissue-specific data on their catalytic kinetics makes precise modeling of CMMG concentrations challenging. Therefore, in this study, we adopted an empirical definition of acyclovir toxicity on the basis of acyclovir plasma concentration. We found that solely increasing the dose might not maintain both efficacy and safety of acyclovir treatment, since the C_{max} in plasma following a 20 mg/kg dose would exceed the minimum toxic level of 25 mg/L [15, 33, 34]. Interestingly, in simulation we observed no drug accumulation in plasma after multiple doses with a commonly used dosing interval of 6–8 h. This suggests that dosing more frequently might be safer compared with increasing the dose. For VZV infections, characterized by higher IC_{50} values, achieving desired efficacy while maintaining safety through adjusting both dose and frequency remains challenging. Our simulation results, however, suggested that extending infusion durations could effectively mitigate peak concentration-related toxicity at higher dosing, thereby improving the balance between efficacy and toxicity. Taking into account both efficacy as determined by the stricter PK target $C_{min} > IC_{50}$ for brain ECF concentrations, alongside toxicity, dosing regimens of 9–17 mg/kg QID ($\geq$ 1 h infusion) for HSV encephalitis and 15–20 mg/kg ($\geq$ 1.5 h infusion) for VZV encephalitis appear effective and safe for adult patients. Although single PK-threshold approaches such as using C_{max} for acyclovir are widely applied to evaluate drug toxicity [15, 33, 34], relying on a single concentration at one time-point might not fully capture the overall risk profile. From a PK/PD perspective, alternative exposure metrics that reflect total exposure such as AUC may offer a more informative assessment of systemic toxicity. As previously noted, adopting a more mechanistic PK/PD approach that incorporates the toxicokinetic profile could probably provide a better understanding of drug-related toxicity. Notably, existing evidence suggests that acyclovir-associated neurotoxicity correlates more strongly with exposure to its metabolite CMMG. Toxicity metrics based on CMMG through, e.g., joint parent–metabolite PK models are therefore likely able to improve the prediction of adverse events compared with approaches based solely on the parent drug.

In this study, we used PBPK modeling combined with a fully Bayesian analysis. Such an approach allowed us to analyze sparse data and integrate existing knowledge, which was particularly suitable for studying drug treatment for CNS disease, which in our case is viral encephalitis where sampling from humans is often extremely limited [20, 21, 35–37]. It is worth mentioning that the literature data we used for the modeling were not from patients with viral encephalitis, which may be associated with different physiological parameter values to be used in the LeiCNS3.0 model. Considering the potential influence of CNS inflammation on pathological changes on BBB permeability and CSF flow and volume, we adjusted the prior distributions for sensitive model parameters to reflect inflamed CNS physiology observed in patients with viral encephalitis. Further effort might be needed in focusing on patients specifically with viral encephalitis to refine the model further for the target population. Additionally, only aggregate data were available in the identified literature, and we were not able to model the random effect to address interindividual variability, which was necessary for individual prediction for dose individualization, e.g., for model-based therapeutic drug monitoring.

5 Conclusions

We have successfully developed a CNS PBPK model using Bayesian methodology for describing acyclovir CNS PK and evaluated the current and alternative acyclovir dose regimens for treating viral encephalitis. The model simulation suggested that the current standard dosing regimen of 10 mg/kg IV TID may be inadequate for treating HSV and VZV encephalitis. Alternative dosing strategies, including 9–17 mg/kg every 6 h via at least a 1-h infusion, or a higher dose of 15–20 mg/kg every 6 h with extended infusion duration

over 1.5 h, may be advised considering both efficacy and toxicity. The choice of target can have an impact on the dose decision. Future efforts should be made to understand the relationship between acyclovir PK and its antiviral effect to better derive dosing strategies for optimal therapeutic outcome.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40262-025-01545-w.

Acknowledgements We would like to extend our sincere gratitude to Dimitra Eleftheriou and Coen van Hasselt for their invaluable advice and insightful discussions throughout this research. Ming Sun thanks the China Scholarship Council for the funding (no. 202106370020).

Declarations

Funding No funding was received for the preparation of this article.

Conflict of Interest The authors declared no competing interests for this work.

Ethics Approval Not applicable.

Consent to Participate Written, informed consent was obtained from all participants.

Consent for Publication Not applicable.

Data Availability Data generated during and analyzed during the current study are not publicly available due privacy but are available on reasonable request.

Code Availability The model codes that support the findings of this study are accessible upon reasonable request.

Author Contributions Conceptualization: E.C.M.D.L. and T.G. Data collection: M.S. Formal analysis and investigation: M.S., M.L.M., E.C.M.D.L., and T.G. Writing, review, and editing: M.S., M.L.M., A.G.M., J.B., E.C.M.D.L. and T.G.

References

1. Mailles A, Stahl JP, Bloch KC. Update and new insights in encephalitis. Clin Microbiol Infect Off Pub Eur Soc Clin Microbiol Infect Dis. 2017;23(9):607–13.
2. Solomon T, Michael BD, Smith PE, et al. Management of suspected viral encephalitis in adults–Association of British Neurologists and British Infection Association National Guidelines. J Infect. 2012;64(4):347–73.
3. Sun M, Manson ML, Guo T, et al. CNS viral infections-what to consider for improving drug treatment: a plea for using mathematical modeling approaches. CNS Drugs. 2024;38(5):349–73.
4. Stahl JP, Azouvi P, Bruneel F, et al. Guidelines on the management of infectious encephalitis in adults. Med Mal Infect. 2017;47(3):179–94.
5. Tunkel AR, Glaser CA, Bloch KC, et al. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2008;47(3):303–27.
6. Britton PN, Eastwood K, Paterson B, et al. Consensus guidelines for the investigation and management of encephalitis in adults and children in Australia and New Zealand. Intern Med J. 2015;45(5):563–76.
7. Raschilas F, Wolff M, Delatour F, et al. Outcome of and prognostic factors for herpes simplex encephalitis in adult patients: results of a multicenter study. Clin Infect Dis Off Pub Infect Dis Soc Am. 2002;35(3):254–60.
8. Aboelezz A, Mahmoud SH. Acyclovir dosing in herpes encephalitis: a scoping review. J Am Pharm Assoc JAPhA. 2024;64(3):102040.
9. Whitley RJ, Alford CA, Hirsch MS, et al. Vidarabine versus acyclovir therapy in herpes simplex encephalitis. N Engl J Med. 1986;314(3):144–9.
10. Sköldenberg B, Forsgren M, Alestig K, et al. Acyclovir versus vidarabine in herpes simplex encephalitis. Randomised multicentre study in consecutive Swedish patients. Lancet. 1984;2(8405):707–11.
11. de Miranda P, Whitley RJ, Blum MR, et al. Acyclovir kinetics after intravenous infusion. Clin Pharmacol Ther. 1979;26(6):718–28.
12. Lycke J, Andersen O, Svennerholm B, et al. Acyclovir concentrations in serum and cerebrospinal fluid at steady state. J Antimicrob Chemother. 1989;24(6):947–54.
13. Zeng L, Nath CE, Blair EYL, et al. Population pharmacokinetics of acyclovir in children and young people with malignancy after administration of intravenous acyclovir or oral valacyclovir. Antimicrob Agents Chemother. 2009;53(7):2918–27.
14. Tod M, Lokiec F, Bidault R, et al. Pharmacokinetics of oral acyclovir in neonates and in infants: a population analysis. Antimicrob Agents Chemother. 2001;45(1):150–7.
15. Abdalla S, Briand C, Oualha M, et al. Population pharmacokinetics of intravenous and oral acyclovir and oral valacyclovir in pediatric population to optimize dosing regimens. Antimicrob Agents Chemother. 2020;64(12):10–1128.
16. Elmokadem A, Zhang Y, Knab T, et al. *Bayesian PBPK modeling using R/Stan/Torsten and Julia/SciML/Turing.Jl.* CPT Pharmacometrics Syst Pharmacol. 2023;12(3):300–10.
17. Kuepfer L, Niederalt C, Wendl T, et al. Applied concepts in PBPK modeling: how to build a PBPK/PD model. CPT Pharmacomet Syst Pharmacol. 2016;5(10):516–31.
18. de Lange ECM, van den Brink W, Yamamoto Y, et al. Novel CNS drug discovery and development approach: model-based integration to predict neuro-pharmacokinetics and pharmacodynamics. Expert Opin Drug Discov. 2017;12(12):1207–18.
19. Saleh MAA, Loo CF, Elassaiss-Schaap J, et al. Lumbar cerebrospinal fluid-to-brain extracellular fluid surrogacy is context-specific: insights from LeiCNS-PK3.0 simulations. J Pharmacokinet Pharmacodyn. 2021;48(5):725–41.
20. Smith JP, Weller S, Johnson B, et al. Pharmacokinetics of acyclovir and its metabolites in cerebrospinal fluid and systemic circulation after administration of high-dose valacyclovir in subjects with

normal and impaired renal function. Antimicrob Agents Chemother. 2010;54(3):1146–51.
21. Lycke J, Malmeström C, Ståhle L. Acyclovir levels in serum and cerebrospinal fluid after oral administration of valacyclovir. Antimicrob Agents Chemother. 2003;47(8):2438–41.
22. Hoffman MD, Gelman A. The No-U-Turn sampler: adaptively setting path lengths in Hamiltonian Monte Carlo. J Mach Learn Res. 2014;15(1):1593–623.
23. Gabry J, Simpson D, Vehtari A, et al. Visualization in Bayesian workflow. J R Stat Soc Ser A Stat Soc. 2019;182(2):389–402.
24. Rayner CR, Smith PF, Andes D, et al. Model-informed drug development for anti-infectives: state of the art and future. Clin Pharmacol Ther. 2021;109(4):867–91.
25. Grit GF, Märtson A-G, Knoester M, et al. Shedding a light on acyclovir pharmacodynamics: a retrospective analysis on pharmacokinetic/pharmacodynamic modelling of acyclovir for the treatment of varicella zoster virus infection in immunocompromised patients: a pilot study. Pharmaceutics. 2022;14(11):2311.
26. Chatterjee A, Smith PF, Perelson AS. Hepatitis C viral kinetics: the past, present, and future. Clin Liver Dis. 2013;17(1):13–26.
27. Nau R, Seele J, Bodilsen J, et al. Optimization of antiviral dosing in Herpesviridae encephalitis: a promising approach to improve outcome? Clin Microbiol Infect Off Pub Eur Soc Clin Microbiol Infect Dis. 2025;31(4):534–41.
28. Helldén A, Lycke J, Vander T, et al. The aciclovir metabolite CMMG is detectable in the CSF of subjects with neuropsychiatric symptoms during aciclovir and valaciclovir treatment. J Antimicrob Chemother. 2006;57(5):945–9.
29. Helldén A, Odar-Cederlöf I, Diener P, et al. High serum concentrations of the acyclovir main metabolite 9-carboxymethoxymethylguanine in renal failure patients with acyclovir-related neuropsychiatric side effects: an observational study. Nephrol Dial Transplant Off Pub Eur Dial Transplant Assoc Eur Ren Assoc. 2003;18(6):1135–41.
30. Gunness P, Aleksa K, Bend J, et al. Acyclovir-induced nephrotoxicity: the role of the acyclovir aldehyde metabolite. Transl Res J Lab Clin Med. 2011;158(5):290–301.
31. Jin S, Cao Q, Yang F, et al. Brain ethanol metabolism by astrocytic ALDH2 drives the behavioural effects of ethanol intoxication. Nat Metab. 2021;3(3):337–51.
32. Martínez SE, Vaglenova J, Sabrià J, et al. Distribution of alcohol dehydrogenase mRNA in the rat central nervous system. Consequences for brain ethanol and retinoid metabolism. Eur J Biochem. 2001;268(19):5045–56.
33. Collignon C, de Marcellus C, Oualha M, et al. Pharmacokinetic profile of acyclovir in a child receiving continuous kidney replacement therapy for acute liver failure. Pediatr Nephrol. 2023;38(10):3493–7.
34. Aboelezz A, Mahmoud SH. Acyclovir dosing in herpes encephalitis: a scoping review. J Am Pharm Assoc. 2003;2024: 102040.
35. Pouplin T, Pouplin JN, Van Toi P, et al. Valacyclovir for herpes simplex encephalitis. Antimicrob Agents Chemother. 2011;55(7):3624–6.
36. Whitley RJ, Blum MR, Barton N, et al. Pharmacokinetics of acyclovir in humans following intravenous administration. A model for the development of parenteral antivirals. Am J Med. 1982;73(1a):165–71.
37. Blum MR, Liao SH, de Miranda P. Overview of acyclovir pharmacokinetic disposition in adults and children. Am J Med. 1982;73(1a):186–92.