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Optimization of Ganciclovir and Valganciclovir starting dose in children by Machine Learning

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Running head: Machine learning optimization of Ganciclovir starting dose in children

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Abstract

Introduction: Ganciclovir (GCV) and Valganciclovir (VGCV) show a large interindividual pharmacokinetic variability, particularly in children. The objectives of this study were: (i) to develop Machine-learning (ML) algorithms trained on simulated pharmacokinetics profiles obtained by Monte-Carlo simulations to estimate the best ganciclovir or valganciclovir starting dose in children; and (ii) to compare its performances on real-world profiles to previously published equation derived from literature POPPK models achieving about 20% of profiles within the target.

Materials and methods: The pharmacokinetic parameters of 4 literature POPPK models in addition to the WHO growth curve for children were used in the `mrgsolve` R package to simulate 10800 pharmacokinetic profiles. ML algorithms were developed and benchmarked to predict the probability to reach the steady-state area-under-the-curve target ($AUC_{0,24}$ within 40-60mg*h/L) based on demographic characteristics only. The best ML algorithm was then used to calculate the starting dose maximizing the target attainment. Performances were evaluated for ML and literature formula in a test set and in an external set of 32 and 31 actual patients (GCV and VGCV respectively).

Results: A combination of Xgboost, neural network and random forest algorithms yielded the best performances and highest target attainment in the test set (36.8% for GCV and 35.3% for the VGCV). In actual patients, the best GCV ML starting dose yielded the highest target attainment rate (25.8%) and perform equally for VGCV with the Franck model formula (35.3% for both).

Conclusion: The ML algorithms exhibit good performances in comparison to previously validated models and should be evaluated prospectively.

Keywords: ganciclovir; machine learning; pediatrics; first dose; simulations

Key Points

- This study aim at developing machine learning algorithms trained on simulated pharmacokinetics profiles obtained by Monte Carlo simulations to estimate the best ganciclovir or valganciclovir starting dose in children.
- The best algorithm was used to calculate the ML starting dose associated with the highest probability to achieve the target (AUC_{0-24} 40-60mg*h/L) and performances for target attainment were compared to previously published equation derived from literature POPPK models in 31 (ganciclovir) and 34 patients (valganciclovir).
- A combination of Xgboost, neural network and random forest algorithms yielded the best performances leading to the highest target attainment in the test set and in patients for valganciclovir and the second best for ganciclovir.

1. Introduction

Cytomegalovirus (CMV) is a severe pathogen in children whose immune system is compromised or immature (like children after organ transplantation). The seroprevalence of CMV is very high and estimated around 85% in the general population and in donors of blood or organs [1]. CMV infection is common in pediatric allogeneic hematopoietic transplant recipients [2] and in solid organ transplant recipients [3]. Despite preventive strategies with oral valganciclovir (VGCV) after transplant for a defined high-risk period (preemptive strategy) and close monitoring of CMV replication, CMV disease can have consequences in transplant patients [4]. Antiviral therapy in patients with CMV replication prevents CMV disease which is associated with poor outcomes [5] as this infection causes significant morbidity and mortality [6].

The most frequently used drugs in preventive strategies and for CMV disease in the immunocompromised children is intravenous ganciclovir (GCV), a synthetic nucleoside guanine analogue, which has a very poor oral bioavailability and VGCV, the prodrug of GCV, which is well absorbed from the gastrointestinal tract in children and rapidly metabolized to GCV in the intestinal wall. The resistance mutations and toxicity of VGCV and GCV are similar due to the rapid conversion of VGCV to GCV, including neutropenia, anemia, thrombocytopenia, diarrhea, and fever [7].

GCV and VGCV exhibit a large interindividual pharmacokinetic variability, particularly in pediatric transplant recipients [8]. Studies identified that renal function (Creatinine Clearance CrCL) and weight, age, reflecting both growth and maturation of organ functions were predictors of GCV clearance [8]. Pharmacokinetic studies have shown that the body Weight (WT) based formula led to underexposure compared with Body Surface Area (BSA)- CrCL-based algorithm, particularly in the youngest and that the probability of target attainment was lower in children than in adults [8]. Due to this variability, therapeutic drug monitoring (TDM) is recommended in children. In relation to the lack of pharmacodynamic studies in children, the surrogate efficacy target determined in adult ($AUC_{0-24} = 40-60$ mg.h/L) has been extrapolated for the prevention of CMV disease in children [9]. Indeed, with prophylaxis, breakthrough CMV viremia was associated with $AUC_{0-24} < 40$ mg.h/L [10] and the risk of neutropenia and anemia increased with increasing GCV exposure ranges from 40-60 mg.h/L to 80-120 mg.h/L [11].

Machine learning (ML) approaches are increasingly used to estimate exposure index [12,13] and have allowed us to derive a starting dose with the best probability of achieving vancomycin target serum concentrations in neonates [12]. However, the development of ML algorithms requires large datasets. To work around this

challenge, we have recently demonstrated that ML algorithms could be efficiently trained on simulated data, obtained using a population pharmacokinetic (POPPK) model from the literature [12,14].

The objectives of this study were: (i) to develop a ML algorithm trained on simulated PK profiles obtained by Monte Carlo simulations based on POPPK models from the literature to estimate the best GCV or VGCV starting dose in children; and (ii) to compare its performances on real-world profiles with dose proposed from formula derived from previously published POPPK models.

2. Materials and Methods

2.1. Simulation of ganciclovir and valganciclovir pharmacokinetic profiles in children

2.1.1. Creation of a covariate database

Ten thousand eight hundred simulated patients with different covariates used in previously published POPPK models of GCV and VGCV were simulated (corresponding to 300 profiles by sex and by age from 1 to 18 years old). In brief, age between 1 to 18 years old was simulated using a uniform distribution, weight and height were simulated based on a truncated normal distribution according to the World Health Organization (WHO) growth standard according to age group (1 year per year) [15], creatininemia was simulated based on a truncated normal distribution between 20 and 250 (micromole/L) independently of the other covariates [16], body surface area (BSA) was calculated with Mostellers formula ($BSA = \sqrt{\frac{Weight \times height}{3600}}$), sex and type of transplant (solid organ or stem cells) were simulated using a uniform distributions. The creatinine clearance (CrCL) was then calculated based on age and creatininemia using the modified Schwarz formula [17]. The simulated covariates were split into 3 subsets for IV GCV and 4 subsets for VGCV to be used for simulation by the POPPK models. Further details on selected models are available in supplemental data 1. We performed Monte Carlo simulations in the mrgsolve R package [18] using previously published POPPK models (2 for GCV [16,20] and 3 for VGCV [16,20,21]), individual covariates simulated and dose recommendations for a prophylaxis treatment ($Dose_{guidelines}$ [5,22,23]; 5 mg/kg once a day for GCV and $7 \times BSA \times CrCL$ for VGCV, max 900mg) to simulate individual

predicted concentrations after IV GCV and VGCV administration at steady state (ss=1 option in mrgsolve). The additive error and proportional error were set close to 0 (0.0001 mg/L for additive and 0.0001% for proportional error) to only take into account the inter-individual variability and covariate effect as previously described [24]. The steady state $AUC_{0-24h,ref}$ was then calculated using trapezoidal rule ($AUC_{0-24,ref}$) based on samples simulated every 6 min. A filter was applied to remove $AUC_{0-24-ref}$ outliers (values outside the 5%-95% interval of simulated values). All the values of covariates, the code used to simulate them are available at: https://github.com/ponthL/ganciclovir_first_dose.git.

2.2. Machine learning analysis

2.2.1. Development of the ML algorithms

All pre-processing and machine learning analyses were performed using the tidy models framework in R version 4.2.2 [25]. Analyses were performed independently for GCV and VGCV. Data were split into a training set (75%) and a test set (25 %) by random selection of simulated patients. A new qualitative variable was created for classification analyses: target attainment $AUC_{0-24h,ref}$: yes/no (target attainment was defined by an $AUC_{0-24h,ref}$ between 40 and 60 mg*h/L).

Preprocessing consisted in normalization (centering and scaling) of numeric variables, and one hot encoding of categorical features. Xgboost (eXtreme gradient boosting training) [26], Neural networks MLP [27] and Random Forests [28] algorithms, were employed in parallel. We also evaluated the combined prediction of the 3 algorithms using the stack R package [29]. We tuned the hyperparameters for each algorithms using ten-fold cross-validations in the training set. Once optimized, the ML algorithms (Xgboost, Neural networks, Random Forest and Stacking of the 3 models) were evaluated in the training set, using another set of cross-validation, based on the accuracy, ROC-AUC, sensibility, specificity, negative predictive value (NPV), and positive predictive value (PPV). The best algorithm based on accuracy was finally evaluated in the test set. The relative importance of each feature was determined using random permutations and a variable importance plot was drawn.

2.2.2. Determination of the best ML starting dose

For each simulated patient, ML algorithm predicted the probability of having an AUC_{0-24} in the target (defined by an AUC_{0-24} between 40 and 60 mg*h/L). Different dose ranging from $0,1 * Dose_{guidelines}$ to $5 * Dose_{guidelines}$ were screened and the one associated with the highest probability of target attainment was selected as the optimal ML

starting dose (= dose_{ML}). Finally, as simulation were drawn at steady state and under the hypothesis of strict linearity of the PK, the AUC₀₋₂₄ML for the dose_{ML} was derived as follows in the train and test sets:

$$AUC_{0-24,ML} = \frac{AUC_{0-24,ref} \times Dose_{ML}}{Dose_{guidelines}}$$

To compare our performance with doses described in the literature in the test set, we selected models and calculated doses using formula derived from these different POPPK models (Dose_{POPPK}) and we calculated the AUC₀₋₂₄ as follows:

$$AUC_{0-24,POPPK} = \frac{AUC_{0-24,ref} \times Dose_{POPPK}}{Dose_{guidelines}}$$

The probability of target attainment for AUC_{0-24,ML} was compared to those of the literature models (AUC_{0-24,POPPK}) in the test set. The calculations of the doses used for comparison extracted from each literature model are available at: https://github.com/ponthL/ganciclovir_first_dose.git.

2.3. External validation in actual patients

Deidentified data from 31 patients treated by GCV and 34 patients by VGCV for whom TDM was routinely performed [16], were used to externally evaluate the ML algorithms. Parental informed consent was obtained for all infants. The study protocol was approved by institutional ethics committee (N°2018-1830). The authors confirmed that they have complied with the World Medical Association Declaration of Helsinki regarding ethical conduct of research involving human subjects. We virtually compared the proportion of target attainment the patients would have reached after starting dose based on guidelines, starting dose proposed by the formula from the POPPK literature models and starting dose proposed by the ML algorithms. The virtual AUC₀₋₂₄ following the different doses were calculated, with the hypothesis of strong linearity, based on the AUC_{0-24, ref} obtained using trapezoidal rule on 6 available concentrations, the Dose_{administered} (based on guidelines), Dose_{POPPK} or Dose_{ML}. The whole methodology applied in this study is summarized in the Figure 1.

3. Results

After outliers filtering out, 9873 profiles were available for GCV (7404 for training and 2469 for testing) and 9809 for VGCV (7356 for training and 2453 for testing). Characteristics of the simulated profiles and real-world patients are summarized in Table 1 for GCV and in Table 2 for VGCV. The distributions of the simulated $AUC_{0-24,ref}$ with GCV and VGCV are presented in the Figure 2.

3.1. Development of the Machine Learning algorithm

The performances of the algorithms trained in the train set with each ML algorithm and in the test set for the best algorithm are available in the Table 3. The value of the optimal hyperparameters for each ML algorithm is reported in the supplemental data 2. The linear combination of the 3 ML algorithms (stacking model) yielded the best performances for GCV and VGCV (the plots of the Stacking model showing the contributions of each model are available in the supplemental data 2 and at: https://github.com/ponthL/ganciclovir_first_dose.git). The variable importance plots for GCV and VGCV to predict the AUC_{0-24} in the target showed that creatinine clearance was the most important variable followed by the weight and height (Figure 3).

3.2. Robustness evaluation in the test set.

Paired boxplots comparing the 2 dose proposals ($Dose_{ML}$ and $Dose_{guidelines}$) in the test set are presented in Figure 4a for GCV and Figure 4b for VGCV. For individuals who had $AUC_{0-24} < 40$ mg.h/L using $Dose_{guidelines}$, ML would have recommended overall higher $Dose_{ML}$ resulting in improving the proportion of $AUC_{0-24,ML}$ in the target. For individuals who had AUC_{0-24} between 40 and 60 mg.h/L using $Dose_{guidelines}$, ML would have recommended similar $Dose_{ML}$. For individuals who had $AUC_{0-24} > 60$ mg.h/L using $Dose_{guidelines}$, it seems that ML would have mostly recommended equal or lower $Dose_{ML}$ resulting in decrease of proportion of $AUC_{0-24,ML}$ above the target.

When split into exposure classes (below, within or above the target), the best target attainment rate was obtained with the $doses_{ML}$ (GCV: 36.8%, N=909/2469; VGCV: 35.3%, N=866/2453) in comparison to the $doses_{guidelines}$ (GCV: 21.3%, N=526/2469 ($p < 0.005$), VGCV: 29.6%, N=727/2453 ($p < 0.005$)) and to the $Doses_{POPPK}$ (Figure

5a (GCV) and 5b (VGCV)). The results stratified by age group (<2, between 2 and 12 and >12 years) are presented in the Supplemental data 3 and 4 for GCV and VGCV respectively.

3.3. External validation in a database from actual patients

Paired boxplots comparing the 2 dose proposals ($Dose_{ML}$ and $Dose_{administered}$) in the real-world patients are presented in Figure 4a for GCV and Figure 4b for VGCV. For GCV and VGCV, overall, the ML algorithm proposed higher $Dose_{ML}$ than the $Doses_{guidelines}$ when the AUC_{0-24} was below the target (<40 mg*h/L), similar when the AUC_{0-24} was in the target and lower $Dose_{ML}$ when the AUC_{0-24} was above the target.

When split into exposure classes for GCV, the best target attainment rate was obtained with the best target attainment rate was obtained with the $doses_{ML}$ (25.8%, N=8/31) followed by the Franck (22.6%, n=7/31) and the $doses_{guidelines}$ (12.9%, N=4/31) (Figure 6a). For VGCV, the best target attainment rate was obtained equally with the $doses_{ML}$ (35.3%, N=12/34) and the Franck $Dose_{POPPK}$ (35.3%, N=12/34) followed by the $doses_{guidelines}$ (20.6%, N=7/34) and by the other $Doses_{POPPK}$ (Figure 6b).

4. Discussion

In the present study, we developed a ML algorithm from simulated PK profiles to predict the starting dose of GCV or VGCV in transplanted children. Our algorithm showed numerically better performances for GCV in comparison to the doses based on literatures formula. For VGCV, the best target attainment rate was equal with the Franck et al doses [16]. A possible explanation is that the largest part of the patient used for the external evaluation of the algorithm were from the same center as those used for the development of the Franck et al POPPK model.

In the present study, instead of simulating from a single study, we performed Monte Carlo simulation from different POPPK studies allowing to increase the diversity of PK profiles obtained. No weighting on the simulations relative to the size of each POPPK study was applied to assess the contribution of each study toward the overall results (as it would be in a meta-analysis approach). However, as shown in the supplemental data 1, the populations were homogeneous across the studies. In previous studies interesting in model averaging or development of ML based on simulations, no *a priori* weighting based on POPPK studies was applied and performances were good [30,31].

The approach developed here could be viewed as a sort of meta-analysis of population pharmacokinetic models from literature. A meta-analysis in population pharmacokinetics typically involves combining data from multiple studies to create a comprehensive model. This approach has its advantages, such as a comprehensive view of the data, and drawbacks, like potential bias from the original models or heterogeneity of data. Using external validation with retrospective local data to externally validate existing POPPK models could be an alternative offering more practical insights specific to the local population.

In contrast, training a ML algorithm on simulated POPPK data does not integrate actual patient data from different studies. Instead, it uses existing models to generate new data for training the ML algorithm. While both approaches aim to enhance drug dosing predictions, the meta-analysis directly pools real-world data, whereas the ML approach indirectly uses existing knowledge to create a new predictive tool.

Our ML estimator slightly improved the target attainment in comparison to the $\text{dose}_{\text{guidelines}}$ or $\text{dose}_{\text{POPPK}}$. VGCV or GCV are subject to a large interindividual variability, and the target drug attainment would only be attained in a small proportion of patients. In a review comparing pharmacokinetics studies [8], only Facchin model [21] showed a target attainment rate for VGCV of over 40% while in our study we achieved a target attainment rate of 35.3% with the ML algorithm. For GCV, Franck et al showed disparities according to the studies with variables target attainment rates among the ages [8]. We similarly observed a difference in target attainment when patients were stratified by age class (supplemental data 3 and 4): under 2 years, between 2 and 12 years, and over 12 years. Patients under 2 years receiving intravenous ganciclovir (IV GCV) showed overexposure compared to the POPPK model predictions, which primarily indicated underexposure. This discrepancy can be attributed to the iterative search for the optimal dose in the training set, resulting in doses up to $5x \text{Dose}_{\text{guidelines}}$. While a maximum dose of $2x \text{Dose}_{\text{guidelines}}$ might have been more appropriate for these patients, we maintained the $5x \text{Dose}_{\text{guidelines}}$ threshold for all patients for consistency purposes. For the VGCV, similar to the POPPK model predictions, we observed overall underexposure in children under 2 years and overexposure in children over 12 years. Inter-individual pharmacokinetic variability is higher in neonates than in adults and the former are characterized by a higher distribution volume and a lower clearance [32]. As the models used for the simulations contained only a few newborns or children under 1 year of age, we chose to develop our model with children starting at 1yo. Taken together, these results suggest that the starting dose should still be followed by TDM to improve the individual target attainment.

We used an iterative increase of the dose to select the one associated with the largest probability of the target attainment. In the case of multiple doses associated with the highest probability, we selected the smallest one. This approach is to our knowledge innovative in proposing the dose that maximize the target attainment. However, for some patient, the highest probability was rather small and a possibility could be to make a proposal only for patient having a probability of at least 0.6 to reach the target.

In this study, the pharmacokinetic profiles used to train the ML algorithms were obtained from Monte Carlo simulations using 3 published POPPK models for IV ganciclovir [16,20] and 4 for VGCV[16,20,21]. The simulations were based on published covariates and their distributions, but we did not simulate the covariates with covariance. Indeed, we simulated each weight and height independently using the World Health Organization growth data and based on gender. To avoid any bias in relation to that, we used a small granularity (1 year per year) in the simulations allowing to prevent from unrepresentative combinations (e.g. 2 years old baby weighting 30 kg). In addition, we removed the outliers values of AUC_{0-24} to avoid unrepresentative combinations.

In this study, Xgboost, Neural network, Random Forests algorithms were compared. We chose these algorithms because we had previously used them successfully on our previous projects. Finally, the stack model which combined the predictions of the 3 models (Xgboost, Neural networks and Random Forest) had the best performance. This stacking-based modeling approach combined information from multiple models and avoided specification of one specific model, to keep only the strengths of each model. This approach has already been used successfully [33,34].

Our study had limitations. The highest one is that we considered a strict linearity in the dose/AUC relationship by using cross-product to estimate the AUC_{0-24} after a given dose or the dose that would have led to a given AUC_{0-24} . Nevertheless, the same approach has been used for the different approaches (guidelines, POPPK and ML) leading to a fair comparison. Due to lack of pharmacodynamic studies in pediatrics, the target of AUC_{0-24} between 40-60 mg·h/mL has been extrapolated from adults' studies explaining why we chose this target range, but it should be refined in the future or at least validated that this target range is relevant for this population.

In the external set, the median dose of VGCV was lower than in the simulations because we had fewer patients with impaired renal function. Another limitation is the small number of variables used for ML estimator development. However, as this ML algorithm was trained on simulated data generated using a previously published POPPK model, we were limited to the covariates selected in the POPPK models. Finally, no simple

equation can be directly derived from the developed ML algorithm and to overcome that, we developed a shiny.App for demonstration: <https://pharmaco.shinyapps.io/valganciclovir/> for VGCV and <https://pharmaco.shinyapps.io/ganciclovir/> for ganciclovir. The source code is available at: https://github.com/ponthL/ganciclovir_first_dose.git

5. Conclusion

In conclusion, we have developed an ML based approach to estimate GCV and VGCV starting dose in pediatrics transplant recipients. The $Dose_{ML}$ estimator improves the exposure target attainment rate. Further prospective investigations are needed to confirm its clinical relevance in this population.

Statements and Declarations

Competing Interests: The authors have no competing interests to declare in relation to this work.

Funding information: No funding was received for this study.

Data availability: The datasets generated during and/or analysed during the current study are not publicly available due to privacy and ethical restrictions but are available from the corresponding author on reasonable request.

Data transparency: All the values of covariates and the code used to simulate them are available at:

https://github.com/ponthL/ganciclovir_first_dose.git.

Author contribution: LP, JBW, PM, ML contributed to the study conception and design. Material preparation, data collection and analysis were performed by BF, AA, JA, PO. AD developed the shiny app. The first draft of the manuscript was written by LP and JBW and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Table 1: Characteristics of the simulated profiles and external validation of actual patients for GCV algorithm development.

	All simulated patients N = 9873 train+test	Simulated patients from Franck et al N= 4904	Simulated patients from Nguyen et al N=4969	Real-world patients N=31
Weight (kg)	32.0 [19.6;50.6]	34.2 [20.7;51.7]	30.2 [18.5;49.0]	21.5[12;32.5]
Creatinine (micromole/L)	49.8 [34.5;70.0]	49.9 [34.7;70.3]	49.7 [34.3;69.9]	36.7 [26.6;51.2]
CrCL (mL/min)	140 [96.8;207]	145 [98.5;211]	136 [94.7;203]	152[111;199.6]
Age (years)	9.00 [5.00;14.0]	10.0 [6.00;14.0]	9.00 [5.00;13.0]	6.8 [2.8;10.1]
Height (cm)	138 [116;159]	140 [119;161]	136 [114;157]	116[87;138]
Dose (mg)	160 [98.1;253]	171 [104;259]	151 [92.4;245]	200[105;380]
Dose (mg/kg)	5	5	5	5 [4.9;5.3]
Male Sex	4916 (49.8%)	2475 (50.5%)	2441 (49.1%)	8 (26%)
Type of transplant				
Transplant stem cells	4948 (50.1%)	2476 (50.5%)	2472 (49.7%)	14 (45%)
solid organ	4925 (49.9%)	2428 (49.5%)	2497 (50.3%)	17 (55%)
AUC _{0-24,ref} (mg*h/L)	33.5 [20.7;52.7]	30.0 [19.1;46.4]	38.3 [22.9;58.6]	32.3[23.8;61.9]

Continuous variables are presented as median [IQR] and categorical variables are presented as number (%). CrCL : creatinine Clearance (using modified Schwartz formula). AUC_{0-24,ref} : Area under the curve obtained using the trapezoidal rules ;

Table 2: Characteristics of the simulated profiles and real-world patients for VGCV algorithm development.

	All simulated patients N = 9809 train+test	Simulated patients from Franck et al Model N=3079	Simulated patients from Facchin et al N=3596	Simulated patients from Nguyen et al Model N=3134	Real-world patients N=34
Weight (Kg)	33.0 [19.5;51.8]	35.3 [21.2;52.1]	33.2 [19.0;51.8]	30.5 [18.5;51.1]	22.4 [9.9;37.1]
Creatinine (micromole/L)	49.8 [34.4;69.9]	49.1 [33.8;68.8]	50.3 [34.6;70.0]	49.9 [34.8;70.0]	95.88 [60.03; 126.90]
CrCL (mL/ min)	141 [97.7;209]	149 [103;215]	140 [96.2;208]	136 [93.9;203]	59.7 [44.9;101.4]
Age (years)	9.0[5.00;14.0]	10.0 [6.00;14.0]	9.00 [5.00;14.0]	9.0 [5.00;14.0]	7.9 [0.5;11.5]
Height (cm)	139 [116;161]	142 [120;162]	139 [115;161]	136 [114;160]	117.8 [78.1;144.3]
Dose(mg)	876 [569;900]	900 [651;900]	900 [582;900]	900 [567;900]	213[151;360]
Dose (mg/kg)	21.1 [16.5;30.0]	21.1 [16.5;29.8]	20.8 [16.4;29.5]	21.5 [16.6;30.7]	19.2[10.8;20.2]
Male Sex	4909 (50.0%)	1570 (51.0%)	1771 (49.2%)	1568 (50.0%)	19 (55.9%)
Type of transplant					
Transplant stem cells	4939 (50.4%)	1569 (51.0%)	1797 (50.0%)	1573 (50.2%)	23 (67.6%)
Solid organ	4870 (49.6%)	1510 (49.0%)	1799 (50.0%)	1561 (49.8%)	11 (32.4%)
AUC _{0-24,ref} (mg*h/L)	55.7 [38.9;73.9]	46.1 [31.7;64.8]	52.0 [38.9;64.0]	73.6 [54.2;88.7]	24.3 [18.3;33.4]

Continuous variables are presented as median [IQR]. CrCL : creatinine Clearance (using modified Schwartz formula). AUC_{0-24,ref} : Area under the curve obtained using the trapezoidal rules ;

Table 3: Performances (%) of the ML algorithms in the train dataset GCV and VGCV to predict AUC₀₋₂₄ in the target

		Train (obtained using resampling)				Test
		Random Forrest	Xgboost	Neural network	Stack of Xgboost+ Random Forrest+ Neural Network	Stack of Xgboost+ Random Forrest+ Neural Network
Ganciclovir	Accuracy	74.8	74.2	69.9	91.9	90.0
	ROC-AUC	86.6	83.3	80.9	97.2	95.1
	Sensitivity	71.7	72.7	66.5	96.0	95.7
	NPV	44.8	43.7	39.6	83.7	81.3
	Specificity	86.5	93.1	82.3	76.5	68.9
	PPV	95.2	91.9	92.5	93.9	91.9
Valganciclovir	Accuracy	66.2	63.8	61.6	70.4	70.3
	ROC-AUC	64.5	61.9	62.3	68.8	67.2
	Sensitivity	81.2	66.7	67.6	69.7	66.1
	NPV	41.2	38.1	44.3	46.2	45.3
	Specificity	34.6	61.3	55.6	58.7	53.9
	PPV	73.1	73.5	68.3	74.5	69.1

Abbreviations: NPV, negative predictive value; PPV, positive predictive value

Figure legends

Figure 1: Graphical summary of the methodology of the study

Figure 2: Distribution of the simulated GCV AUC₀₋₂₄ (a) and VGCV AUC₀₋₂₄ (b) for the development of the machine learning algorithms (AUC is area under the curve in mg*h/L)

Figure 3: Variable importance plot for the ML algorithm in the train set to predict AUC₀₋₂₄ in the target

Figure 4: Paired boxplots comparing the 2 doses proposals (guidelines, ML Doses) and split into 3 groups: AUC₀₋₂₄ calculated with doses_{guidelines} in the target (40-60 mg*h/L), below the target (<40mg*h/L) and above the target (> 60 mg*h/L) in the simulation set and in real-world patients for GCV (a) and VGCV (b)

Figure 5: Target attainment rate for doses_{guidelines}, doses_{POPPK} and dose_{ML} in the test set for GCV (a) and VGCV (b)

Figure 6: Target attainment rate for doses_{guidelines}, doses_{POPPK} and dose_{ML} in real-world patients for GCV (a) and VGCV (b)