Received: 20 March 2022 | Revised: 12 January 2023 | Accepted: 16 January 2023

DOI: 10.1002/psp4.12945

ARTICLE

Leveraging mathematical modeling to analyze nonadherence for hydroxyurea therapy in sickle cell disease

Akancha Pandey[1] | **Rubesh Raja**[1] | **Jeremie H. Estepp**[2,3] | **Doraiswami Ramkrishna**[1]

[1]Davidson School of Chemical Engineering, Purdue University, West Lafayette, Indiana, USA

[2]Department of Hematology, St. Jude Children's Research Hospital, Memphis, Tennessee, USA;

[3]Department of Global Pediatric Medicine, St. Jude Children's Research Hospital, Memphis, Tennessee, USA; and

Correspondence
Doraiswami Ramkrishna, Davidson School of Chemical Engineering, Purdue University, 480 Stadium Mall Drive, West Lafayette, IN 47907, USA.
Email: ramkrish@purdue.edu

Present address
Akancha Pandey, AbbVie Inc., South San Francisco, California, USA

Jeremie H. Estepp, Agios Pharmaceuticals, Cambridge, Massachusetts, USA

Abstract

Nonadherence is common in individuals with sickle cell disease (SCD) on hydroxyurea therapy and can be observed with waning improvements in hematologic parameters or biomarkers like mean cell volume and fetal hemoglobin level over time. We modeled the impact of hydroxyurea nonadherence on longitudinal biomarker profiles. We estimated the potential nonadherent days in individuals exhibiting a drop in biomarker levels by modifying the dosing profile using a probabilistic approach. Incorporating additional nonadherence using our approach besides existing ones in the dosing profile improves the model fits. We also studied how different patterns in adherence give rise to various physiological profiles of biomarkers. The key finding is consecutive days of nonadherence are less favorable than when nonadherence is interspersed. These findings improve our understanding of nonadherence and how appropriate intervention strategies can be applied for individuals with SCD susceptible to the severe impacts of nonadherence.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Sickle cell disease (SCD) is a monogenic disorder affecting millions of people worldwide. Nonadherence is a common problem during hydroxyurea treatment of individuals with SCD.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study addresses the impact of nonadherence on the biomarkers' trajectories using an integrated pharmacokinetic-pharmacodynamic model.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This study proposes that nonadherence patterns can have long-term effects which need to be addressed by defining a threshold for the biomarkers and a metric that can be used to detect potential organ failure. The suggested approach can help optimize the treatment of individuals with nonadherence.

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HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

Currently, the nonadherence is not factored in while doing drug discovery, development, and therapeutics. Nonadherence is a significant challenge associated with many chronic illnesses, which can change the course of the disease if not properly intervened. Our approach can be easily transitioned to study nonadherence of different treatments of chronic diseases.

INTRODUCTION

Nonadherence to the treatment regimen is a significant issue that primarily affects individuals suffering from chronic illnesses on long-term therapies. The nonadhering subjects cost the United States $100 to $290 billion in avoidable healthcare costs every year.[1,2] The annual adjusted medication nonadherence cost ranged from ~$900 to ~$52,000 per individual per year across various disease states.[3] In a World Health Organization (WHO) report, the adherence rate in developed countries was about 50%, and in developing countries, even lower.[4] Nonadherence can have repercussions, such as worsening clinical manifestations, increasing healthcare costs, and sometimes death.[5]

Life-long hydroxyurea (HU) therapy reduces morbidity and mortality in individuals with sickle cell disease (SCD).[6–8] It reduces healthcare utilization yet remains underutilized.[9,10] SCD-related complications include vaso-occlusive pain crises, chronic anemia, organ damage, and early mortality.[11,12] Additionally, SCD has a negative impact on health-related quality of life (HRQOL).[13] HU therapy reduces acute SCD-related complications,[14–18] development of end-organ damage,[19,20] mortality,[6] and positively impacts HRQOL.[13,21] Subjects with low adherence to HU have lower fetal hemoglobin (HbF) and mean cell volume (MCV) and experience more fatigue, vaso-occlusive pain, and depression, thus lower HRQOL.[22] Similar to other chronic illnesses, such as diabetes and hypertension, the HU usage in the SCD population is suboptimal.[23] Specifically, the adherence rate for HU in the pediatric population varied between 12% and 100%.[24] The barriers to HU usage can be individual-related, physician-related, or system-related.[25] The various reasons for medication nonadherence include but are not limited to forgetfulness or recall barriers, need for caregiver reminders, forgetting to carry pills while traveling or going out, running out of medication, discontinuation due to adverse effects, discontinuation when the individual believes their SCD is under control, interference with daily life, concerns about side effects and long-term effects, and difficulties with obtaining the drug and refill.[25,26]

There are various methods for quantifying nonadherence. Loiselle et al.[24] provided a detailed review of the adherence measure used in various studies. The adherence measure comprises subjective and objective methods.[24] In the subjective method, the adherence is evaluated using the self-report, parent-proxy report, medical provider rating. The adherence rate is reported as the number of days participants actually take the medication divided by the number of days they are scheduled to take one. The objective method includes measuring adherence using bioassays, such as urine tests, pharmacy refill records, pill counts, and electronic monitoring.[24] Badaway et al.[22] developed a modified Morisky adherence scale, where a higher score indicated adherence that correlated with high MCV and HbF, and a lower score was linked to lower HRQOL measured in terms of increased depression, fatigue, pain, and social isolation.

In this paper, we developed a probabilistic approach to infer nonadherence from the biomarker profiles of MCV and HbF. We used our previously developed model to describe the MCV and HbF dynamics.[27] Using our approach, we estimated the dosing profile of HU treatment based on one biomarker (MCV) and validated the profile using the other (HbF). We also investigated the effect of different dosing profiles on HU treatment.

METHODS

The nonadherence can happen at the three phases of therapy: initiation, implementation, and persistence phases.[28] During the initiation stage, the treatment is initiated or is not initiated, and the response is binary. During the implementation stage, the participant can delay the treatment, miss certain doses, or take extra doses. During the persistence phase, the participant can continue or discontinue the treatment.[28] This work focuses on the latter form of nonadherence, which happens during the implementation and persistence phases where the participants were already initiated on the treatment. We addressed nonadherence by two methods. First, potential days of nonadherence were estimated utilizing changes in biomarker levels in addition to already existing nonadherence based on pharmacy record, which can help identify nonadherence patterns of participants. Second, nonadherence was artificially induced in various patterns to investigate the impact of these nonadherence patterns on the

pharmacokinetic-pharmacodynamic (PK-PD) profiles of individuals with SCD.

Incorporating nonadherence using pharmacy refill records

In our previous work, we developed computational models to analyze the biomarker profiles for 85 subjects from the HUSTLE clinical trial (NCT00305175; total of 260 participants) and we used the pharmacy refill record to incorporate the nonadherence in the dosing profile[17,27] (Text S1 and S2). In this analysis, we retrospectively analyzed the longitudinal data of 40 subjects that includes hematologic parameters prior to and during HU therapy leaving out participants without sufficient data points or having large time gaps, participants with adherence "adequately" inferred from pharmacy data, and participants receiving blood transfusion for our nonadherence study. Here, for the participants whose biomarker profiles can be directly modeled based on the pharmacy refill records with low sum of squares of normalized errors per data point, we call their adherence "adequately" inferred from pharmacy data. All participants for HUSTLE provided informed consent, and HUSTLE was approved by the institutional review board at St. Jude Children's Research Hospital. Pharmacy refill records were used to calculate the daily dose (Text S1, Figure S1)[27] from which the daily average drug concentration was calculated using the PK model (Text S2).[27] The mean cell HbF was calculated as shown in Text S2 and was used for modeling and analysis purposes.[27] The models for HU PK, MCV, and HbF originally developed in our previous paper[27] have been described in detail in Text S2. In this work, the integrated PK-PD model was extended to study and analyze nonadherence inferred in addition to the missing doses calculated from the pharmacy refill data (see next section). Similar to our previous study, the model was applied separately for the biomarker levels of each participant. All the models were implemented in MATLAB R2020b and the model parameters were estimated using a combination of MATLAB functions *lsqnonlin*, *fmincon*, and *patternsearch* by minimizing the weighted sum of square errors for individual biomarkers.[29] The following section explains how the additional nonadherence days were inferred from declines in MCV or HbF data over time.

Inferring nonadherence from biomarker data

During HU therapy, the participant might exhibit a drop in the biomarker levels, but the dosing profile might not contain any nonadherent information. For a participant who was adherent based on the pharmacy record but not from the biomarker levels, the probability of taking the drug between two measurements was estimated from the biomarker levels. In the HUSTLE study, there were participants who had not missed any doses as seen from the pharmacy refill record and those who had missed doses from the pharmacy refill record. While making this distinction, it was assumed that if participants were in possession of the drug, it was administered. However, participants can be in possession of the drug and not administer it. In this scenario, longitudinal changes in hematologic parameters (MCV and HbF) were observed with a decrease in these biomarkers. Declining biomarker levels could then indicate the nonadherence even when the drug possession is high for a participant. This information of nonadherence despite having access to HU can then be incorporated into the model.

The potential days when the participant might have missed the dose were evaluated, and the dosing profile was changed to see if just by changing the doses whether the model fit improved. The identification of missing days was first started with one biomarker, MCV and validated for the other, HbF. Because the HbF measurements are less frequent than the MCV, if we start with HbF, we might miss out on correct dosing prediction for the intermediate timepoints. To elaborate, once the potential days for nonadherence were estimated for MCV, the modified dosing profile was incorporated in HbF data to see if the model fit improved for HbF data as well. The first step in the process was to estimate the model parameters after fitting the model to the data with the initial dosing profile from the pharmacy record. In the next step, keeping the model parameters constant, the dose was modified by changing the participant's probability of taking the drug each day. The probabilities were changed where there was a mismatch between the model prediction and the data from the MCV versus time plot. Once a better fit was obtained, the MCV data was refit with the new dosing profile to obtain a new set of model parameters. In this way, the system can go through multiple iterations to fit the data better. The process was automated for the entire treatment duration to calculate potential days when the participants did not take the drug.

Figure 1 shows the probabilistic approach used to infer potential days of nonadherence. Here, we allocate a daily probability value for taking drugs between any two consecutive biomarker measurements. This probability value is updated through our probability model. In the beginning, an initial guess about the participant's probability (p_{init}) of taking the drug was made. Here, the assumption is that the daily probability of taking the drug in between two consecutive timepoints measured

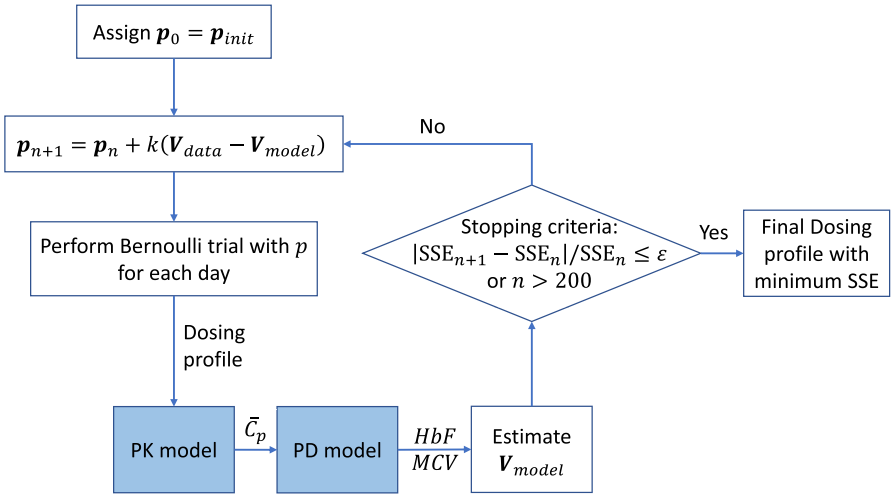

FIGURE 1 Probabilistic algorithm to infer nonadherence from biomarker data. p, set of probabilities of taking the drug for consecutive timepoints; n, number of iterations; k, scaling factor; V_{model}, biomarker's model prediction; V_{data}, biomarker's data, $\overline{C}_p$, daily average drug concentration obtained from the PK model; HbF, fetal hemoglobin; MCV, mean cell volume; PD, pharmacodynamic; PK, pharmacokinetic; SSE, sum of squares of errors; ε, small value chosen to match the desired tolerance of 1e-4.

remains the same. The p_{init} is a vector of $(N_{\text{exp}} - 1)$ probabilities between two consecutive timepoints with N_{exp} as the number of clinical timepoints. Then, for every pair of consecutive timepoints, the model prediction at the end timepoint (V_{model}) was compared with the data (V_{data}). The probability was decreased for those data points if V_{model} was greater than V_{data} and vice versa, as shown in Equation 1 (Figure 1). Then, the dose for every day was computed by performing a Bernoulli trial with probability p obtained. This generated a sequence of 1 and 0, with 1 implying that the participant has taken the drug and 0 implying that the participant has missed the drug. The modified dosing profile was then fed to the PK-PD model, and the entire process was repeated until we minimize the sum of squares of errors or if maximum iterations were completed (Figure 1). We derived the p_{init} from the initial dosing information from the pharmacy data (Text S1). This probability is updated after every iteration as follows:

$$p_{n+1} = p_n + k\left(V_{\text{data}} - V_{\text{model}}\right) \tag{1}$$

where k is the scaling factor (which is 0.01, in our case), n is the iteration number.

Imposing nonadherence in simulation

Apart from inferring when the potential nonadherence could have happened, the effect of imposing nonadherence was investigated. Additional missing days were introduced in a representative participant dose profile to study how different patterns of nonadherence impact HbF and MCV dynamics. The nonadherence was incorporated in the existing model in two ways: deterministic and probabilistic. In a deterministic manner, the exact days of missing doses were known. In a probabilistic manner, the assumption was that the participant took the drug every day with a fixed probability, p (note that this daily probability is different from probability vector, p_n). Using p, a Bernoulli trial was conducted every day to generate a sequence of 1 and 0 with 1 as adherence and 0 as nonadherence.

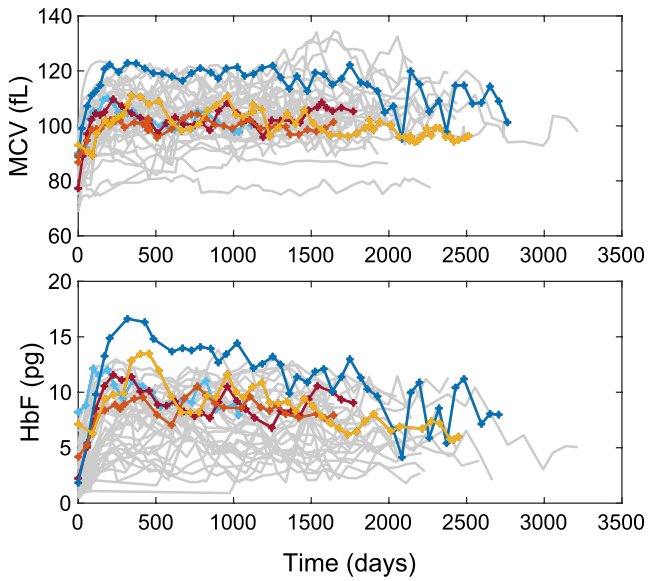

FIGURE 2 Mean cell volume (MCV) and fetal hemoglobin (HbF) plot of 40 participants who displayed nonadherence behavior. The five representative participants, whose nonadherent analysis are shown in Figure 3, are highlighted.

RESULTS

Nonadherence observed in the data

Looking at the clinical data of MCV and HbF, the majority of participants in the HUSTLE study seem to be

adherent at some timepoints and nonadherent at other timepoints. Figure 2 shows the biomarker dynamics for the 40 selected participants. This observation is time-dependent as some participants are adherent at the beginning and nonadherent later. Next, the potential days of nonadherence were estimated using the probabilistic approach described in our Methods section.

Inferring nonadherence from biomarker data

Here, we show how our nonadherence model predicts the potentially correct dosing profile using the probabilistic approach for the participants. In Figure 3, the daily average drug concentration (Avg C_p), MCV, and HbF for five representative participants are shown (refer to Figure S2 and Tables S1–S4 for all 40 individuals). For time periods with several nearby missed doses, the Avg C_p curve seems like a shaded region. The model prediction based on the original dosing profile which is the minimal nonadherence possible based on pharmacy data are shown in blue. We identify regions in the MCV where its value drops, but the model fails to capture this drop. This situation could imply that the participant has missed the drug, even though the dosing profile does not indicate that. Assuming that this drop in biomarker value is due to nonadherence, we used our approach to predict the potentially correct dosing profile (see Methods). The MCV model fit improved for the newly predicted dosing shown in red (Figure 3).

The modified dosing profile was further validated by refitting the HbF model with the new dosing profile obtained earlier from refitting MCV using the probabilistic approach. Like MCV, with the modified dosing profile, the model could capture the drop in HbF, as seen in Figure 3. Therefore, the HbF model fit also improved after incorporating nonadherence. This study inferred nonadherence from the participant data and incorporated that into the model to improve the model fit of the participant.

Imposing nonadherence in simulation

To study the impact of different patterns of nonadherence on the physiological profiles of biomarkers, the nonadherence was imposed in deterministic and probabilistic ways. The multiple patterns of nonadherence imposed and their influence on the key variables of interest, MCV, and HbF, are discussed in the following parts.

Imposing nonadherence in a deterministic manner

The impact of skipping several doses in a row, also called "drug holidays," was studied. In Figure 4, the nonadherence is introduced by missing the doses in a row. The MCV, HbF, and Avg C_p are shown from top to bottom. The dose is missed after initial 200 days of not missing a dose. We define %miss as the percentage of missed days. A threshold for MCV is set to be 90 fL and HbF to be 5 pg below which it is not desirable for the MCV and HbF to go. The thresholds for biomarkers are not standard values; arbitrarily selected values are used to interpret the simulation result. The critical region is defined as the region below the threshold values. The percentage of time the MCV and HbF remain below the threshold, percentage of time below threshold (%tbt) is computed. The HbF and MCV keep decreasing with increasing consecutive nonadherent days. For the representative participant and the threshold values selected, with the increase in nonadherence days, the %tbt remained 0 for the subject missing the dose for 10 consecutive days for MCV (%miss = 2) and the subject missing dose for 40 consecutive days for HbF (%miss = 9). For high %miss, the %tbt increased with an increased number of consecutive missed days (Figure 4).

In Figure 5, the green plot shows the effect of missing the dose after every 4 days in a 4:1 pattern, and the red plot shows the impact of missing the dose for 80 consecutive days on five occasions. Here, the number of missed days for the two cases remains close to ~400 days (%miss = 17 to 18). The MCV and HbF for the latter case drop below their set threshold values (%tbt = 20 for MCV, %tbt =11 for HbF), but the MCV and HbF never drop below the threshold values (%tbt = 0) if the doses are missed in a pattern of 4:1 and stay at higher values.

Imposing nonadherence in a probabilistic manner

In Figure 6, the participant takes the drug with a fixed daily probability, p, for the entire duration. With fixed p, a Bernoulli trial is conducted every day to generate a sequence of 1 and 0, with 1 indicating adherence and 0 indicating nonadherence. With an increase in p, the participant's MCV and HbF increased. The participant in Figure 6 manages to stay out of the critical region for MCV and HbF for $p = 0.75$ and 1 for the arbitrary selected threshold. Whereas for lower probabilities of adherence, the biomarkers' stay below their respective threshold values possibly indicating the reduced effectiveness of the treatment.

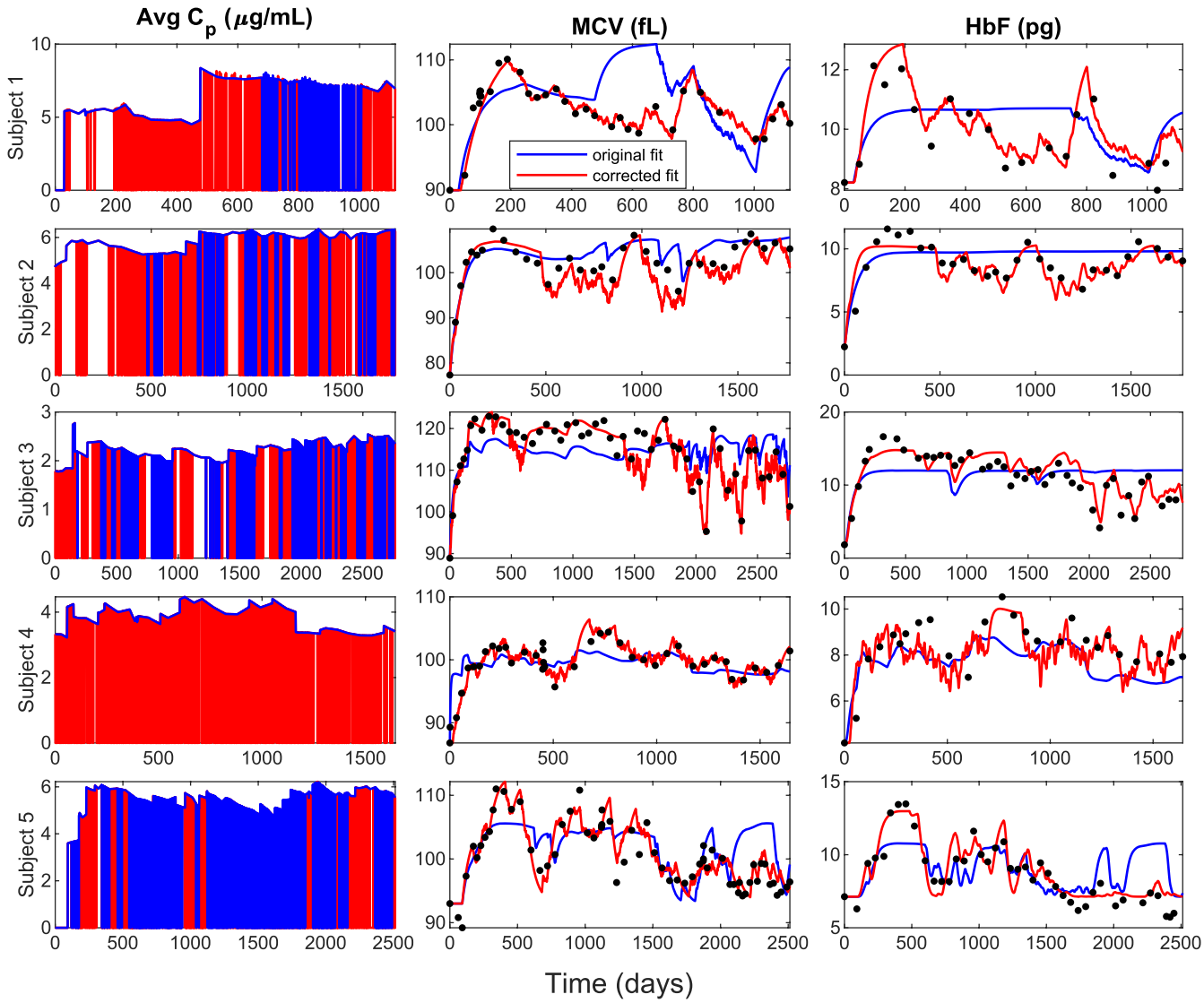

FIGURE 3 Incorporating nonadherence using the probabilistic approach to improve the mean cell volume (MCV) and fetal hemoglobin (HbF) fits for five representative participants. From left to right columns, Avg C_p ($\overline{C}_p$), MCV, and HbF are shown. Black dot represents data, blue represents the model prediction for the original dosing profile as predicted by the pharmacy data, and red represents the model prediction for the corrected dosing profile based on our nonadherence approach. For the model and parameters, refer Text S2 and Tables S1–S4, respectively. For model prediction for additional participants, refer Figure S2.

DISCUSSION

Nonadherence is a longstanding problem and one of the significant challenges associated with HU treatment in individuals with SCD that confounds clinicians and healthcare providers. In this work, the nonadherence was explored and included by estimating the potential days where nonadherence could have happened using a probabilistic algorithm. This approach was validated by calculating the modified dosing profile from one variable and using this modified dosing profile to improve the fit for another variable. The highlight of the work is that incorporating nonadherence in the dosing profile using a probabilistic approach improves the model fit for the nonadherent participant (Figure 3 red) when compared to the dosing profile from the limited number of observations of the pharmacy refill data (Figure 3 blue). For example, in subject 1 (Figure 3), we see that the Avg C_p increased around 500 days with the expectation that the biomarker levels improved. But we can see that the MCV and HbF keep decreasing during this period indicating the presence of unknown nonadherence. Using our approach, we recomputed the nonadherence days that helps in matching the model prediction of the biomarker profiles with the data. In this process, we re-estimated the participant-specific intrinsic biomarker model parameters that are not biased based on the dose profiles from pharmacy data. These newly estimated parameters can better

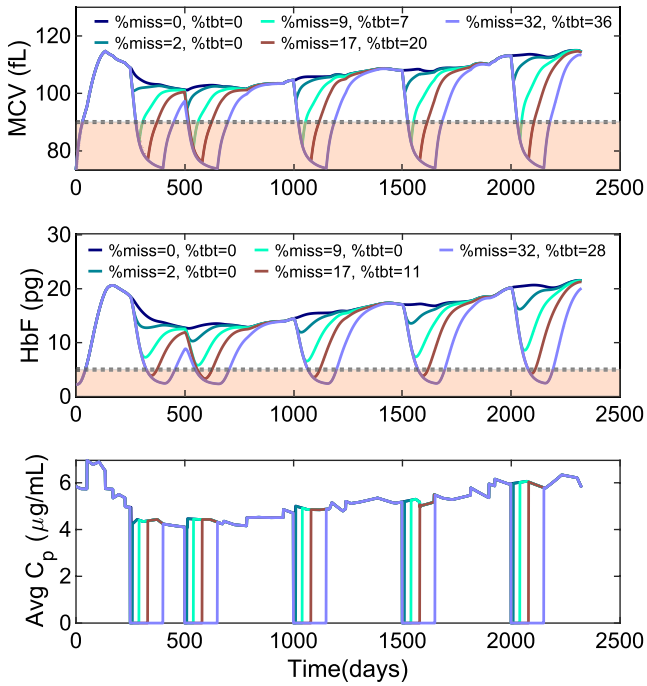

FIGURE 4 Missing the dose on consecutive days. The dose was missed starting at time = 250, 500, 1000, 1500, 2000th day for 0 (%miss = 0), 10 (%miss = 2), 40 (%miss = 9), 80 (%miss = 17), and 150 (%miss = 32) consecutive days. Avg C_p, daily average drug concentration; light red shaded region marks the critical region below the arbitrarily selected threshold value; %miss, the percentage of missed dose; % tbt, the percentage of time mean cell volume (MCV) and fetal hemoglobin (HbF) remain below their respective threshold values; MCV threshold—90 fL; HbF threshold–5 pg.

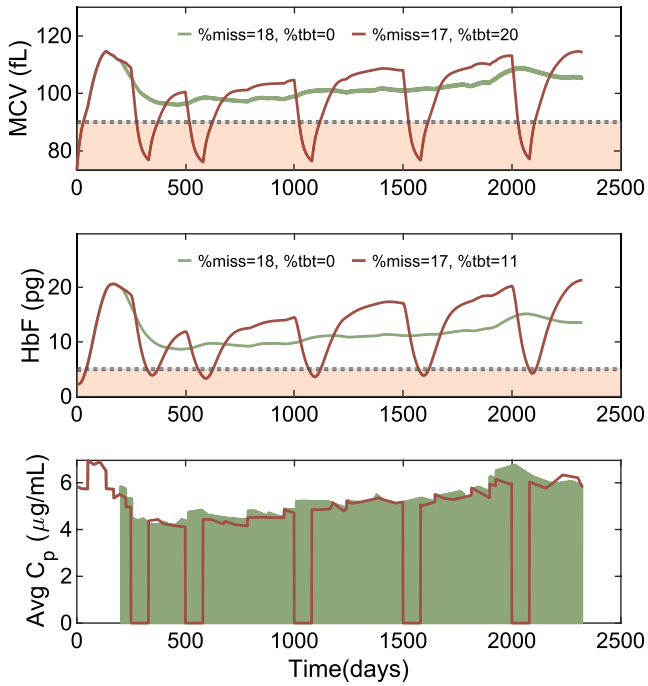

FIGURE 5 Comparison of missing the dose after every 4 days (4:1; green) versus missing the dose consecutively for 80 days (red). The light red shaded region indicates the critical region below the arbitrarily selected threshold value. Avg C_p, daily average drug concentration; %miss, the percentage of missed dose; %tbt, the percentage of time mean cell volume (MCV) and fetal hemoglobin (HbF) remain below their respective threshold values; MCV threshold—90 fL; HbF threshold–5 pg.

define the subject biomarker profiles and can be used to predict and test different dosing scenarios. This probabilistic approach, thus, can help in understanding the specific issues of nonadherence because it can project a potentially corrected daily dosing profile, allowing clinicians to address these issues. This study can help identify the nonadherence pattern of participants to guide clinicians in deciding whether the dose should be adjusted or what forms of nonadherence are acceptable. Further, the effect of skipping the drug on the biomarkers' trajectory was studied and analyzed to investigate how different patterns of nonadherence leads to various physiological profiles. Missing the dose once in a few days when the nonadherent days are more distributed might be less disadvantageous than missing the dose continuously when the nonadherent days are concentrated in a region. This study can help identify the drug forgiveness, the number of missing consecutive doses that still have positive treatment outcomes, and identify less harmful nonadherence patterns.

Nonadherence has been previously studied including the work by Efron and Feldman where the effect of compliance on clinical trial were studied through statistical analysis by estimating the dose response curve from the treatment and control compliance response curves.[30] One study compared approaches in various study designs to estimate dose–response using adherence data from two measurements.[31] Probabilistic models, such as the Markov chain model, was used to simulate compliance data from electronic monitoring device to compute correct dosing history which reduces population PK parameter estimation bias.[32,33] Lu et al.[34] developed a technique to delete PK observations which are likely to have incorrect dosing history and erroneous in order to remove the bias in parameter estimates.

Nonadherence in various patterns has been explored in other disease areas as well. A recent study found that a single missed dose of methotrexate for rheumatoid arthritis after its initiation would not have much therapeutic impact, but missing three or more doses consecutively would make the polyglutamate derivatives (MTX glu) level drop below the therapeutic range.[35] Another study investigated the effect of nonadherence on exposure to oral immunosuppressants in renal transplant subjects and proposed a drug adherence-exposure model to identify nonadherence patterns for high-risk participants with unsuccessful

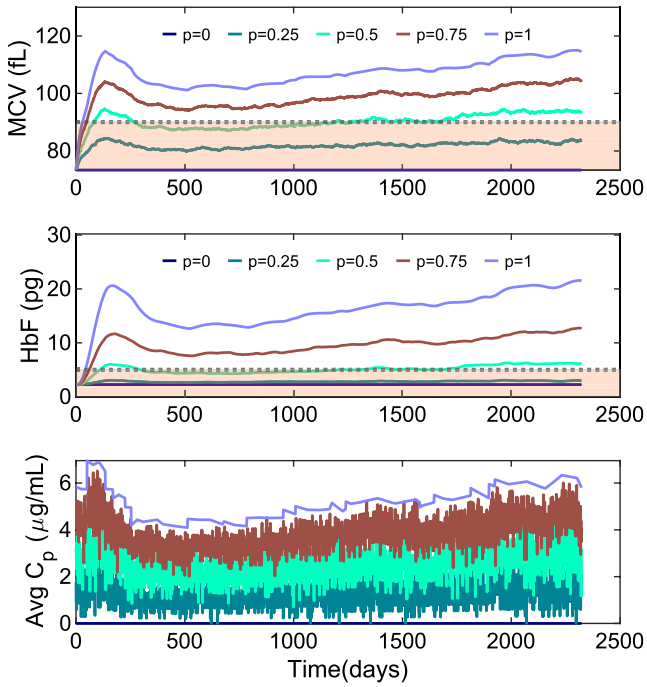

FIGURE 6 Plot of representative participant taking the drug with a fixed daily probability, p, and the effect of varying participant's p on mean cell volume (MCV) and fetal hemoglobin (HbF). The light red shaded region indicates the critical region below the arbitrarily selected threshold value. Avg C_p, daily average drug concentration; MCV threshold—90 fL; HbF threshold–5 pg.

transplants.[36] A meta-analysis using a random-effect model across multiple studies and participants suggested that the threshold for optimal adherence might be wider than the prescribed greater than 95% adherence to antiretroviral therapy (ART) to see clinical benefits.[37] This can help individuals with slightly lower adherence initiate ART. One group studied adherence by comparing alternate day dosing with daily dosing and found that the alternate-day dosing is as effective as daily dosing for atorvastatin in reducing low-density cholesterol and total cholesterol in participants with high amounts of cholesterol[38,39] and also in type 2 diabetic individuals.[40] But nonadherence should be analyzed with caution, especially for diseases where drug resistance is developed, as one study indicated that nonadherence might be responsible for developing resistance and treatment failure in tuberculosis.[41] Further, the nonadherence along with drug PK-PD characteristics impacts the outcome of treatment,[42] and, therefore, one such study suggested the need to include nonadherence in the design of clinical trials[43] to capture real-world scenarios. These studies help bolster our findings and hypothesis of how subjects with specific nonadherence patterns can stay out of the critical region and still derive clinical benefit from HU.

In one study, an adherence rate threshold for different drugs was defined to be drug-specific and not a universal value.[44,45] They defined the adherence rate threshold to be the minimum adherence rate for which the same amount of time at a target is achieved as with an adherence rate of 1.[44] The severity of nonadherence can be quantified using a metric. One such metric used in this work is the fraction of time (%tbt) the participant's biomarker level stays below the threshold value (in the critical region). The clinicians usually advise individuals with SCD to start back on the HU treatment once their biomarkers' levels fall. But this approach lacks the informed long-term impact of nonadherence on individuals' health. Even though the biomarker level can reach a steady-state in a span of few months or so after resuming HU, missing HU doses can have a long-term impact on organs. So, here, it is proposed that if a threshold can be defined for both biomarkers, a metric can be used to calculate the severity of nonadherence. When the MCV and HbF manage to stay above the respective threshold values, it can be assumed that the participant still manages to derive some benefits from the drug, if not the full benefit by being fully adherent. Therefore, if the biomarker falls and remains below the threshold value for an extended period, it might signal potential organ failure.

Sometimes, a lack of knowledge of the potential benefit of the drug and the requirement to take daily doses deter individuals with SCD from initiating and continuing the treatment. Even though the ideal case would be that the participant takes the drug every day, identifying the adherence rate threshold and drug forgiveness can motivate them to start and implement HU treatment. The HU initiation and implementation in participants can reduce healthcare utilization and the associated cost and our modeling approach can be boon in predetermining the optimum dosing schedule and especially, the allowed nonadherence for the participant. Our approach also relies on simple probabilistic approach compared to other methods discussed above. Even with this simple formulation, we were able to predict the dosing profile from complex biomarkers' dynamics. Whereas this approach is studied for HU treatment of individuals with SCD here, with some modifications, it can be applied to study nonadherence in any drug-disease combination. A key limitation in our modeling approach is that we attribute the variation in the biomarkers' profiles only to the treatment adherence and based on this assumption, we estimate the nonadherence profiles. But the variation could be a result of other factors. Blood transfusion could be one of the key factors to this variation. Sometimes, there can be a decrease in MCV and HbF in participants because of blood transfusion and this does not necessarily correspond to increasing severity, and is an effect of newly transfused blood cells with high adult hemoglobin but

low HbF and low volume. However, we have not applied our model for those participants because we have not included effects of blood transfusion in our modeling approach. Another limitation is that the threshold was arbitrarily selected. But, with the help of clinical prognosis, a threshold for MCV and HbF can be defined below which the drop in MCV and HbF is not desirable. Further studies through clinical data and simulation are needed to validate this study.

AUTHOR CONTRIBUTIONS

A.P., R.R., J.H.E., and D.R. wrote the manuscript. A.P. and D. R. designed the research. A.P. and R.R. performed the research. A.P. and R.R. analyzed the data. J.H.E. and D.R. contributed data/analytical tools.

ACKNOWLEDGMENTS

A.P. would like to thank Kunaal Joshi for his feedback on the modeling approach and Kaushal Kamal Jain and Parul Verma for their valuable inputs on models and writing.

FUNDING INFORMATION

The HUSTLE cohort data collection, extraction, and participant activities was funded by American Lebanese Syrian Associated Charities (ALSAC).

CONFLICT OF INTEREST STATEMENT

J.H.E. received research funding support from Global Blood Therapeutics, Forma Therapeutics, Pfizer, and Eli Lilly and Co. J.H.E. provided consultancy to Daiichi Sankyo, Esperion, and Global Blood Therapeutics. J.H.E. also received research funding support from American Society of Hematology (ASH) and National Heart, Lung, and Blood Institute (NHLBI). Following completion of the activities contained in this manuscript, J.H.E. changed employers to Agios Pharmaceuticals, which had no role in design of the study, analysis or interpretation of the results, or drafting of the manuscript. All other authors declared no competing interests for this work.

ORCID

Akancha Pandey https://orcid.org/0000-0001-6907-1489

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Pandey A, Raja R, Estepp JH, Ramkrishna D. Leveraging mathematical modeling to analyze nonadherence for hydroxyurea therapy in sickle cell disease. *CPT Pharmacometrics Syst Pharmacol*. 2023;12:748-757. doi:10.1002/psp4.12945