Invited Review

Drug-Drug Interactions, Dosing, Formulations, and Other Pharmacologic Issues in HIV Management: A Week on Consultation With Your HIV Clinical Pharmacologist

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Abstract: *Antiretroviral therapy is highly effective, but variability in HIV drug exposure can lead to differences in treatment efficacy, toxic effects, and the emergence of resistance. Each HIV clinician should have a detailed knowledge of HIV clinical pharmacology, including the management of drug-drug interactions, appropriate dosing, and the influence of different formulations. This review illustrates these concepts using a series of consultations with an HIV clinical pharmacologist during a typical week.*

Keywords: HIV, pharmacology, drug-drug interactions, HIV, pediatrics, pharmacokinetics, therapeutic drug monitoring

Introduction

More than 30 years ago, with the introduction of the first effective combination antiretroviral (ARV) regimen, it became apparent that the drugs could exhibit substantial variability in treatment response among people with HIV (PWH). The pharmacokinetic profiles of HIV protease inhibitors, which were introduced around 1996 and included ritonavir, saquinavir, and indinavir, were not optimal and exhibited limited absorption, short elimination half-lives, and high susceptibility to drug-drug interactions (DDIs). Adherence of more than 95% was needed to achieve sustained virologic suppression and to prevent the emergence of drug resistance.

Pharmacology has played a crucial role in HIV prevention and treatment, and clinical pharmacologists have contributed through research, education, and clinical consultation to optimize outcomes. These contributions have spanned from the early days of protease inhibitor-based triple therapy to more recent innovations such as long-acting injectable cabotegravir/rilpivirine (LA CAB/RPV).

One of the basic principles of clinical pharmacology is the concentration-effect relationship, ie, without drug exposure, there is no pharmacologic activity. In 1538, the Swiss physician Paracelsus stated that "every substance can be toxic, dependent on the dose" or, to put it in terms of current clinical understanding, dependent on the concentration. In modern clinical pharmacology, these principles have been developed into the concept of a therapeutic range (**Figure 1**). Ideally, every patient on the same dose of a medication maintains a plasma concentration within the therapeutic range during the entire dose interval. A certain threshold concentration is needed to inhibit viral enzymes such as HIV protease and integrase, to maintain virologic suppression. However, many factors can influence pharmacokinetic variability, leading to toxic or to subtherapeutic levels of the ARV agent. Knowledge of these factors is crucial for the optimal care of PWH. HIV clinical pharmacologists provide specialized expertise

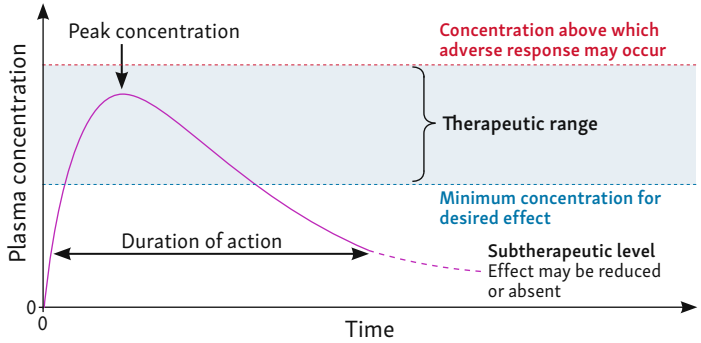


Figure 1. Therapeutic range (or "window"): concentrations associated with desired clinical effect and acceptable tolerability. Adapted from Smith R.[24]

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and collaborate with health care practitioners to improve outcomes in PWH. To illustrate the role of clinical pharmacology in optimizing HIV care, this review presents a week in the life of a clinical pharmacologist, highlighting real-life consultations in which pharmacologic expertise contributed to the clinical management of PWH.

Monday

Dr M. calls: "We have a patient on dolutegravir [DTG]/lamivudine, with a well-suppressed viral load and a suspected prosthetic valve endocarditis with a coagulase-negative Staphylococcus aureus. *We would like to add rifampicin 600 mg twice daily to treat the biofilm. With rifampicin 600 mg once daily, we need to adjust the dose of DTG to 50 mg twice daily. What is your advice for this higher dose of rifampicin?"*

Rifampicin is a strong inducer of CYP3A and UGT1A1, which are hepatic enzymes that are responsible for dolutegravir metabolism

Dr M. is an HIV physician and is aware of the well-known DDI between rifampicin and DTG.[1] Rifampicin is a strong inducer of cytochrome P450 3A (CYP3A) and uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), which are hepatic enzymes that are responsible for DTG metabolism. Trough levels of DTG will be reduced by 72% or more, leaving the individual at risk of virologic failure. To manage this DDI, the DTG dose should be increased from 50 mg once daily to 50 mg twice daily. This is described in the prescribing information of DTG-containing regimens and is also available in online DDI resources such as the HIV Interaction Checker developed by the University of Liverpool.[2]

In this individual, however, a higher dose of rifampicin is being prescribed, leading to the question of whether the higher dose will result in a stronger induction of metabolic enzymes, or whether the capacity is already maximal at the standard dose of 600 mg daily. If there is a stronger induction of CYP3A and UGT1A1, is DTG 50 mg twice daily still sufficient? This question is relevant in this patient with *S aureus* infection and in individuals with tuberculosis (TB), in whom higher doses of rifampicin (up to 35 mg/kg) are being tested to shorten the treatment duration.[3]

This specific research question has been addressed in the SAEFRIF (Pharmacokinetics, Safety/Tolerability, and Efficacy of High-Dose Rifampicin in Tuberculosis-HIV Coinfected Patients on Efavirenz- or Dolutegravir-Based Antiretroviral Therapy: Study Protocol for an Open-Label, Phase II Clinical Trial) study at the TB-HIV outpatient clinic of the Infectious Diseases Institute at Makerere University in Uganda.[4] PWH who were newly diagnosed with TB were randomly assigned to standard-dose (10 mg/kg) or to high-dose (35 mg/kg) rifampicin as part of their standard TB regimen. Participants were on or planning to start DTG-containing ARV therapy. DTG was dosed at 50 mg twice daily in accordance with the prescribing information and switched to once daily 2 weeks after completing TB treatment because the enzyme-inducing effects of rifampicin slowly reverse over a period of 1 to 2 weeks. Pharmacokinetic sampling for DTG trough concentrations was performed during and after rifampicin coadministration, enabling intraparticipant comparisons. The data showed that DTG trough levels averaged 0.46 mg/L with high-dose rifampicin and 0.80 mg/L with standard-dose rifampicin; the latter value is close to measurements in patients on DTG 50 mg once daily without rifampicin. Thus, as an interim conclusion, high-dose rifampicin does provide a higher level of enzyme induction than standard-dose rifampicin.

The next question is whether this information is clinically relevant, which depends on the therapeutic range of DTG. Two thresholds have been proposed in the literature. The first, 0.3 mg/L, is the average concentration of lower doses of DTG that have been shown to be noninferior to 50 mg once daily[5] and can therefore be seen as a conservative threshold. The second, 0.064 mg/L, is the protein-adjusted 90% inhibitory concentration value for DTG and can be seen as the absolute minimum concentration required for ARV activity. In this study, there was a lower proportion of individuals on high-dose rifampicin achieving the 0.30 mg/L threshold than in those on standard-dose rifampicin (60.9% vs 92.9%, respectively; P=.014); for the 0.064 mg/L threshold, there was no difference in proportion of individuals achieving that goal (P=.999). Viral load responses in the rifampicin groups were similar, suggesting that the 0.064 mg/L threshold as a target makes more sense than the conservative value of 0.30 mg/L.

In the individual described above, despite stronger enzyme induction caused by higher-than-standard doses of rifampicin, it is very likely that DTG trough levels with 50 mg twice daily dosing will remain in the therapeutic range. There is therefore no reason to change the standard management of this DDI.

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Tuesday

Dr J. approaches you at a meeting: "I recently saw a 27-year-old man with HIV who switched from doravirine/lamivudine/tenofovir disoproxil fumarate [TDF] to injectable LA CAB/RPV every 2 months and developed virologic failure after 8 months of treatment. Resistance testing showed mutations for CAB [N155S] and RPV [E138K]. HIV-1 was retrospectively analyzed and determined to be subtype A6. He is a body builder and is taking anabolic androgen steroids and testosterone and has a muscular physique and a body mass index [BMI] of 35 kg/m². Do you think the anabolic steroids have influenced the hepatic metabolism of the CAB or RPV? Can you do drug levels?"

High concentrations of testosterone due to supplemental injections can cause enzyme induction, and possibly lower drug levels of CAB and RPV

LA CAB/RPV is a highly effective treatment but confirmed virologic failure may occur in 1% to 2% of cases after 1 year of treatment, often with multiclass drug resistance. Clinical trials have shown that subtype A6, preexisting RPV mutations, and BMI above 30 kg/m² are risk factors for virologic failure, with an increased risk observed only in individuals with at least 2 of these factors.[6] Low CAB or RPB levels increase this risk of virologic failure but the clinical relevance in the absence of other risk factors remains to be determined.

To assess whether a DDI may be involved in this case, it is first necessary to review what is known about the effect of enzyme inducers on the pharmacokinetics of LA CAB/RPV injections. During clinical drug development, studies were performed with rifampicin and oral CAB and RPV (showing >80% reductions in trough levels of these agents) but data are lacking on the impact of rifampicin (or other enzyme inducers) on LA intramuscular injections of these agents. In this case, physiologically based pharmacokinetic modeling may be helpful, predicting that when used with rifampicin, overall exposure to CAB will be reduced by 61% and overall exposure to RPV will be reduced by 38%.[7]

The next question is whether anabolic steroids can behave as an enzyme inducer (like rifampicin), but this has not been investigated in detail. Data from more than 30 years ago demonstrated that propranolol glucuronidation correlated with testosterone levels;[8] in other words, high concentrations of testosterone due to supplemental injections can cause enzyme induction, and possibly lower drug levels of CAB and RPV.

Another, more indirect explanation for the altered pharmacokinetics of CAB/RPV in this individual is his intensive bodybuilding activity, which may have contributed to faster drug release from the intramuscular depot. Finally, a single case of faster elimination of CAB/RPV in a young athletic person injecting anabolic steroids has been reported.[9]

Therapeutic drug monitoring may be useful in this situation, provided it is available. Fortunately, it is routinely available in the Netherlands. We therefore measured the trough concentrations and determined them to be 0.91 mg/L for CAB and 0.026 mg/L for RPV. These values are 43% lower and 61% lower, respectively, than reported median population values, suggesting an enzyme-inducing effect.

As discussed in the previous case, not every reduction in trough level is clinically relevant. The clinical significance depends on the size of the reduction and the width of the therapeutic range. There is much debate regarding therapeutic targets for CAB and RPV,[10] but the consensus in the Netherlands is 0.66 mg/L for CAB and 0.032 mg/L for RPV, which means that the DTG level is still therapeutic, but the RPV level is subtherapeutic. In combination with the presence of the A6 subtype, which only became apparent at confirmed virologic failure, and the high BMI, which was not considered to be obesity by the treating physician, lower levels of RPV in particular may have contributed to the virologic failure in this patient.

Although this potential DDI was recorded after virologic failure had been documented, sharing the insights gained from such cases in peer-reviewed journals remains valuable despite the inherent limitations of case reports.[11] An alternative to formal publication is submitting cases with suspected DDIs to the Clinical Cases DDI platform.[12] Case submissions are reviewed by the editorial board and this platform can facilitate the rapid dissemination of clinically relevant information when information is incomplete or there is insufficient time to prepare a manuscript for traditional publication channels.

Wednesday

You attend the weekly HIV outpatient rounds and Mr V. is discussed. He is a 63-year-old man who was diagnosed with HIV in 2011. He is currently virologically suppressed on LA CAB/RPV but, for logistic reasons, needs to switch to a daily oral ARV regimen. The treating physician wants to start the patient on DTG/lamivudine but a DDI alert is generated because he is currently taking metformin 1500 mg daily. His

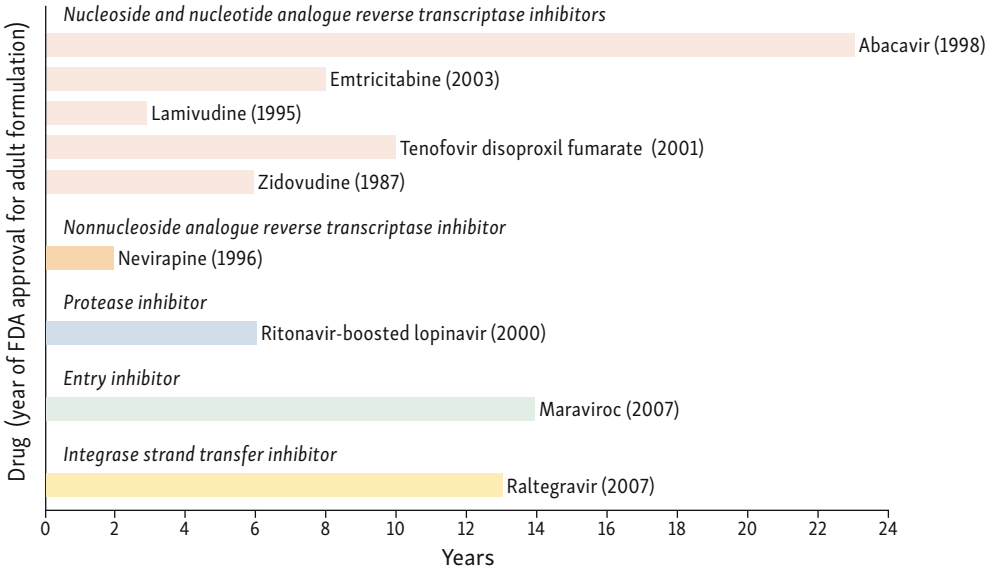


Figure 2. Time between year of US Food and Drug Administration (FDA) approval for adult formulation and first pharmacokinetic data for neonates published in a peer-reviewed journal by 2021. The median time until neonatal pharmacokinetic data are available is 8 years. Adapted from Jacobs TG and colleagues.[17]

BMI is 35 kg/m². Should the metformin be replaced with an SGLT2 inhibitor because of the high BMI?

Metformin is one of the most widely used medications worldwide, and its use will increase in the aging population of PWH. However, metformin is associated with DDIs with certain HIV drugs, in particular DTG, because the plasma concentrations of metformin increase through the inhibition of the renal efflux transporter, organic cation transporter 2 (OCT2). A healthy volunteer study showed that the metformin area under the plasma concentration-time curve (AUC) increased by 79% when coadministered with DTG once daily, potentially leading to metformin-associated toxicity.[13]

It is important to note that DDIs can be managed through a variety of strategies. A DDI alert does not always indicate that a combination of drugs is contraindicated. In this particular patient, a number of options are available for consideration:

1. Replace the precipitant drug (DTG → ?)
2. Replace the object drug (metformin → ?)
3. Modify the dose of the object drug (metformin)
4. Intensify patient monitoring (blood glucose, adverse events)

Each of these options may be appropriate, depending on patient-specific considerations. For instance, with option 1, bictegravir may be a good alternative to DTG because it causes less potent inhibition of OCT2, resulting in a less pronounced increase in metformin plasma concentration.[14] Alternatively, with option 2, seeking an alternative to metformin, the Interaction Checker of the University of Liverpool may prove useful, as one can search by drug class and determine that SGLT2 inhibitors such as canagliflozin, dapagliflozin, and empagliflozin are not associated with a DDI with DTG. Modifying the metformin dose, as with option 3, is a rational intervention because it minimizes the risk for toxicity while maintaining metformin plasma concentrations within the therapeutic range. Over the last 13 years, the US Food and Drug Administration (FDA)-approved prescribing information for DTG has evolved regarding the management of DDI with metformin. Initially, in 2013, the DTG prescribing information stated that a dose adjustment of metformin may be necessary; however, in 2019, it was updated to recommend limiting the dose of metformin to 1000 mg daily. Currently, in 2026, no specific recommendation is provided other than a reference to the metformin prescribing information. In this context, a recent publication from South Africa is noteworthy.[15] In this study, individuals receiving DTG and metformin underwent the standard metformin dose reduction to 1000 mg daily; however, suboptimal glycemic control occurred among women who were obese. Thus, although a dose reduction might be appropriate in a particular individual, it may not be suitable in all cases.

> ***Although a metformin dose reduction might be appropriate in a particular individual, it may not be suitable in all cases***

Finally, is option 4, ie, intensifying the monitoring of blood glucose levels and adverse events, followed by individualized adjustment of the metformin dose. With this approach, the presence of a DDI is only one factor among several considerations. This option was accepted by the HIV physician and the patient, demonstrating that a DDI alert does not always require a change in medication.

Thursday

You receive a call in the very early hours of the morning on your private cell phone from an HIV pediatrician: "We have a neonate prematurely born at a gestational age [GA] of 24 weeks and 4 days to a mother with HIV. The mother's HIV has been undetectable since 2016. The baby received zidovudine for 4 weeks after birth and has not been breastfeeding. The first HIV test, performed within 24 hours of birth, was negative. However, 6 weeks after birth, 2 weeks after zidovudine treatment was terminated, the HIV RNA level was 1.9 x 10^5 copies/mL. Today, 3 days later, the HIV RNA level is 1.2 x 10^7 copies/mL. Current GA is 31 weeks and the neonate weighs approximately 1 kg. Resistance testing results are expected on Monday. We would like to discuss the treatment options for this neonate with you as soon as possible."

In 2008, Violari and colleagues demonstrated that early treatment of infants with HIV saves lives.[16] Although access to the most potent ARV drugs, such as integrase strand transfer inhibitors, has improved for children with HIV, data for neonates are lacking. In 2022, Jacobs and colleagues published a viewpoint article[17] to stimulate pharmacokinetic studies in neonates with HIV to accelerate access to therapeutic drugs. This review examined the first pharmacokinetic data in newborns for all ARV agents and noted a median lag time of 8 years after FDA approval of the adult formulation (**Figure 2**).

Current guidelines, therefore, still recommend older ARV agents such as zidovudine and nevirapine (plus lamivudine) for term and preterm infants with a postmenstrual age of more than 32 weeks. Raltegravir is an alternative to nevirapine in term infants weighing at least 2 kg. The neonate in the current case was preterm, with a postmenstrual age of 31 weeks. Furthermore, nevirapine is not a recommended choice for patients with a high viral load. More modern agents such as DTG would be more attractive options.

Importantly, in 2025, the PETITE-DTG (Safety and Pharmacokinetics of Dolutegravir Dispersible Tablets and Oral Films in Term Neonates Exposed to HIV in South Africa) study[18] presented the first data on the pharmacokinetics of DTG in neonates. Bekker and colleagues used a 2-stage approach: in stage 1, a single dose of DTG 5 mg was administered to neonates exposed to HIV who weighed at least 2 kg and who were receiving standard postexposure prophylaxis. A pharmacokinetic model was built and safety was evaluated. In stage 2, newborns receiving standard postexposure prophylaxis received chronic dosing of DTG 5 mg every 48 hours in weeks 1 and 2, and DTG 5 mg every 24 hours in weeks 3 and 4. DTG was well tolerated, target concentrations were achieved, and none of the newborns acquired HIV. The authors concluded that their data supported the inclusion of DTG in national and international guidelines.

Based on the PETITE-DTG study data, the abovementioned neonate was given a smaller dose of DTG (2.5 mg every 48 hours) in combination with zidovudine plus lamivudine because this child was preterm and had a body weight of only 1 kg. DTG plasma concentrations were measured at 2 hours, 24 hours, and 48 hours. Results were 2.1 mg/L, 0.54 mg/L, and 0.42 mg/L, respectively. The elimination half-life was estimated to be 69 hours, which is severely prolonged (adult elimination half-life, 14 h). The concentration at 48 hours was above the conservative target of 0.30 mg/L for DTG. Over time, DTG doses were adjusted based on changes in body weight and supported by therapeutic drug monitoring.

Friday

You are invited to a meeting of the national HIV Preexposure Prophylaxis [PrEP] Guidelines Committee. During the coffee break, a committee member approaches you: "We increasingly see patients who have undergone bariatric surgery and are candidates for oral PrEP with TDF/emtricitabine [FTC]. What should we tell them? Is bariatric surgery a contraindication to TDF/FTC PrEP? Should we adjust the dose of TDF/FTC? Is there a role for pharmacokinetic measurements? Are tenofovir alafenamide/FTC, intramuscular CAB, or subcutaneous lenacapavir appropriate alternatives?"

> ***There is no indication that a history of bariatric surgery influences TDF/FTC absorption, and daily PrEP should therefore be effective***

TDF/FTC is highly effective for HIV PrEP when taken with good adherence, but its efficacy is dependent on good absorption. It is unknown whether bariatric surgery was an exclusion criterion for subjects in the pivotal PrEP trials. Kingma and colleagues described general concepts of oral drug dosing following bariatric surgery. They concluded that in the absence of well-performed studies, it is difficult to provide recommendations in those who have undergone bariatric surgery, and that risk assessment is required on an individualized basis.[19]

Data on the pharmacokinetics of TDF/FTC treatment in PWH who have undergone bariatric surgery demonstrate that the plasma trough levels of tenofovir are generally around 0.05 mg/L, which is similar to levels in those who have not undergone bariatric surgery.[20] In some case reports, data have been collected before and 3 to 6 months after bariatric surgery, and demonstrate no influence from the surgery.[21] Data on tenofovir pharmacokinetics in PrEP users are much more limited, but do not suggest a major impact.[22] The data reported to date are on individuals taking daily oral PrEP, with the exception of 1 patient who used on-demand PrEP and who appeared to have a low tenofovir concentration.[22]

TAF/FTC is FDA approved in the US for HIV PrEP. The intracellular pharmacokinetic measurements of tenofovir diphosphate in a small number of individuals do not suggest a major impact from bariatric surgery.[23] However, in areas where PrEP is not publicly funded or reimbursed, TAF/FTC is substantially more expensive than generic TDF/FTC, which may limit its use.

Finally, LA agents such as intramuscular CAB and subcutaneous lenacapavir have the theoretic advantage of bypassing gastrointestinal absorption and may be attractive alternatives when available and affordable.

In summary, there is no indication that a history of bariatric surgery influences TDF/FTC absorption, and daily PrEP should therefore be effective.

Conclusion

Collectively, this week of consultations demonstrates that clinical pharmacology is an important tool for optimizing the treatment of PWH. Its applications to DDIs, dosing, and adverse effects help to inform HIV prevention and treatment decisions in routine clinical care. The cases also illustrate the ongoing need to integrate pharmacologic principles into the management of HIV ARV regimens.

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All relevant financial relationships with ineligible companies have been mitigated.

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