Updates on the Pharmacology of Antiretrovirals and DAAs

Report from the 16th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy, 26-28 May 2015, Washington, DC

Written by Mark Mascolini

Sixteen years ago the International Workshop on Clinical Pharmacology of HIV Therapy began in Noordwijk, a sleepy preseason seaside resort south of Amsterdam, with about 40 abstracts and not many more attendees. Triple antiretroviral therapy was only 4 years old and HCV therapy relied on thrice-weekly interferon and perhaps ribavirin. Publication of the first randomized trial of pegylated versus standard interferon for chronic HCV infection was still a year away.¹

In 2016 clinicians routinely cure HCV infection with 12 or 24 weeks of direct-acting antiviral (DAA) therapy combining agents from two or three classes, typically excluding interferon and ribavirin. Despite access to five classes of antiretrovirals, a cure for HIV infection remains elusive, though avidly explored, and one-pill once-daily combinations can keep HIV in check for years.

The 16th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy reflected these sea changes in 82 abstracts, 19 presented orally, and 18 invited talks with topics ranging from drug-drug interactions to nanoformulations to Ebola. Of the 19 oral abstracts, 11 (58%) involved antiretrovirals, 6 (32%) involved DAAs, and 2 (10%) involved both. If you count four invited lectures on drug-drug interactions between DAAs and antiretrovirals, those proportions change to 48% of talks on antiretrovirals, 26% on DAAs, and 26% on both.

This review of all oral abstract reports at the workshop, plus a few invited lectures and posters, begins with the one study appraising potential drug-drug interactions between common DAA combinations and current antiretroviral favorites. Complete slide sets for most oral presentations are online at http://www.infectiousdiseasesonline.com/16th-hivhep-pk-presentations/.

**DRUG-DRUG INTERACTIONS WITH DAAs**

**Frequent potential interactions between standard DAAs and ARVs**

Nearly three quarters of HIV/HCV-coinfected people in care at a Denver clinic faced the possibility of moderate or severe interactions between the antiretrovirals they were taking and four popular DAA combinations, according to results of a retrospective analysis.² Among patients prescribed one of those four DAA regimens, 20% would not be able to switch antiretrovirals to avoid DAA interactions because of antiretroviral resistance.

This retrospective study considered 125 adults who were prescribed antiretrovirals within the past year and were candidates for HCV therapy with a contemporary DAA combination. The possible DAA regimens were simeprevir and sofosbuvir (SIM/SOF), sofosbuvir and ledipasvir (SOF/LDV), sofosbuvir and daclatasvir (SOF/DCV), and ritonavir-boosted paritaprevir, dasabuvir, and ombitasvir (3D). The investigators rated DAA-antiretroviral interactions as severe if possible interactions were unsafe and contraindicated, moderate if possible interactions required additional monitoring and/or dose adjustments, and no significant interaction if regimens were safe when given together and required no dose adjustments. The researchers did not assess potential interactions between DAAs and non-HIV drugs being taken.
Among the 125 study participants, 101 (81%) were taking tenofovir, 50 (40%) an HIV protease inhibitor, 44 (35%) raltegravir, and 20 (16%) efavirenz. Of the antiretroviral regimens taken, 70% could have moderate or severe interactions with SIM/SOF, 64% with SOF/LDV, 61% with 3D, and 47% with SOF/DCV (Figure 1). Overall, 88 of 125 regimens (70.4%) could have a moderate or severe interaction with one of the four DAA regimens.

Among the antiretroviral regimens prescribed, 64% could have severe interactions with SIM/SOF, 40.8% with 3D, 9.6% with SOF/LDV, and none with SOF/DCV. While 54% of antiretroviral regimens had potential interactions with SOF/LDV, 46.6% had potential moderate interactions with SOF/DCV, 20% with 3D, and 7% with SIM/SOF. About half of the antiretroviral regimens (52%) would have no significant interactions with SOF/DCV, 38% would have no interactions with 3D, 34% with SOF/LDV, and 29% with SIM/SOF.

Clinicians prescribed SOF/LDV for 35 of 125 patients (28%) during the study period. Two of these 35 (5.7%) were taking antiretrovirals contraindicated with SOF/LDV and thus requiring a treatment change. Seventeen of the 35 (48.6%) had potential moderate interactions between their antiretrovirals and SOF/LDV, 10 of whom switched their antiretrovirals before starting SOF/LDV and 7 of whom continued their antiretrovirals. Of these 7 people, 3 had adherence problems and low viremia, 2 were taking a salvage combination, and 2 simply preferred to stay with their current antiretrovirals. The remaining 16 people had no potential interactions between their antiretrovirals and SOF/LDV.

The investigators analyzed HIV resistance profiles in all 35 people prescribed SOF/LDV by genotype, phenotype, and/or Phenosense. Seven of these 35 (20%) would not be able to change their antiretroviral combination because of resistance. Five of these 7 did not have significant interactions between their antiretrovirals and SOF/LDV, but 2 had moderate interactions.

The Denver team concluded that 70% of antiretroviral-treated people in this clinic would have potential antiretroviral-DAA interactions if prescribed one of four popular DAA regimens. The investigators believe their findings "illustrate the need for expertise in management of drug-drug interactions in this population and that many patients will require a change to antiretroviral therapy or increased monitoring."

Gilead Sciences presented a separate analysis on potential interactions between ledipasvir/sofosbuvir and antiretrovirals. Ledipasvir, an NS5A inhibitor, and sofosbuvir, a nucleotide polymerase inhibitor, are combined in a once-daily fixed-dose (90/400 mg) tablet for HCV genotype 1 or 4 infection. Both agents are substrates of the transporter enzymes P-glycoprotein (P-gp) and BCRP, and ledipasvir inhibits those enzymes. Research indicates that ledipasvir/sofosbuvir increases tenofovir exposure in people taking tenofovir disoproxil fumarate (TDF), so people taking the DAAs with TDF should be monitored for adverse reactions associated with TDF.
Potential interactions between 3D regimen and four comedications

The dose of hydrocodone should be halved or monitoring increased when hydrocodone is coadministered with the 3D anti-HCV regimen of paritaprevir/ritonavir, ombitasvir, and dasabuvir, according to results of studies in healthy volunteers. Three other comedications—carisoprodol, cyclobenzaprine, and diazepam—may have decreased exposure when taken with 3D and thus require clinical monitoring (Table 1). No interactions were found between 3D and acetaminophen, metformin, or sulfamethoxazole/trimethoprim.

Table 1. Dosing recommendations for eight comedications with 3D

<table>
<thead>
<tr>
<th>Medication (dose)</th>
<th>Drug class</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen (300 mg)</td>
<td>Analgesic/antipyretic</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td>Metformin (500 mg)</td>
<td>Antidiabetic</td>
<td></td>
</tr>
<tr>
<td>Sulfamethoxazole (800 mg BID)</td>
<td>Antimicrobial</td>
<td></td>
</tr>
<tr>
<td>Trimethoprim (160 mg BID)</td>
<td>Antimicrobial</td>
<td></td>
</tr>
<tr>
<td>Carisoprodol (250 mg)</td>
<td>Muscle relaxant</td>
<td>No a priori dose adjustment required; increase dose if clinically indicated</td>
</tr>
<tr>
<td>Cyclobenzaprine (5 mg)</td>
<td>Muscle relaxant</td>
<td></td>
</tr>
<tr>
<td>Diazepam (2 mg)</td>
<td>Benzodiazepine/anxiolytic</td>
<td></td>
</tr>
<tr>
<td>Hydrocodone (5 mg)</td>
<td>Opioid analgesic</td>
<td>Reduce dose by half and/or monitor clinical response</td>
</tr>
</tbody>
</table>

BID, twice daily.

Source: Akshanth Polepally, AbbVie, and colleagues.

Licensed for treatment of HCV genotype 1 infection, 3D consists of the ritonavir-boosted NS3/4A protease inhibitor paritaprevir, the NS5A inhibitor ombitasvir, and the NS5B polymerase inhibitor dasabuvir. Ombitasvir and paritaprevir are coformulated as a once-daily agent, while dasabuvir is a separate twice-daily medication.

To evaluate potential interactions between 3D and eight frequently prescribed medications, AbbVie investigators recruited healthy volunteers for pharmacokinetic studies. The targeted drugs were diazepam, hydrocodone bitartrate/acetaminophen, sulfamethoxazole/trimethoprim, metformin, carisoprodol, and cyclobenzaprine. For all comedications except sulfamethoxazole/trimethoprim, volunteers first took a single dose of the comedication, took no drug for several days, then took a single dose of the comedication 2 weeks after starting 3D dosing; 3D alone continued for a few more days after coadministration. For sulfamethoxazole/trimethoprim, volunteers took a single 3D dose followed by 8 days with no drug, then started sulfamethoxazole/trimethoprim and took 3D 3 days later; sulfamethoxazole/trimethoprim continued for 3 more days after coadministration.

Calculating central value ratios (CVR) and 90% confidence intervals (CI) for area under the concentration-time curve (AUC) and maximum concentration (Cmax) for each comedication and each 3D component, the AbbVie team found no clinically meaningful interactions between 3D and acetaminophen, sulfamethoxazole, trimethoprim, or metformin. None of the eight comedinations affected plasma exposures of the 3D drugs.

Hydrocodone Cmax was 27% higher with than without 3D (CVR 1.27, 90% CI 1.14 to 1.40) and hydrocodone AUC was 90% higher with 3D (CVR 1.90, 90% CI 1.72 to 2.10). As a result, the researchers recommended halving the hydrocodone dose and/or monitoring clinical response to hydrocodone taken with 3D.

Three other comedinations had potentially important interactions with 3D that call for clinical monitoring to determine whether higher doses of the comedinations are needed: Carisoprodol AUC fell 38% with 3D (CVR 0.62, 90% CI 0.55 to 0.70), and carisoprodol Cmax was 46% lower with 3D (CVR 0.54, 90% CI 0.47 to 0.63). But 3D did not significantly affect concentrations of the carisoprodol...
metabolite meprobamate. Coadministered 3D was associated with 40% lower cyclobenzaprine AUC (CVR 0.60, 90% CI 0.53 to 0.68), 32% lower cyclobenzaprine Cmax (CVR 0.68, 90% CI 0.61 to 0.75), and 26% lower AUC of norcyclobenzaprine, a metabolite (CVR 0.74, 90% CI 0.64 to 0.85). When diazepam was taken with 3D, diazepam AUC was 22% lower than without 3D (CVR 0.78, 90% CI 0.73 to 0.82), and nordiazepam AUC was 44% lower with 3D (CVR 0.56, 90% CI 0.45 to 0.70).

No serious adverse events, new or unexpected safety findings, or clinically meaningful changes in laboratory values arose during coadministration of 3D with these medications.

In a separate presentation, AbbVie spelled out what is known about interactions between 3D and antiretrovirals. No dose adjustments are needed when 3D is taken with tenofovir/emtricitabine, abacavir/lamivudine, raltegravir, dolutegravir, atazanavir, or darunavir. Lopinavir is not recommended or contraindicated with 3D, efavirenz is contraindicated, and rilpivirine is not recommended. Potential interactions between 3D and elvitegravir/cobicistat have not been evaluated.

**Grazoprevir plus elbasvir raise levels of rosvastatin, but not pravastatin**
Grazoprevir, an HCV NS3/4A protease inhibitor, and elbasvir, an NS5A inhibitor, increased concentrations of rosvastatin but not pravastatin in a two-part study. Neither statin affected pharmacokinetics of grazoprevir or elbasvir.

Grazoprevir and elbasvir are coformulated at doses of 100 mg and 50 mg once daily. The fixed-dose combination yielded high 12-week sustained virologic response rates in 421 HCV therapy-naive people with or without cirrhosis and with chronic genotype 1, 4, or 6 HCV infection. Grazoprevir and elbasvir have also proved effective in treatment-experienced patients, in those with chronic kidney disease, and in HIV/HCV-coinfected individuals.

Prior research found no clinically relevant interactions between grazoprevir and pitavastatin. Grazoprevir is associated with increased atorvastatin exposure. Grazoprevir and elbasvir are both CYP3A and P-gp substrates, and grazoprevir is an OATP1B substrate. In vitro data suggest both agents may inhibit BCRP efflux transporters in the intestine. Rosuvastatin is a substrate of BCRP, OATP1B, and CYP2C9. Pravastatin is an OATP1B substrate and relies partly on CYP3A for metabolism. Merck investigators hypothesized that grazoprevir/elbasvir may raise rosvastatin exposure through intestinal BCRP inhibition and that grazoprevir may have a minor boosting effect on pravastatin via weak CYP3A inhibition.

This two-part study involved 24 healthy volunteers, 12 for the rosvastatin analysis and 12 for the pravastatin analysis. Participants took a single 10-mg dose of rosvastatin on day 1 followed by a 3-day washout. On days 1 through 9, they took 200 mg of grazoprevir once daily, adding 10 mg of rosvastatin on day 7. Then they added 50 mg of elbasvir once daily to grazoprevir for 11 days and took 10 mg of rosvastatin on day 9. In the pravastatin trial, participants took a single 40-mg pravastatin dose on day 1, took 200 mg of grazoprevir and 50 mg of elbasvir once daily on the next 9 days, and took another 40-mg dose of pravastatin with grazoprevir/elbasvir on day 9.

No serious adverse events arose during either trial. One person stopped treatment because of increased creatine phosphokinase that occurred during grazoprevir-only administration but was unrelated to study drugs. Neither statin affected exposure of grazoprevir or elbasvir.

When rosvastatin was coadministered with grazoprevir, rosvastatin AUC0-24 was 85% higher than with rosvastatin alone, and rosvastatin Cmax was more than 4 times higher (Table 2). Taking rosvastatin with grazoprevir had only a modest impact on rosvastatin 24-hour concentration (C24). Adding elbasvir to grazoprevir further increased rosvastatin AUC0-24 and Cmax but had no impact on rosvastatin C24 (Table 2).
Table 2. Impact of grazoprevir with or without elbasvir on rosuvastatin exposure

<table>
<thead>
<tr>
<th></th>
<th>Rosuvastatin + grazoprevir/rosvastatin alone</th>
<th>Rosuvastatin + grazoprevir + elbasvir/rosvastatin alone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GMR (90% CI)</td>
<td>GMR (90% CI)</td>
</tr>
<tr>
<td>AUC0-24</td>
<td>1.85 (1.56 to 2.19)</td>
<td>2.68 (2.26 to 3.17)</td>
</tr>
<tr>
<td>Cmax</td>
<td>4.25 (3.25 to 5.56)</td>
<td>5.49 (4.29 to 7.04)</td>
</tr>
<tr>
<td>C24</td>
<td>0.80 (0.70 to 0.91)</td>
<td>0.98 (0.84 to 1.13)</td>
</tr>
</tbody>
</table>

Source: Luzelena Caro, Merck & Co, and colleagues.

The Merck team proposed that higher rosuvastatin exposure with grazoprevir suggests increased statin absorption due to grazoprevir inhibition of intestinal BCRP efflux. The further increase in rosuvastatin exposure with elbasvir, they suggested, reflects an additional but smaller impact of elbasvir on intestinal BCRP inhibition.

Grazoprevir plus elbasvir resulted in 28% higher pravastatin AUC0-24 (GMR 1.28, 90% CI 1.08 to 1.51) and Cmax (GMR 1.28, 90% CI 1.05 to 1.55), findings consistent with grazoprevir inhibition of CYP3A. The investigators characterized these changes as not clinically relevant and concluded that pravastatin may be coadministered with grazoprevir/elbasvir without dose adjustment. They proposed limiting rosuvastatin dosing to 10 mg daily with grazoprevir/elbasvir. In phase 2 and 3 trials, participants tolerated up to 10 mg of rosuvastatin, up to 20 mg of atorvastatin, and standard-dose pravastatin.

In a separate presentation, Merck reviewed interactions between grazoprevir/elbasvir and antiretrovirals. Studies to date indicate that tenofovir disoproxil fumarate, emtricitabine, abacavir, lamivudine, raltegravir, dolutegravir, and rilpivirine may be coadministered with grazoprevir/elbasvir without dose adjustment. Moderate or strong CYP3A or P-gp inducers, such as efavirenz and etravirine, are not recommended for coadministration because they may decrease concentrations of the DAAs. Because HIV protease inhibitors may increase grazoprevir and elbasvir exposure, they are not recommended for coadministration.

Dialysis does not affect circulating sofosbuvir or metabolite

Hemodialysis did not substantially affect accumulation of sofosbuvir or the sofosbuvir metabolite SOF-007 in an observational study of 13 sofosbuvir-treated patients. The investigators believe their findings are consistent with three-times-weekly or daily full-dose sofosbuvir in patients on hemodialysis.

Researchers from Bichat-Claude Bernard Hospital in Paris who conducted this study noted that HCV is an independent risk factor for chronic kidney disease (CKD) and that HCV infection progresses faster in people with CKD. Treatment of HCV infection significantly reduces proteinuria and stabilizes serum creatinine in patients with CKD, but little is known about sofosbuvir use in patients on hemodialysis.

To fill this gap in data on sofosbuvir safety, dosing, and efficacy in hemodialysis patients, the Bichat-Claude Bernard team conducted this prospective multicenter study of people requiring hemodialysis and taking 400 mg of sofosbuvir daily or 400 mg three times weekly. Eight study participants had cirrhosis, and all patients were treatment naive or null or partial responders to peginterferon plus ribavirin with or without boceprevir. They were taking sofosbuvir with 60 mg of daclatasvir once daily, 90 mg of ledipasvir once daily, 150 mg of simeprevir once daily, or 200 mg of ribavirin once daily.

To measure concentrations of sofosbuvir, the sofosbuvir metabolite SOF-007, and other anti-HCV medications, researchers collected plasma samples during routine therapeutic monitoring before hemodialysis, after a 4 hours-hemodialysis, and 1.5 hours after the last sofosbuvir dose after hemodialysis ended. They determined hemodialysis extraction ratio by comparing paired pre- and post-dialysis plasma concentrations.

Of the 13 study participants, 11 were men, 8 Caucasian, 4 African, and 1 Asian. Median age stood at
52 years (interquartile range 43.5 to 60.8), and 3 patients had HIV infection. Eight had cirrhosis, 7 had not received previous anti-HCV therapy, 4 were null responders, and 2 were relapsers. Eight took sofosbuvir daily, 5 took sofosbuvir three times weekly, 9 took daclatasvir, 2 simeprevir, 1 ledipasvir, and 1 ribavirin.

The investigators collected 100 samples before hemodialysis, 81 after hemodialysis, and 75 at 1.5 hours after the last dose. Sofosbuvir did not accumulate before or after hemodialysis with either once-daily or thrice-weekly dosing. Pre- and posthemodialysis plasma concentrations of SOF-007 were higher in once-daily patients than in thrice-weekly patients (Figure 2), and estimated SOF-007 extraction ratio was 52%, a result consistent with historical data. Nor did SOF-007 accumulate before hemodialysis in patients taking sofosbuvir once daily. Concentrations of daclatasvir, simeprevir, ledipasvir, or ribavirin did not differ before and after hemodialysis.

![SOF plasma concentrations (median, ng/mL)](image1)

![SOF-007 plasma concentrations (median,ng/mL)](image2)

**Figure 2.** Hemodialysis had no significant impact on accumulation of sofosbuvir in 8 patients taking 400 mg of sofosbuvir daily or in 5 taking 400 mg three times weekly. (Source: Aude Desnoyer, Bichat-Claude Bernard Hospital, and colleagues.⁹)

To date, 7 patients have a sustained virologic response and no relapses have occurred. Response results are pending in the remaining 6 patients. All study participants tolerated treatment well. A single grade 3 adverse event (Streptococcus sepsis) was not related to treatment. Aspartate and alanine aminotransferase declined significantly during treatment, as did gamma-glutamyl transferase. Total plasma bilirubin and platelets did not change significantly with treatment.

The researchers concluded that sofosbuvir and SOF-007 do not accumulate in plasma of HCV patients requiring hemodialysis and taking sofosbuvir once daily or three times weekly. And hemodialysis did not remove simeprevir, daclatasvir, ledipasvir, or ribavirin. SOF-007 half-life was slightly higher in 1 patient (38 hours) on once-daily sofosbuvir than in patients with normal renal function, but this finding was compatible with once-daily sofosbuvir administration. The investigators advised close monitoring of hemodialysis patients on full-dose sofosbuvir, including clinical, biological, cardiovascular, and therapeutic drug monitoring.

**Interactions between daclatasvir and HIV PIs, and between DCV-TRIO and SSRIs**

Two workshop presentations analyzed interactions between the HCV NS5A replication complex inhibitor daclatasvir and (1) darunavir/ritonavir and lopinavir/ritonavir or (2) selective serotonin reuptake inhibitors (SSRIs).¹¹

Being studied as DCV-TRIO in combination with the NS3 protease inhibitor asunaprevir and the nonnucleoside NS5B polymerase inhibitor beclabuvir, daclatasvir is a substrate of the CYP3A4

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metabolizing enzyme, which ritonavir strongly inhibits. Previous research in healthy volunteers recorded a 2.1-fold increase in daclatasvir AUC when daclatasvir was taken with atazanavir/ritonavir. As a result, the recommended dose of daclatasvir with atazanavir/ritonavir is 30 mg daily, half the standard dose.

To learn whether ritonavir-boosted darunavir or lopinavir also affects daclatasvir pharmacokinetics, Bristol-Myers Squibb (BMS) researchers recruited 28 healthy volunteers who took daclatasvir alone at 60 mg daily for 4 days. On days 5 to 14 volunteers began 800/100 mg of darunavir/ritonavir once daily or 400/100 mg of lopinavir/ritonavir twice daily while lowering the daclatasvir dose to 30 mg once daily.

Observed daclatasvir AUC and Cmax were lower with the 30-mg dose plus darunavir or lopinavir than with the 60-mg dose of daclatasvir alone. Dose-normalized daclatasvir AUC was slightly higher with darunavir/ritonavir or lopinavir/ritonavir than with daclatasvir alone (Table 3), while dose-normalized daclatasvir Cmax was moderately lower with darunavir/ritonavir or lopinavir/ritonavir than with daclatasvir alone (Table 3).

Table 3. Dose-normalized daclatasvir* AUC and Cmax with vs without DRV/r or LPV/r

<table>
<thead>
<tr>
<th></th>
<th>With/without darunavir/ ritonavir (800/100 mg QD)</th>
<th>With/without lopinavir/ ritonavir (400/100 mg BID)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUCtau (GMR, 90% Cl)</td>
<td>1.406 (1.317 to 1.501)</td>
<td>1.154 (1.070 to 1.244)</td>
</tr>
<tr>
<td>Cmax (GMR, 90% Cl)</td>
<td>0.768 (0.697 to 0.846)</td>
<td>0.673 (0.611 to 0.742)</td>
</tr>
</tbody>
</table>

*Daclatasvir at 30 mg QD with protease inhibitor, 60 mg QD without protease inhibitor.
Source: Timothy Eley, Bristol-Myers Squibb, and colleagues.

To determine whether daclatasvir affects concentrations of darunavir or lopinavir, the BMS team evaluated 11 people taking a stable 600/100-mg twice-daily darunavir/ritonavir regimen and 6 taking a stable 400/100-mg twice-daily lopinavir/ritonavir regimen. All participants started 30 mg of daclatasvir once daily with peginterferon and ribavirin. Geometric mean ratios comparing darunavir or ritonavir concentrations with or without daclatasvir found that daclatasvir had no clinically meaningful impact on AUCtau, Cmax, or Ctau of the protease inhibitors.

The BMS investigators concluded that doses of darunavir/ritonavir or lopinavir/ritonavir do not have to be adjusted when coadministered with daclatasvir. They proposed that the standard 60-mg once-daily dose of daclatasvir is optimal in people taking darunavir/ritonavir or lopinavir/ritonavir. A separate study by BMS researchers determined that the integrase inhibitor dolutegravir and daclatasvir may be coadministered with no dose adjustments.

Dosing DCV-TRIO with an SSRI—escitalopram or sertraline—resulted in 32% to 38% lower SSRI exposure in healthy volunteers, but the clinical relevance of this finding remains uncertain since SSRI dosing is adjusted on the basis of clinical outcome.

BMS researchers noted that depression affects up to 60% of people with HCV infection, sometimes as a side effect of therapy. Thus people with HCV may be prescribed an SSRI. Both escitalopram and sertraline are P-gp substrates, the BMS team observed. Escitalopram is metabolized via CYP3A4 and CYP2C19, and sertraline via those two enzymes and CYP2D6. The DCV-TRIO regimen consists of daclatasvir, asunaprevir, and beclabuvir. Daclatasvir is a moderate P-gp inhibitor and asunaprevir a weak P-gp inhibitor in vivo. Asunaprevir is a moderate inhibitor of CYP2D6 and a weak inducer of CYP3A4 in vivo.

The study involved 41 healthy adults, 27 of them men, averaging about 40 years in age and 26 to 27 kg/m(2) in body mass index. Twenty-two participants were white and 17 black. For 7 days, 18 participants took 10 mg of escitalopram daily and 23 took 50 mg of sertraline daily. After a 5-day washout, participants resumed their SSRIs for 17 days with DCV-TRIO (30 mg of daclatasvir, 200 mg
of asunaprevir, and 75 mg of beclabuvir twice daily) plus an additional beclabuvir dose of 75 mg twice daily to adjust for exposure differences between people with and without HCV infection.

Neither escitalopram nor sertraline affected exposure of daclatasvir, asunaprevir, beclabuvir, or BMS-794712, a metabolite of beclabuvir. DCV-TRIO lowered Cmax and AUCtau of both SSRIs by about one third and C24 of both SSRIs by about 40% compared with concentrations attained without DCV-TRIO (Table 4).

### Table 4. Exposure of escitalopram and sertraline with versus without DCV-TRIO

<table>
<thead>
<tr>
<th></th>
<th>Escitalopram</th>
<th>Sertraline</th>
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<tbody>
<tr>
<td></td>
<td>GMR (90% CI) with/without DCV-TRIO</td>
<td>GMR (90% CI) with/without DCV-TRIO</td>
</tr>
<tr>
<td>Cmax</td>
<td>0.68 (0.64 to 0.73)</td>
<td>0.68 (0.65 to 0.71)</td>
</tr>
<tr>
<td>AUCtau</td>
<td>0.65 (0.61 to 0.69)</td>
<td>0.62 (0.60 to 0.65)</td>
</tr>
<tr>
<td>C24</td>
<td>0.61 (0.55 to 0.66)</td>
<td>0.58 (0.55 to 0.62)</td>
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</tbody>
</table>

Source: Malez AbuTarif, Bristol-Myers Squibb, and colleagues.

Sixteen study participants (39%) reported adverse events, but there were no serious adverse events, and no one stopped a study drug because of an adverse event. Adverse event incidence was higher with sertraline (13 people, 56.5%) than with escitalopram (3 people, 16.7%). Two people taking sertraline with DCV-TRIO had a moderate adverse event (syncope and viral gastroenteritis).

The BMS investigators noted that the clinical relevance of lower SSRI exposure with DCV-TRIO is unclear because SSRIs are dose-adjusted based on clinical outcome. They suggested that patients taking DCV-TRIO with escitalopram or sertraline “should be monitored for changes in depressive symptoms, and SSRI up-titration considered if appropriate.”

### SOFOSBUVIR AND DACLATASVIR FOR HCV-3 AND IN RBCs

**Predicted SVR24 with daclatasvir/sofosbuvir in HCV-3 cirrhotics**

Population viral kinetic (PVK) modeling of data on 12-week daclatasvir/sofosbuvir efficacy predicted 24-week sustained virologic response (SVR24) supporting that combination without ribavirin for HCV genotype 3 (HCV-3) patients with cirrhosis. Research shows higher rates of liver cancer and liver decompensation in people infected with HCV-3 than in those with other genotypes, according to Bristol-Myers Squibb (BMS) investigators who conducted this study. They characterized treatment of HCV-3 as “a significant unmet medical need.” Subgroup analysis of the ALLY-3 trial of daclatasvir/sofosbuvir showed a lower SVR12 in HCV-3 patients with versus without cirrhosis (63% versus 96%). SVR12s have been even lower with sofosbuvir/ribavirin in series of HCV-3 patients with cirrhosis or treatment experience.

To explore the possibility that 24 weeks of daclatasvir/sofosbuvir would promote higher response rates in cirrhotic HCV-3 patients, the BMS team developed a two-strain model to characterize a competition between a drug-susceptible HCV strain and a drug-resistant strain. They identified the most resistant variant in each of 152 treated people in ALLY-3 by population-based sequencing of HCV RNA. The PVK model included the replication capacity of the resistant virus from each patient and their cirrhosis status. The BMS team fit the PVK model to 1608 HCV RNA plasma concentration records in ALLY-3. They used stochastic simulation to evaluate SVR12 and SVR24 in HCV-3 cirrhotic and noncirrhotic patients after 12 and 24 weeks of daclatasvir/sofosbuvir.

The analysis yielded 500 simulated trials, each including 100 hypothetical participants. Simulated
SVR12 for people treated with daclatasvir/sofosbuvir for 12 weeks was 59% for patients with cirrhosis and 93% for patients without cirrhosis, nearly matching the observed SVR12s of 63% and 96% for cirrhotics and noncirrhotics in ALLY-3 (Figure 3) and thereby confirming the validity of the model. For hypothetical patients treated for 24 weeks, the model simulated an SVR24 of 89% for patients with cirrhosis and 99% for patients without cirrhosis (Figure 3). The simulated 89% SVR24 in cirrhotic patients nearly matches an observed 90% SVR12 in ALLY-3 among treatment-naive participants.

BMS investigators concluded that this PVK model "supports 24 weeks of daclatasvir plus sofosbuvir without ribavirin for HCV genotype 3 cirrhotic patients, a population with high unmet medical need."

**Higher sofosbuvir metabolite level in RBCs predicts SVR24**

Higher levels of the active sofosbuvir metabolite GS-331007 triphosphate (007-TP) in red blood cells (RBCs) trended toward association with SVR24 in HCV genotype 1 patients taking sofosbuvir/ribavirin in the SPARE trial. Levels of 007-TP were approximately 300-fold lower in RBCs than in peripheral blood mononuclear cells (PBMCs) but had an approximately 3-fold longer half-life.

Previous research by these University of Colorado Denver researchers found a median 007-TP concentration of 859 fmol/10^6 PBMCs and a 26-hour PBMC half-life. The investigators planned this new study to assess the intracellular pharmacology of 007-TP in RBCs, to analyze clinical variables associated with 007-TP in RBCs, and to determine relationships between 007-TP and SVR24.

SPARE randomized 47 people with any liver disease stage, including compensated cirrhosis, to 400 mg of sofosbuvir daily plus low-dose (600 mg) or weight-based (1000 or 1200 mg) ribavirin for 24 weeks. SPARE investigators collected whole blood samples on day 3 and weeks 4, 12, and 24. The Denver investigators analyzed continuous associations between RBC 007-TP and clinical variables by linear regression and dichotomous variables by unpaired t tests. They determined predictors of SVR24 by univariate and multivariable logistic regression.

Of the 47 study participants, 32 (68%) were men and 37 (79%) African American; 30% had F3 or F4 fibrosis, and 47% took low-dose ribavirin. Twenty-nine people (62%) attained SVR24, and 18 had viral relapse. Median ribavirin-TP measured 122 pmol/10^6 RBCs (range 33.4 to 320). Median RBC 007-TP rose from 1.44 fmol/10^6 cells on day 3 to consistently higher concentrations at week 4 (2.43 fmol/10^6 cells), week 12 (2.91 fmol/10^6 cells), and week 24 (2.50 fmol/10^6 cells). Modeled accumulation phase half-life through 24 weeks stood at 69 hours, nearly 3-fold longer than the half-life in PBMCs (26 hour).

Steady-state RBC 007-TP levels were 42% lower in men than women (P = 0.005). There was a trend toward higher day-3 RBC 007-TP concentrations in people with SVR24 (P = 0.13) (Figure 4). Fibrosis stage F2 or lower (odds ratio [OR] 3.41), pretreatment HCV RNA below 800,000 IU/mL (OR 6.09),
and female sex (OR 5.29) predicted SVR24 in univariate analysis (Figure 4). Less advanced fibrosis ($P = 0.04$) and lower baseline HIV RNA ($P = 0.02$) remained significant predictors of SVR24 in a multivariable model.

The trend toward higher RBC 007-TP concentrations in patients with SVR24 persisted in the multivariable model but did not reach statistical significance. Still, the researchers suggested that RBC 007-TP may prove a useful predictor of response to sofosbuvir. The significant association between less advanced fibrosis and lower HCV RNA before treatment begins led the investigators to propose that “decreased liver disease severity at treatment start may result in better sofosbuvir-based treatment outcomes.”

**Longer sofosbuvir/ribavirin duration improves HCV-3 response**

Extending sofosbuvir/ribavirin duration from 12 to 16 weeks independently improved SVR in HCV genotype 3 (HCV-3) patients in three sofosbuvir/ribavirin trials. Other clinical factors and higher ribavirin exposure were also associated with SVR.

A once-daily inhibitor of HCV NS5B polymerase, sofosbuvir is licensed in the United States, Europe, and elsewhere for treatment of HCV infection in combination with other antivirals. Sofosbuvir plus peginterferon/ribavirin yielded high SVR12 rates in patients with HCV genotype 1, 4, 5, or 6, while genotype 2 patients have responded to sofosbuvir/ribavirin. SVR12 rates have proved lower in patients with genotype 3 HCV treated for 12 or 16 weeks.

Logistic regression analysis in HCV-3 patients found treatment duration the primary driver of SVR, with contributions from treatment experience, gender, cirrhosis, and weight-adjusted ribavirin dose, and inconsistent associations with exposure of GS-331007, the primary metabolite of sofosbuvir. Gilead Sciences researchers conducted this study to assess the impact of ribavirin exposure (AUC) on SVR12 in the phase 3 trial population. If ribavirin exposure was associated with SVR12, they further aimed to compare the contribution of ribavirin exposure and clinical factors.

The analysis involved 388 HCV-3 patients in three trials who had samples available for AUC determination. The Gilead team used a population pharmacokinetic (PopPK) model to estimate steady-state ribavirin AUC. Univariate analysis explored SVR12 across ribavirin exposures assessed as baseline ribavirin dose, steady-state PopPK estimate (AUC0-24), and ribavirin AUC0-24 adjusted for dose modifications (AUC0-24 ADJ). The investigators used multivariate logistic regression to examine the relationship between SVR12 and clinical factors such as treatment duration, sex, treatment experience, cirrhosis, GS-331007 exposure, and ribavirin AUC0-24 ADJ.

Whether figured as AUC0-24, AUC0-24 ADJ, or weight-based baseline ribavirin dose, higher ribavirin
exposure was associated with SVR12 ($P < 0.0001$ for all associations). In multivariate logistic regression analysis, higher ribavirin AUC0-24 ADJ was significantly associated with SVR12 in 388 HCV-3 patients (Table 5). The association of GS-331007 AUC and SVR12 fell just short of statistical significance (Table 5). Being in the 75th percentile for ribavirin exposure rather than the 25th percentile approximately doubled the odds of SVR12. Both longer treatment duration and being treatment naïve when starting sofosbuvir/ribavirin more than quadrupled the odds of SVR12 (Table 5). Female sex and starting sofosbuvir/ribavirin without cirrhosis approximately doubled odds of SVR12.

<table>
<thead>
<tr>
<th>Table 5. SVR12 predictors with sofosbuvir/ribavirin in 388 HCV-3 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odds ratio</td>
</tr>
<tr>
<td>Treatment duration (16 vs 12 weeks)</td>
</tr>
<tr>
<td>Treatment naïve</td>
</tr>
<tr>
<td>No cirrhosis</td>
</tr>
<tr>
<td>Female sex</td>
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<tr>
<td>RBV AUC024 ADJ (per h$^*$µg/mL)</td>
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<tr>
<td>GS-331007 AUC (per h$^*$µg/mL)</td>
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</tbody>
</table>

Source: Brian Kirby, Gilead Sciences, and colleagues.¹⁹

The Gilead team concluded that treatment duration was the strongest predictor of sustained virologic response with sofosbuvir/ribavirin in phase 3 trial participants with genotype 3 infection. A phase 3 study of sofosbuvir/ribavirin in genotype 3 patients (VALENCE) showed that extending treatment to 24 weeks improves SVR rates. But the impact of ribavirin exposure on response over 24 weeks remains unknown.

Four liver function scales sensitive but need improvement

Four scales of liver impairment proved sensitive but “far from ideal” in an analysis of 1841 people enrolled in hepatic impairment studies.²⁰ National Cancer Institute (NCI) criteria appeared to be the most sensitive system for classifying exposure changes.

This database analysis by Islam Younis of the Food and Drug Administration assessed sensitivity of four liver impairment scales by comparing proportions of AUC ratios (hepatic impairment/normal) $≥ 2$ according to impairment level determined by each scale. The scales compared were Child-Pugh classification criteria, NCI criteria, model for end-stage liver disease (MELD), and Maddrey discriminant function (MDF). The database included 1841 participants in 65 hepatic impairment studies that classified liver impairment. According to Child-Pugh criteria, 692 people (38%) had normal liver function, 351 (19%) had mild impairment, 512 (28%) had moderate impairment, and 286 (16%) had severe impairment.

With Child-Pugh criteria, the probability of observing an AUC ratio $≥ 2$ was 0.1 for mild liver impairment, 0.24 for moderate impairment, and 0.35 for severe impairment (Table 6). As Child-Pugh score increased, so did average AUC ratio. With the NCI system, the probability of an AUC ratio $≥ 2$ was 0.14 for mild group 1 impairment, 0.24 for mild group 2 impairment, 0.36 for moderate impairment, and 0.46 for severe impairment. Comparing Child-Pugh and NCI criteria, Younis found that the two systems agreed on 94.7% of normal classifications. But 53.6%, 48.8%, and 45.2% of participants classified by Child-Pugh criteria as having mild, moderate, and severe liver impairment were classified as normal, mild, and moderate by NCI criteria.
According to the MELD scale the probability of observing an AUC ratio $> 2$ was 0.33 for a MELD score $> 10$. Comparison of MELD with Child-Pugh results showed that 17.1%, 53.9%, and 95.4% of participants in the Child-Pugh mild, moderate, and severe groups had a MELD score $> 10$. Linear regression indicated a significant positive slope when comparing AUC ratios with MELD score ($R^2 = 0.11, P < 0.0001$), meaning higher MELD scores meant higher AUC ratios. The Maddrey discriminant function score also correlated positively with AUC ratios ($R^2 = 0.02, P < 0.0001$).

Younis concluded that all four classification systems are sensitive in measuring exposure changes in people with hepatic impairment, though all scales were “far from optimal.” He proposed that NCI criteria appear to be the most sensitive liver function classification system. Younis called for continued analysis to improve the ability of liver impairment classification scales to detect exposure changes.

### ANTIRETROVIRAL ACTIVITY AND INTERACTIONS

**Less tenofovir in plasma, more in cells, with TAF than TDF**

Plasma tenofovir (TFV) concentrations lay 91% lower with tenofovir alafenamide (TAF) than with tenofovir disoproxil fumarate (TDF) in a three-trial analysis. But intracellular tenofovir-diphosphate (TFV-DP), the active form of the drug, proved more than 4-fold higher with TAF than with TDF. These findings could explain lower and milder signals of bone and kidney toxicity in parallel phase 3 trials comparing TAF with TDF, each with elvitegravir, cobicistat, and emtricitabine (E/C/F).

Bone and renal toxicity are infrequent but well-appreciated side effects of TDF. Gilead Sciences designed TAF both for potency and for safety. TAF has proved more stable in plasma than TDF, with intact TAF reaching target T cells where it is metabolized to TFV-DP (Figure 5). Relatively high plasma concentrations of TFV with TDF could contribute to toxicity as drug travels via plasma to nontarget cells. A proof-of-concept study established that TAF yields lower plasma TFV concentrations and higher TFV-DP levels in PBMCs than TDF.

![Figure 5. Tenofovir alafenamide (TAF), a tenofovir prodrug, is designed to yield lower tenofovir plasma concentrations and higher tenofovir-diphosphate intracellular levels than tenofovir disoproxil fumarate (TDF).](source: Joseph Custodio, Gilead Sciences, and colleagues.)

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**Table 6. Sensitivity of three liver impairment scales**

| Probability of observing AUC ratio (hepatic impairment/normal) $> 2$ |
|-----------------|-----------|--------|
| Mild            | Moderate  | Severe |
| Child-Pugh      | 0.1       | 0.24   | 0.35  |
| Mild group 1    | Mild group 2 | Moderate | Severe |
| NCI             | 0.14      | 0.24   | 0.36  | 0.46  |
| MELD            | < 10      | > 10   | 0.33  |
Identical phase 3 trials in different populations established the virologic noninferiority of coformulated TAF/E/C/F compared with TDF/E/C/F (Stribild) in antiretroviral-naive people through 48 weeks. The Gilead team initially selected exposures associated with 25 mg of TAF as the target range for clinical development. Because cobicistat boosts TAF by inhibiting intestinal P-gp, the coformulation with E/C/F uses 10 mg of TAF, which provides exposures comparable to 25-mg single-agent TAF.

This analysis of plasma and PBMC concentrations combined data from the two phase 3 trials and one phase 2 trial. The investigators assessed plasma tenofovir in 55 people taking TAF and 36 taking TDF (each with E/C/F). They measured intracellular TFV-DP in 31 people taking TAF and 19 taking TDF. Intracellular TFV-DP AUCltau measured 12.2 ng*h/mL with TAF and 2.79 ng*h/mL with TDF, more than a 4-fold difference (GMR 437, 90% CI 286 to 669). TNF in plasma lay 91% lower with TAF than TDF (mean AUCltau 307 versus 3480 ng*h/mL, GMR 8.90, 90% CI 8.20 to 9.65).

The researchers proposed that "lower plasma TFV exposures from E/C/F/TAF versus Stribild or other TDF-containing regimens may potentially reduce off-target effects associated with TFV, in particular renal and bone toxicity." Higher intracellular TFV-DP concentrations with TAF than TDF, they suggested, "demonstrated stable and effective loading of the active moiety TFV-DP into the target cells by TAF."

**TAF pharmacokinetics and activity in adolescents**

Through 24 weeks of a single-arm trial in African, US, and Thai adolescents, TAF had pharmacokinetics similar to those seen in adults and yielded high virologic response rates when coformulated with elvitegravir, cobicistat, and emtricitabine (E/C/F/TAF).

In identical phase 3 trials that enrolled 1744 antiretroviral-naive adults, coformulated E/C/F/TAF proved noninferior to E/C/F/TDF (Stribild) through 48 weeks, with 92% and 90% having a viral load below 50 copies/mL. Markers of renal and bone safety favored the E/C/F/TAF arm. The open-label phase 3 trial in adolescents enrolled 48 treatment-naive youngsters from 12 to 18 years old and weighing at least 35 kg. All study participants had a viral load exceeding 1000 copies/mL, a CD4 count above 100 cells/mm$^3$, and an estimated glomerular filtration rate (eGFR) above 90 mL/min. At the Pharmacology Workshop, researchers presented a planned 24-week interim analysis.

Almost two thirds of the 48 adolescents (63%) lived in Uganda, with smaller contingents in the United States (19%), Thailand (13%), and South Africa (6%). Age ranged from 12 to 17 years (median 15) and weight from 35 to 89 kg (median 52). The study group included 28 girls and 20 boys, most (88%) were black, and two thirds were vertically infected. One in five study participants had a pretreatment viral load exceeding 100,000 copies/mL, median pretreatment load stood around 42,000 copies/mL, median CD4 count at 452 cells/mm$^3$, median serum creatinine at 0.57 mg/dL, and median eGFR at 158 mL/min (range 101 to 284). Median time since HIV diagnosis measured 1 year.

Twenty-three youngsters had virologic data through 24 weeks, 21 of them (91%) with a viral load below 50 copies/mL. The 2 adolescents with a viral load above 50 copies/mL at week 24 had a sub-50-copy load on the next measure. Pharmacokinetics of TAF, elvitegravir, cobicistat, and emtricitabine were similar to those recorded historically in adults. As in the just-reported adult analysis, tenofovir exposure in plasma was approximately 90% lower with TAF than TDF.

No trial participants stopped taking study drugs because of adverse events. One E/C/F/TAF-related serious adverse event (visual impairment and intermediate uveitis) resolved completely with ophthalmic steroids without stopping the antiretrovirals. As expected because of renal tubular creatinine secretion inhibition by cobicistat, median serum creatinine rose 0.06 mg/dL through 24 weeks of treatment. No cases of proximal renal tubulopathy developed.

Median height-adjusted z-score for spine bone mineral density (BMD) fell 0.02 through 24 weeks, and only 2 of 23 adolescents had a 4% or greater decrease in height-adjusted z-score for spine BMD. Median height-adjusted z-score for total body-less-head BMD fell 0.09, and no participants had a 4% or greater decrease in z-score for total body-less-head BMD.
Modeling indicates tenofovir persists in cells days after TDF/FTC/RPV stops

More than three quarters of model-predicted intracellular tenofovir diphosphate (TFV-DP) concentrations in 18 volunteers lay above preexposure prophylaxis (PrEP) target levels 3 days after dosing of coformulated TDF/FTC/rilpivirine (RPV) stopped. In contrast, most model-predicted intracellular emtricitabine triphosphate (FTC-TP) levels lay below the PrEP target 24 hours after dosing stopped.

Determining how long active antiretroviral metabolites persist in PBMCs after dosing stops is critical for managing late or missed doses and for predicting PrEP durability. To estimate TFV-DP and FTC-TP durability in PBMCs after dose cessation, University of Liverpool researchers turned to samples from healthy volunteers collected in the 9 days after they stopped TDF/FTC and the nonnucleoside rilpivirine. Sampling occurred 0, 2, 4, 8, 12, 24, 36, 48, 60, 72, 96, 120, 144, 168, 192, and 216 hours after dosing stopped following a 14-day course.

This study measured TFV and FTC concentrations only in plasma. To predict levels of TFV-DP and FTC-TP in PBMCs, the researchers developed a nonlinear mixed effects model using plasma data from the present study and time-matched plasma and PBMC data from a prior study. The analysis included 245 TFV samples from the rilpivirine study and 180 matched TFV plasma and cell samples from a study of TDF/FTC and efavirenz cessation in healthy volunteers. The Liverpool team developed separate population PK models for tenofovir and FTC and validated them by statistical and graphical methods. They compared predicted TFV-DP and FTC-TP levels in PBMCs in the days after dosing stopped with target concentrations based on data from the iPrEx trial of daily TDF/FTC PrEP: 16 fmol/10⁶ PBMCs for TFV-DP and 3.7 pmol/10⁶ PBMCs for FTC-TP.

Eleven of 18 study participants (61%) were women, median age measured 31 years, median weight 75 kg, and median body mass index 24 kg/m². Ten volunteers were Caucasian, 4 black African or Caribbean, and the others Asian, Hispanic, or of mixed ethnicity. Participants tolerated the 2-week TDF/FTC course well, with no grade 3 or 4 adverse events.

A two-compartment oral model described clearance as 67 L/hour for tenofovir and 20 L/hour for FTC. Including weight and creatinine clearance significantly improved the tenofovir model. The models predicted a half-life of 116 hours for TFV-DP and 37 hours for FTC-TP. Predicted geometric mean intracellular AUC0-24 was 1456 fmol*h/10⁶ cells (CV% 66%) for TFV-DP and 87.8 fmol*h/10⁶ cells (CV% 80%) for FTC-TP. Predicted intracellular geometric mean AUC0-168 was 7495 fmol*h/10⁶ cells (CV% 66%) for TFV-DP and 273 fmol*h/10⁶ cells (CV% 70%) for FTC-TP.

Most predicted TFV-DP intracellular concentrations lay above the iPrEx-determined PrEP target concentration of 16 fmol/10⁶ cells 24 to 72 hours after dosing stopped (Figure 6). For FTC-TP, most predicted intracellular concentrations lay below the iPrEx-determined PrEP target of 3.7 pmol/10⁶ cells 24 to 72 hours after dosing stopped (Figure 6).

Figure 6. Modeling indicated that most predicted intracellular tenofovir diphosphate (TFV-DP) concentrations lay above a target established for PrEP up to 72 hours after dosing stopped in healthy volunteers. Most predicted intracellular emtricitabine triphosphate (FTC-TP) concentrations lay below the PrEP target. (Source: Laura Dickinson, University of Liverpool, and colleagues.)
The University of Liverpool researchers noted that, although the models are relatively simple, they describe the data well and allow refinement if additional data become available. External datasets are required to further evaluate the models, but the authors observed that predicted TDF-DP and FTC-TP concentrations generally agreed with values reported in the literature.

**Dolutegravir detectable in plasma longer than elvitegravir after dosing stops**

Elvitegravir concentrations remained detectable in plasma in 13 of 17 volunteers 60 hours after dosing stopped but were always below the protein binding-adjusted 95% inhibitory concentration (IC95).\(^{27}\) Dolutegravir remained detectable in all 17 volunteers 72 hours after dosing stopped and above the protein binding-adjusted 90% inhibitory concentration (IC90) in 16 of them.

Elvitegravir (coformulated with cobicistat and TDF/FTC) and dolutegravir have emerged as potent HIV integrase inhibitors, but research had not assessed their persistence in plasma after dosing stops. To address that question, researchers as Chelsea and Westminster Hospital and colleagues at other institutions conducted this open-label, two-session pharmacokinetic trial in healthy volunteers. Longer drug persistence after dosing stops, the researchers noted, could mean greater “forgiveness” after missed doses and could indicate which antiretrovirals are good PrEP candidates.

This trial enrolled healthy volunteers between 18 and 65 years old who took 50 mg of dolutegravir once daily for 10 days, took no drugs during a 9-day washout, then took 150 mg of elvitegravir daily coformulated with cobicistat and TDF/FTC for 10 days. Plasma sampling occurred before the last dose of each course then 2, 4, 8, 12, 24, 36, 48, 60, 72, 96, 120, 144, 168, 192, and 216 hours after dosing.

Seventeen volunteers completed the study, 12 of them women. Nine volunteers were white and 8 black. Age ranged from 26 to 52 years (median 39) and body mass index from 19 to 34 kg/m\(^2\) (median 26). Participants tolerated the antiretrovirals well, and no grade 3 or 4 adverse events developed.

Geometric mean AUC0-24 and C24 for dolutegravir were 55,505 ng/mL*h and 1324 ng/mL and for elvitegravir 22,965 ng/mL*h and 419 ng/mL. Geometric mean dolutegravir half-life within the 24-hour dosing interval proved shorter (14.3 hours) than its elimination half-life to the last measurable concentration within 216 hours (23.1 hours). The reverse proved true for elvitegravir, with a geometric mean half-life within the dosing interval of 10.8 hours versus 5.2 hours for elimination half-life to the last measurable concentration.

Dolutegravir has a protein binding-adjusted IC90 of 64 ng/mL. Geometric mean dolutegravir plasma concentration measured 1324 ng/mL 24 hours after the last dose and all 17 volunteers had a concentration above the IC90 at that point (**Table 7**). Mean plasma concentration stood at 427 ng/mL 48 hours after the last dose, and all volunteers remained above the IC90. Mean dolutegravir concentration measured 240 ng/mL 60 hours after the last dose, all 17 volunteers had detectable dolutegravir, and 16 of 17 remained above the IC90. At 72 hours after the last dose, mean dolutegravir plasma concentration measured 131 ng/mL, all volunteers had detectable dolutegravir, and 16 of 17 volunteers remained above the IC90. Mean dolutegravir concentration fell to 52.2 ng/mL 96 hours after the last dose, all volunteers still had detectable dolutegravir concentrations, and 4 of 17 remained above the IC90 at that point.

Elvitegravir protein binding-adjusted IC95 is 45 ng/mL. Geometric mean elvitegravir plasma concentration was 419 ng/mL 24 hours after the last dose, and all volunteers had a concentration above the IC95 (**Table 7**). At 48 hours after the last dose, mean elvitegravir plasma concentration measured 8.3 ng/mL, 16 of 17 volunteers still had detectable elvitegravir in plasma, but all of them below the IC95. At 60 hours after the last dose, mean elvitegravir in plasma measured 2.5 ng/mL, 13 of 17 volunteers still had detectable elvitegravir, but all concentration were below the IC95.
### Table 7. Dolutegravir and elvitegravir detectability in plasma after last dose

<table>
<thead>
<tr>
<th>Hour after last dose</th>
<th>Variable</th>
<th>Dolutegravir</th>
<th>Elvitegravir</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>IC90 64 ng/mL</td>
<td>IC95 45 ng/mL</td>
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<tr>
<td>24</td>
<td>GM concentration (ng/mL)</td>
<td>1324</td>
<td>419</td>
</tr>
<tr>
<td></td>
<td>Proportion detectable in plasma</td>
<td>100% (17/17)</td>
<td>100% (17/17)</td>
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<tr>
<td></td>
<td>Proportion above IC90</td>
<td>100% (17/17)</td>
<td>100% (17/17)</td>
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<tr>
<td>48</td>
<td>GM concentration (ng/mL)</td>
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<tr>
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<td>GM concentration (ng/mL)</td>
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<td></td>
<td>Proportion detectable in plasma</td>
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</tr>
<tr>
<td></td>
<td>Proportion above IC90</td>
<td>23.5% (4/17)</td>
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</tr>
</tbody>
</table>

GM, geometric mean; IC90, protein binding-adjusted 90% inhibitory concentration; IC95, protein binding-adjusted 95% inhibitory concentration.

Source: Emilie Elliot, Chelsea and Westminster Hospital, and colleagues.

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**Doubling dolutegravir dose yields no resistance advantage in model**

Raising the dose of dolutegravir from 50 to 100 mg twice daily would not significantly improve 24-week virologic response in integrase inhibitor-experienced patients, according to logistic regression modeling results. The same model predicted that strong inducers of dolutegravir metabolism or metal cation-containing multivitamins would have negligible impact on 24-week response to dolutegravir.

Dolutegravir, an HIV integrase inhibitor, is licensed at a dose of 50 mg twice daily for patients with integrase inhibitor-resistant virus or for treatment-naive or experienced patients taking a strong UGT1A or CYP3A inducer (efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin). A mutation at integrase position Q148 coupled with other mutations lowers susceptibility to dolutegravir.

To determine whether doubling the dose would improve virologic response at 24 weeks, GlaxoSmithKline (GSK) investigators developed an exposure-response model that would identify predictors of virologic response. Simulations estimated the probability of being a 24-week sub-50-copy responder with (1) 100 mg twice daily with food, (2) moderate to strong enzyme inducers, and (3) metal cation-containing vitamin supplements (such as those with iron or zinc).

The analysis involved 247 treatment-experienced patients in three randomized trials (VIKING, VIKING-3, and VIKING-4). The group had a median age of 48 years (range 19 to 68) and a median baseline viral load of 4.38 log10 copies/mL (about 24,000 copies/mL). Almost two thirds (64%) of these trial participants had no Q148 mutation at baseline, 23% had a Q148 mutation plus one other mutation, and 13% had a Q148 mutation plus 2 or more other mutations.

Models based on dolutegravir minimum concentration (Cmin) or average concentration predicted 24-week virologic response equally well. Significant response predictors in these models were baseline viral load and CD4 count and baseline mutation category (no Q148 mutations, Q148 plus 1 other mutation, and Q148 plus 2 or more mutations). The models adequately reflected week 24 results observed in trials with these mutation sets.

Simulating week-24 response by mutation category, the best-case scenario assumed dose-proportional dolutegravir pharmacokinetics and taking dolutegravir with a moderate-fat meal to increase Cmin by an additional 45% over that observed in VIKING studies (in which the prandial state was unknown). With this scenario, doubling the dolutegravir dose increased the predicted median
week 24 sub-50-copy response rates from 80% to 88% with no Q148 mutations, from 60% to 71% with Q148 plus 1 mutation, and from 30% to 48% with Q148 plus 2 mutations (Figure 7). But the GSK team noted that 90% prediction intervals for 24-week response with the 50-mg dose and the 100-mg dose overlapped substantially and that previous work showed dolutegravir pharmacokinetics are less than dose proportional. If the model assumed an unknown prandial state—and thus a mix of fasted and fed patients—doubling the dolutegravir dose also had minimal impact on 24-week response.

![Figure 7](image)

*Figure 7. Modeling 24-week virologic response to dolutegravir in patients with or without a mutation at integrase position Q148 predicted that doubling the dose from 50 to 100 mg twice daily with food would have a modest impact on response. (Source: Kimberly Adkinson, GlaxoSmithKline, and colleagues.)*

The model predicted that giving the 50-mg twice-daily dose with strong enzyme inducers would lower 24-week response rates 5% in the group with no Q148 mutations, 8% in those with Q148 plus 1 mutation, and 5% in those with Q148 plus 2 or more mutations. Again, broadly overlapping prediction intervals suggested comparable 24-week responses with and without enzyme inducers. Finally, the model predicted metal cation-containing multivitamins have a negligible impact on 24-week response.

The GSK team concluded that these simulations support the currently recommended dolutegravir dose of 50 mg twice daily in most patients with integrase inhibitor-resistant virus. Simulations also confirmed current recommendations for dosing moderate to strong enzyme inducers with dolutegravir or taking the integrase inhibitor with metal cation-containing vitamin supplements.

**Modelers propose darunavir/ritonavir pediatric dosing different from WHO**

Modeling and simulation indicated that current World Health Organization (WHO) pediatric dosing recommendations for darunavir/ritonavir yield low darunavir exposure in a low weight band and high exposure in a high weight band. Alternative pediatric dosing recommendations based on this model would yield darunavir exposure more closely matching that in adults while keeping the five current WHO pediatric weight bands and a fixed darunavir:ritonavir ratio.

Current (June 2013) WHO pediatric darunavir/ritonavir dosing recommendations differ from US licensed recommendations. WHO uses five pediatric weight bands and a constant 6:1 darunavir:ritonavir ratio. This approach could allow development of a darunavir/ritonavir fixed-dose combination that permits dosing in line with recommendations across WHO weight bands, which are aligned across different antiretroviral products. Licensed recommendations use eight weight bands and ratios varying from 5.8:1 to 7.5:1. To further evaluate these differences and propose recommendations that would yield darunavir exposures consistent with those seen in adults (while keeping the WHO weight bands and a fixed darunavir:ritonavir ratio), Janssen Pharmaceutica researchers conducted this modeling study.

The Janssen team began with an established population pharmacokinetic model for darunavir/ritonavir based on pooled richly sampled data from adult and pediatric populations. With this model, the researchers simulated darunavir/ritonavir PK profiles according to WHO dosing recommendations for the five weight bands. They found that recommended WHO dosing for children...
in the 14-to-20-kg weight band leads to low darunavir exposure (below the 80% to 130% target range based on adult AUC). The WHO suggested dose for the 25-to-35-kg weight band leads to high darunavir exposure (above the 80% to 130% target range).

Further simulations of AUC and pharmacokinetic profiles after administering darunavir/ritonavir as 240/40-mg tablets established alternative doses that would yield darunavir AUC comparable to adults for each of the five WHO weight bands (Table 8).

Table 8. Proposed alternative twice-daily pediatric darunavir/ritonavir dosing based on modeling and simulation

<table>
<thead>
<tr>
<th></th>
<th>Formulation*</th>
<th>Darunavir dose</th>
<th>Ritonavir dose</th>
<th>DRV:RTV ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>1 adult tablet</td>
<td>600 mg</td>
<td>100 mg</td>
<td>6:1</td>
</tr>
<tr>
<td>Children</td>
<td>&gt; 35 kg</td>
<td>Adult dose</td>
<td>600 mg</td>
<td>100 mg</td>
</tr>
<tr>
<td></td>
<td>25 to &lt; 35 kg</td>
<td>2 pediatric tablets</td>
<td>480 mg</td>
<td>80 mg</td>
</tr>
<tr>
<td></td>
<td>20 to &lt; 25 kg</td>
<td>1.5 pediatric tablets†</td>
<td>360 mg</td>
<td>60 mg</td>
</tr>
<tr>
<td></td>
<td>14 to &lt; 20 kg</td>
<td>1.5 pediatric tablets†</td>
<td>360 mg</td>
<td>60 mg</td>
</tr>
<tr>
<td></td>
<td>10 to &lt; 14 kg</td>
<td>1 pediatric tablet</td>
<td>240 mg</td>
<td>40 mg</td>
</tr>
</tbody>
</table>

*Assuming a fixed-dose combination pediatric tablet of 240/40 mg of darunavir/ritonavir.
†Two tablets AM, one tablet PM.
Source: Herta Crauwels, Janssen Pharmaceutica, and colleagues.29

The researchers proposed that adjusting current WHO recommendations “could improve the anticipated darunavir exposure” in children to be more comparable to that in adults while keeping a fixed darunavir:ritonavir dosing ratio and standardized weight bands. Janssen has presented these findings to the Pediatric Antiretroviral Working Group convened by WHO.

CYP3A5*1 allele, black race not tied to lower maraviroc level in large analysis
Contrary to earlier findings in a small study, the CYP3A5*1 allele was not associated with lower maraviroc concentrations in a large analysis of the racially diverse MERIT study population.30 The CYP3A5*1/*1 allele was more prevalent in blacks than whites in MERIT, but maraviroc at the recommended dose yielded good concentrations regardless of race or CYP3A5 genotype.

Maraviroc, an HIV entry inhibitor, is a substrate for CYP3A4, P-gp, and OATP1B1. Recent in vitro work indicates that maraviroc is also a substrate for CYP3A5.31,32 Research in healthy volunteers found that the 8 volunteers homozygous for the CYP3A5*1 allele had 41% lower maraviroc exposure than 8 volunteers with no CYP3A5*1 alleles after a single 300-mg dose.33 CYP3A5*1/*1 prevalence in blacks ranges from 39% to 70% and is very low in whites.

Pfizer/ViiV Healthcare investigators conducted this retrospective analysis of data from the MERIT trial to determine prevalence of CYP3A5 alleles in the study population and to assess the impact of CYP3A5 genotype on maraviroc exposure. MERIT was a 5-year phase 2b/3 trial comparing maraviroc at 300 mg once or twice daily with efavirenz, each with zidovudine/lamivudine.34 For the new analysis, researchers extracted DNA from 863 blood samples and genotyped it for CYP3A5. They determined frequencies of CYP3A5 alleles in the study population and used population pharmacokinetic estimates of average concentration (Cavg) for maraviroc dosed at 300 mg twice daily from the original analysis.

Of these 863 people, 61% had no CYP3A5*1 alleles (mutant), 29% had 1 CYP3A5*1 allele, and 11% had 2 CYP3A5*1 alleles (wild-type). Among white trial participants, 84% had no CYP3A5*1 alleles, while 78% of blacks had 1 or 2 CYP3A5*1 alleles.
There were 494 study participants with data on both CYP3A5*1 genotype and maraviroc exposure. The proportion of participants with Cavg at or above 75 ng/mL (associated with near-maximal virologic efficacy in MERIT) did not differ substantially among the three allele groups: 89.8% for no CYP3A5*1 alleles, 93.7% for 1 CYP3A5*1 allele, and 92.5% for 2 CYP3A5*1 alleles (Figure 8). Nor did proportions of black participants with Cavg at or above 75 ng/mL differ significantly between those with no CYP3A5*1 alleles (93.9%), 1 CYP3A5*1 allele (96.7%), or 2 CYP3A5*1 alleles (93.2%). And proportions of white participants with Cavg at or above 75 ng/mL did not differ significantly by allele group.

A separate analysis of MERIT trial participants found that maraviroc pharmacokinetic variability could not be explained by CYP3A5 genotype alone or by a CYP3A4/CYP3A5 cluster in univariate or multivariate analyses. The researchers concluded that approximately 90% of MERIT patients attain a maraviroc Cavg at or above 75 ng/mL when taking maraviroc at recommended doses, regardless of CYP3A5 genotype or race.

NEW ANTIRETROVIRALS AND RELATED ISSUES

No exposure-response relationship seen with investigational nonnucleoside
Analysis of phase 2 trial data discerned no exposure-response relationship between week-48 virologic outcomes and concentrations of doravirine, an investigational nonnucleoside reverse transcriptase inhibitor. A separate evaluation of doravirine pharmacokinetics in healthy volunteers switching to doravirine after treatment with efavirenz found transiently decreased doravirine exposure when treatment with doravirine started immediately after efavirenz stopped.

In vitro studies show that doravirine remains active against virus bearing the nonnucleoside-related mutation K103N, the nonnucleoside Y181C mutation, or both K103N and Y181C. Doravirine AUC and Cmax are dose proportional over a clinically relevant dosing range. A phase 2 trial evaluated four doses of doravirine (25, 50, 100, and 200 mg once daily) and efavirenz, each with TDF/FTC, in an antiretroviral-naive population.

Merck investigators conducted a new analysis to explore doravirine exposure-response relationships based on 48-week virologic outcomes. The analysis used sparsely sampled plasma concentrations collected through week 24 of the phase 2 trial plus densely sampled phase 1 pharmacokinetic data in a population pharmacokinetic model to provide individual post hoc estimates of steady-state doravirine concentrations. Proportions of participants with a viral load below 40 copies/mL at week 48...
of the phase 2 trial were 72.5% with 25 mg of doravirine, 72.1% with 50 mg, 76.2% with 100 mg, 82.9% with 200 mg, and 71.4% with efavirenz.

Matching individual steady-state pharmacokinetic estimates (AUC0-24, Cmax, and Ctrough) with week-48 viral load, the Merck team found no apparent trends between doravirine PK parameters and virologic response. Nor could they discern any trends between doravirine concentrations and virologic outcome when they stratified patients by pretreatment viral load above or below 100,000 copies/mL.

The Merck researchers believe these findings imply attainment of an exposure-response plateau over the dose range studied in this phase 2 trial. On this basis of this finding and consideration of potential drug-drug interactions, activity against mutant HIV strains, and forgiveness of missed doses, Merck selected 100 mg once daily as the dose for phase 3 trials.

Giving doravirine with multiple doses of rifampin, a strong CYP3A4 inducer, reduces doravirine exposure. Efavirenz moderately induces CYP3A4. Because clinicians may switch patients from poorly tolerated efavirenz to doravirine, Merck is planning a phase 2 trial to assess outcomes after an efavirenz-to-doravirine switch. To prepare for that trial, they conducted a three-period study in healthy volunteers. In period 1, volunteers took 100 mg of doravirine daily in the morning for 5 days followed by a 7-day washout. In period 2 they took 600 mg of efavirenz daily at bedtime for 14 days. With no washout, in period 3 they took 100 mg of doravirine once daily in the morning for 14 days.

Seventeen volunteers were men with ages ranging from 21 to 53 years; and 3 volunteers were women with ages ranging from 46 to 53. Three people failed to complete the study, 2 because of papular rash during the efavirenz treatment period and 1 for personal reasons.

One day after efavirenz treatment stopped, doravirine 24-hours concentration (C24h) was 85% lower than with doravirine alone (GMR 0.15, 95% CI 0.10 to 0.23) (Figure 9). Fourteen days after efavirenz stopped, doravirine C24h had rebounded but remained 50% lower than with doravirine alone (GMR 0.50, 95% CI 0.39 to 0.64). Doravirine trough concentrations after efavirenz treatment stopped exceeded the C24h target based on efficacy against wild-type virus (78 nM). Efavirenz geometric mean concentrations dropped steadily from 3180 ng/mL to 95.7 ng/mL 14 days after efavirenz stopped. Efavirenz remained detectable in all volunteers for 9 days after efavirenz stopped.

Merck will explore the clinical relevance of transiently lower doravirine exposure immediately after stopping efavirenz treatment in the phase 2 trial of virologically suppressed patients switching from efavirenz to doravirine.
QTcF prolongation modeling to select attachment inhibitor dose

Modeling and simulation indicated that a 600-mg twice-daily dose of the HIV attachment inhibitor BMS-663068 is less likely to cause QTcF prolongation than a 1200-mg once-daily dose. As a result, the 600-mg twice-daily dose has been selected for phase 3 trials in antiretroviral-experienced patients.

BMS-663068, the prodrug metabolized to BMS-626529, binds to HIV-1 gp120 at a step before the CCR5 antagonist maraviroc and prevents viral attachment to CD4 cells. BMS-626529 is further metabolized by CYP3A4 and hydrolysis. Clinical data indicate that BMS-626529 is generally well tolerated and has no dose-related safety signals, a Bristol-Myers Squibb team reported.

The QT study (AI438016) demonstrated the potential for BMS-626529 to prolong the QTcF interval at a supratherapeutic BMS-663068 dose of 2400 mg twice daily but not at a clinically studied dose of 1200 mg once daily. Treatment-experienced patients may take a ritonavir-boosted protease inhibitor as part of their antiretroviral regimen, and a prior drug interaction study showed that ritonavir increases BMS-626529 Cmax by 31% to 79%. The dose-response relationship defined in a phase 2b trial (AI438011) led to selection of two doses for further study, 600 mg twice daily and 1200 mg once daily for administration with a ritonavir-boosted protease inhibitor.

The analysis presented at the Pharmacology Workshop aimed to characterize BMS-626529 exposure relative to QTcF interval changes using data from the AI438016 trial, then to use this model-based analysis to predict QTcF interval prolongation with the 600-mg twice-daily dose and the 1200-mg once-daily dose when administered with a ritonavir-boosted protease inhibitor. According to FDA guidance, a positive QT signal occurs when the mean QT/QTC ratio exceeds 5 msec and the 95% upper confidence limit is 10 msec or greater.

Bristol-Myers Squibb researchers considered four models to predict exposure-QTc relationships, three direct-response models and one indirect-response model. Based on diagnostic plots, visual predictive checks, and Monte Carlo simulations, the investigators chose the indirect response model. With this model, they estimated the relative risk of QTcF prolongation with BMS-663068 at a dose of 600 mg twice daily or 1200 mg once daily with or without a ritonavir-boosted protease inhibitor in simulations of 1000 trials.

Cmax simulations indicated that 600 mg twice daily with or without a ritonavir-boosted protease inhibitor is associated with a lower risk of yielding a Cmax approaching the risk threshold for QTcF prolongation (Figure 10). Estimated QTcF change at median Cmax stood at 2.98 msec with 600 mg of BMS-663068 twice daily with ritonavir (upper confidence interval 5.58 msec) and at 5.42 msec with 1200 mg once daily with ritonavir (upper confidence interval 7.94 msec).

Because of these findings as well as clinical and safety data, Bristol-Myers Squibb chose the 600-mg twice-daily dose of BMS-663068 for phase 3 trials in antiretroviral-experienced patients.
**Study of 50 vs 100 mg RTV with ATV fails to show bioequivalence**

A two-period study of ritonavir boosting with 50 mg instead of the standard 100 mg in people with HIV infection found marginally lower atazanavir exposure with the lower boost. This 12-person analysis failed to show bioequivalence of 50 mg to 100 mg because of high interpatient variability.

Even low doses of ritonavir, the much-used protease inhibitor booster, can cause gastrointestinal intolerance and dyslipidemia. A ritonavir boosting dose of 50 mg has been studied with 1500 mg of saquinavir in HIV-positive Thai patients and with 300 mg of atazanavir in healthy volunteers. But a standard ritonavir boosting dose has not been formally established.

Ottawa Hospital researchers conducted this study to assess the pharmacokinetics and safety of 50 versus 100 mg of ritonavir with 300 mg of atazanavir once daily. Study participants had to be between 18 and 70 years old and taking 300/100 mg of atazanavir/ritonavir with a viral load below 40 copies/mL. No one could be taking drugs known to interact with atazanavir in the 4 weeks before or during the study, including rifabutin, rifampicin, proton pump inhibitors, or azoles. No one had a history of antiretroviral failure or genotypic resistance to protease inhibitors.

Participants continued taking 300/100 mg of atazanavir/ritonavir in the morning with a standardized meal for 7 days. Then they switched immediately to 50 mg of ritonavir (half a tablet) for 7 days.

Researchers collected samples before the last dose and over 24 hours at the end of each dosing interval. They calculated geometric mean ratios (GMR) for AUC, Cmax, and Cmin with 100 versus 50 mg, and they used the standard definition of bioequivalence—90% confidence intervals within the range 0.80 to 1.25.

The 12 study participants had a median age of 50 years (interquartile range 44 to 59), 9 were men, and 3 were black. Median weight stood at 78 kg, median body mass index at 25.5 kg/m², and median CD4 count at 507 cells/mm³. Five people were taking tenofovir.

GMRs for atazanavir with 100 versus 50 mg of ritonavir stood at 0.905 (90% CI 0.724 to 1.132) for AUC, 0.968 (90% CI 0.765 to 1.225) for Cmax, and 0.717 (90% CI 0.537 to 0.957) for Cmin (Figure 11). Ritonavir GMRs for 100 versus 50 mg were 0.359 for AUC, 0.380 for Cmax, and 0.429 to Cmin. Three study participants (25%) had an atazanavir Cmin below the target concentration of 0.15 mg/L, but no one lost virologic control.

Measurements of total bilirubin, total cholesterol, and triglycerides with 100 and 50 mg of ritonavir disclosed no clinical or statistical differences between the standard and lower doses. The researchers suggested this lack of difference could reflect the small sample size, close-to-normal baseline values, and short study duration. They argued that a larger clinical study is warranted to confirm the clinical efficacy and safety of protease inhibitor boosting with 50 mg of ritonavir daily.

**Figure 11.** Atazanavir exposure was slightly lower with a 50-mg ritonavir boost than with the standard 100 mg in 12 patients switching from a suppressive 300/100-mg regimen to 300/50 mg. (Source: Pierre Giguère, Ottawa Hospital, and colleagues.)
Modeling predicts need to adjust cancer drug doses with antiretrovirals

A modeling study predicted that two antineoplastic agents, erlotinib and gefitinib, need dose adjustments when administered with ritonavir, efavirenz, or etravirine. Models determined that ritonavir will boost exposure of erlotinib and gefitinib, while both nonnucleosides will lower exposure of the anticancer agents.

Researchers from Barcelona’s Hospital Universitari Germans Trias i Pujol, noted that incidence of certain non-AIDS cancers is rising among people with HIV. Drug-drug interactions between antineoplastic agents and antiretrovirals are anticipated but remain poorly studied. To address this issue, the researchers developed a physiologically based pharmacokinetic (PBPK) model to explore drug-drug interactions between two anticancer agents (erlotinib and gefitinib) and three antiretrovirals (ritonavir, efavirenz, and etravirine).

Erlotinib and gefitinib are epidermal growth factor receptor inhibitors prescribed for non-small cell lung cancer. Both are metabolized by CYP3A4, which ritonavir inhibits and efavirenz and etravirine induce. Erlotinib is dosed at 150 mg once daily, the maximum tolerated dose. Gefitinib is dosed at 250 mg once daily, one third the maximum tolerated dose.

In collaboration with colleagues at the University of Liverpool, the investigators based the model on in vitro data from the literature describing the chemical properties, absorption, distribution, metabolism, and elimination of the two antineoplastics and three antiretrovirals. The models simulated steady-state AUC0-24 and Cmax in plasma in virtual populations of 50 healthy volunteers taking standard doses of erlotinib or gefitinib alone or with 100 mg of ritonavir daily, 600 mg of efavirenz daily, or 200 mg of etravirine twice daily. The investigators calculated geometric mean ratios (GMR) and 90% confidence intervals comparing anticancer agent concentrations with versus without the antiretrovirals. They also modeled various dose-adjustment strategies.

The researchers validated the model with CYP3A4 probe drugs (midazolam with or without ritonavir, maraviroc with or without efavirenz or etravirine). Model-simulated parameters with each antineoplastic agent or antiretroviral agreed with reference values reported in the literature.

The models determined that ritonavir tripled or quadrupled exposure of both erlotinib and gefitinib (Table 9). Efavirenz and etravirine each significantly lowered exposure of both antineoplastic agents (Table 9). Simulation of dose adjustments indicated that the dose of erlotinib should be lowered from 150 mg once daily to 25 mg once daily if given with 100 mg of ritonavir and raised to 200 mg once daily if given with standard-dose efavirenz or etravirine (Table 10). Similarly, simulations indicated that the dose of gefitinib should be lowered from 250 mg once daily to 375 mg once daily with standard-dose efavirenz or etravirine. Ongoing refinement of this model could have a minor impact on the results presented.

<table>
<thead>
<tr>
<th>Interactions with ritonavir</th>
<th>Interactions with efavirenz</th>
<th>Interactions with etravirine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Erlotinib</strong></td>
<td><strong>Gefitinib</strong></td>
<td></td>
</tr>
<tr>
<td>GMR (90% CI): ERL/RTV vs ERL alone</td>
<td>GMR (90% CI): GEF/RTV vs GEF alone</td>
<td></td>
</tr>
<tr>
<td>AUC024</td>
<td>4.53 (4.11 to 4.99)</td>
<td>3.85 (3.62 to 4.09)</td>
</tr>
<tr>
<td>Cmax</td>
<td>3.79 (3.48 to 4.14)</td>
<td>3.12 (2.96 to 3.29)</td>
</tr>
<tr>
<td><strong>Gefitinib</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GMR (90% CI): ERL/EFV vs ERL alone</td>
<td>GMR (90% CI): GEF/EFV vs GEF alone</td>
<td></td>
</tr>
<tr>
<td>AUC024</td>
<td>0.85 (0.76 to 0.95)</td>
<td>0.67 (0.60 to 0.75)</td>
</tr>
<tr>
<td>Cmax</td>
<td>0.89 (0.82 to 0.97)</td>
<td>0.71 (0.65 to 0.77)</td>
</tr>
</tbody>
</table>

Table 9. Erlotinib and gefitinib exposure with versus without three antiretrovirals
GMR (90% CI): ERL/ETR vs ERL alone  
GMR (90% CI): GEF/ETR vs GEF alone

<table>
<thead>
<tr>
<th></th>
<th>AUC024</th>
<th>Cmax</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GMR (0.55 to 0.66)</td>
<td>0.64 (0.58 to 0.71)</td>
</tr>
<tr>
<td></td>
<td>0.60 (0.55 to 0.66)</td>
<td>0.69 (0.64 to 0.74)</td>
</tr>
</tbody>
</table>
| EFV, efavirenz; ERL, erlotinib; ETR, etravirine; GEF, gefitinib; GMR, geometric mean ratio and 90% confidence interval; RTV, ritonavir.
| Source: José Moltó, Hospital Universitari Germans Trias i Pujol, and colleagues. | | |

**Table 10.** Simulated erlotinib and gefitinib dose adjustments with three antiretrovirals

<table>
<thead>
<tr>
<th>Drug</th>
<th>Alone</th>
<th>With 100 mg RTV QD</th>
<th>With 600 mg EFV QD or 200 mg ETR BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib</td>
<td>150 mg QD</td>
<td>25 mg QD</td>
<td>200 mg QD</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>250 mg QD</td>
<td>125 mg QD</td>
<td>375 mg QD</td>
</tr>
</tbody>
</table>

BID, twice daily; EFV, efavirenz; ETR, etravirine; QD, once daily; RTV, ritonavir.
Source: José Moltó, Hospital Universitari Germans Trias i Pujol, and colleagues.

The researchers proposed that this PBPK modeling approach “may be a useful tool for both prediction of drug-drug interactions and selection of doses to explore in prospective clinical trials.”

**Disulfiram activates latent HIV in patients on suppressive ART**

Disulfiram (the alcohol-dependence drug Antabuse) activated latent HIV as measured by cell-associated unspliced RNA (CA-US RNA) in 30 people taking suppressive antiretroviral therapy (ART). The exposure-response relationship was linear at the three disulfiram doses studied, and a few study participants had enhanced responses to disulfiram.

Shock-and-kill strategies to activate and eradicate latent HIV integrated in resting memory CD4 cells include use of epigenetic modifiers (such as histone deacetylase inhibitors), protein kinase C agonists (such as bryostatin), cytokines (such as IL-7), and other agents (such as TLR7 agonists). Research to date indicates that most of these agents have a modest impact on reactivation, and agents with stronger reactivating activity may pose a higher risk of toxicity.

Licensed for treatment of alcohol dependence, disulfiram is a familiar and generally well tolerated medication. Drug screening determined that disulfiram upregulates HIV gene expression in cell lines. Standard disulfiram dosing for alcohol cessation starts at 500 mg daily for 1 to 2 weeks, followed by a maintenance dose ranging from 125 to 500 mg. Anecdotally, doses up to 6 g have been used, noted University of California, San Francisco researchers who conducted this study.

Research indicates that disulfiram does not affect antiretroviral pharmacokinetics, but antiretrovirals can alter the impact of disulfiram on alcohol metabolism. A pilot study of 500 mg of disulfiram given for 14 days to 16 people on suppressive ART found that it did not decrease the size of the latent HIV reservoir. But the trial detected a possible dose-related effect that the authors said supported the idea of a study like the one presented at the Pharmacology Workshop.

The researchers proposed that this PBPK modeling approach “may be a useful tool for both prediction of drug-drug interactions and selection of doses to explore in prospective clinical trials.”

Adverse events were mild. Hypophosphatemia developed in 3 people taking 500 mg, 2 taking 1000 mg.
mg, and 2 taking 2000 mg. Other grade 1 adverse events included mild headache, drowsiness, dry mouth, and abdominal discomfort in participants taking 1000 or 2000 mg of disulfiram.

Disulfiram clearance measured 0.35 L/hour (CV% 20%), volume of distribution 1.6 L, and absorption constant 0.12 h\(^{-1}\). Median steady-state disulfiram AUC measured 573 mg*h/L at the 500-mg dose, 2845 mg*h/L at 1000 mg, and 8355 mg*h/L at 2000 mg. The 2000-mg dose yielded a supraproportional increase in disulfiram exposure, which the researchers proposed reflected saturation of the first-pass effect.

Pharmacodynamic modeling indicated that disulfiram and its four metabolites had a linear exposure response in increasing CA-US RNA, indicating activation of latent virus. The impact was most notable with the metabolite diethylidithiocarbamate-methyl ester, though the researchers noted these conclusions should be interpreted with caution given the small number of participants studied. If further work confirms that disulfiram metabolites are driving activation of latent HIV, the researchers suggested, disulfiram dosing could optimize exposure to specific metabolites. The observed exposure-response relationship suggested to the investigators that even higher doses may have a greater impact on viral reactivation.

Approximately 10% of participants reactivated latent HIV to levels that disulfiram exposure alone would not explain, a finding suggesting that additional unmeasured factors may also contribute to viral reactivation in these individuals. Disulfiram did not appear to have a significant exposure-response effect on plasma RNA, though analyses are ongoing.
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