



## New Antivirals and New Antiviral Strategies

*Report from the 18th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy, 14-16 June 2017, Chicago, IL, USA*

*Written by Mark Mascolini*

Since its inauguration 18 years ago, the **International Workshop on Clinical Pharmacology** has broadened its focus from antiretrovirals to include hepatitis virus agents and—in the 2017 edition—other antivirals that do not fit into those two bins. Organized and programmed by two panels of eminent pharmacologists and clinicians, the workshop draws attendance from leading researchers in academia, industry, and government agencies. The highly interactive format of this workshop allows ample time for exchanges between presenters and attendees.

The 2017 meeting featured studies of newer antiretrovirals—notably the integrase inhibitor dolutegravir and the protease inhibitor darunavir—plus an array of coformulated direct-acting antivirals (DAAs) for HCV infection. Novel analyses explored an ingestible adherence sensor, a model to predict virologic failure, and a strategy to use CYP3A induction data to predict drug interactions mediated by other metabolizing enzymes and transporters. But the meeting began with five studies evaluating a nonantiviral—the boosting agent cobicistat. These studies analyzed the impact of cobicistat on protease inhibitors, tenofovir disoproxil fumarate versus tenofovir alafenamide, and oral contraceptives.

This report summarizes all oral abstract presentations, grouped into five topics: cobicistat, dolutegravir and rilpivirine, direct-acting antivirals, new antivirals and new antiviral strategies, and novel analyses (not all of them mathematical modeling studies). Slides for most oral abstract presentations are available online at <http://www.infectiousdiseasesonline.com/18antiviralpk-presentation/>. At the same link readers can find slides to several comprehensive invited lectures, including an analysis of investigational therapy for HBV infection by Jordan Feld (Toronto Western Hospital Liver Center), an overview of long-acting antivirals by Mark Milad (Bill & Melinda Gates Foundation), and a debate of the need for additional HCV drugs, with Nancy Reau (Rush University Medical Center) taking the pro position and Jürgen Rockstroh (University of Bonn) advocating the contrary view.

## COBICISTAT IN THE CROSSHAIRS

### Does TDF need a lower dose with boosters?

Patients taking tenofovir disoproxil fumarate (TDF) as part of a cobicistat-boosted regimen had significantly higher tenofovir trough concentrations than people taking TDF with other regimens, including ritonavir-boosted protease inhibitors (PIs).<sup>1</sup> Compared with patients taking TDF in other regimens, those taking TDF with elvitegravir/cobicistat had more than a doubled risk of stopping TDF in the first year of therapy.

Researchers from Luigi Sacco University Hospital in Milan noted that the dose of tenofovir alafenamide (TAF) is lowered from 25 to 10 mg daily when administered with cobicistat or ritonavir. But no such boosting-based dose reduction applies to the standard 300 mg of TDF. Higher tenofovir trough concentrations with TDF have been linked to kidney toxicity.

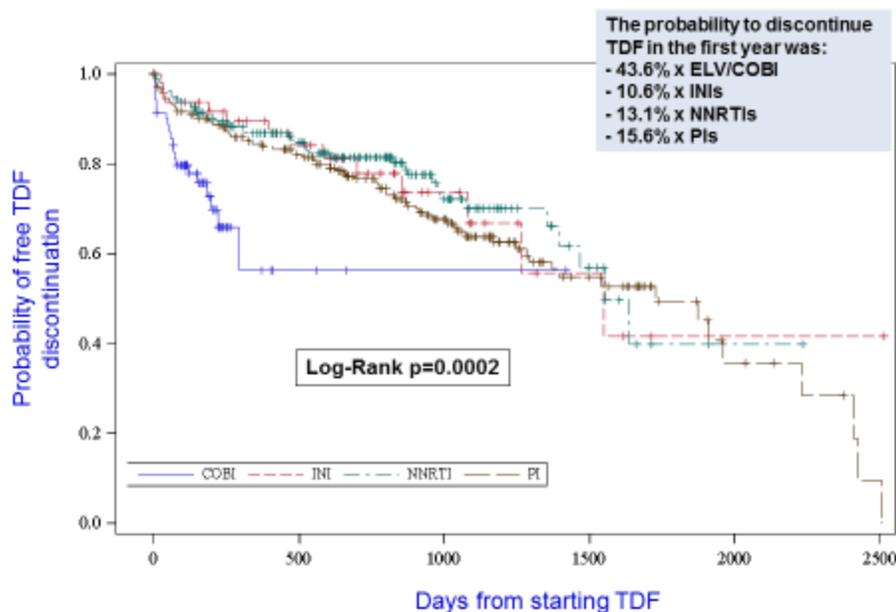
The Luigi Sacco team conducted this retrospective single-center study to identify predictors of tenofovir trough levels with TDF and to examine the role of cobicistat boosting on TDF durability. They included adults taking a TDF-based regimen for at least 3 months who had at least one tenofovir trough measured. They excluded people with severe hepatic impairment (Child-Pugh class B or C) or with creatinine clearance below 80 mL/min before starting TDF.

The study group included 212 people taking TDF with a ritonavir-boosted PI, 176 taking it with a nonnucleoside, 46 taking it with dolutegravir or raltegravir, and 76 taking it with elvitegravir/cobicistat. About 70% of study participants were men; age averaged about 47 years and weight around 70 kg.

Tenofovir troughs were significantly higher with elvitegravir/cobicistat or a ritonavir-boosted PI than with nonnucleosides or unboosted integrase inhibitors. Multivariate regression analysis independently linked elvitegravir/cobicistat to higher tenofovir troughs than ritonavir-boosted regimens (beta 0.27,  $P = 0.001$ ). Other independent predictors of tenofovir trough were age (beta 0.01,  $P < 0.001$ ), body weight (beta -0.01,  $P = 0.006$ ), and serum creatinine (beta 0.32,  $P < 0.0001$ ). An exploratory analysis of individual antiretrovirals found higher tenofovir troughs with elvitegravir/cobicistat and ritonavir-boosted lopinavir or atazanavir than with other agents assessed.

Kaplan-Meier analysis determined that the probability of stopping TDF was highest with elvitegravir/cobicistat (43.6%) than with boosted PIs (15.6%), nonnucleosides (13.1%), or unboosted integrase inhibitors (10.6%) ( $P = 0.0002$ ) (**Figure 1**). A Cox proportional hazards model linked elvitegravir/cobicistat versus PIs to a greater probability of stopping TDF in the first year of therapy (hazard ratio [HR] 2.284,  $P = 0.0067$ ). Every 10 ng/mL higher tenofovir concentration also predicted a greater chance of stopping TDF (HR 1.02,  $P = 0.0048$ ).

## Results V: clinical outcome



**Figure 1.** In a study of 510 adults, the TDF discontinuation rate in the first year of therapy was significantly higher with elvitegravir/cobicistat than with other regimens, including ritonavir-boosted PIs. (Source: Dario Cattaneo, Luigi Sacco University Hospital, Milan, and colleagues.<sup>1</sup>)

The researchers cautioned that some TDF discontinuation were “not driven by clear-cut clinical evidence, but rather by ‘perceptions’ of the attending physician.” But given their overall data, they proposed that “the lack of proper dose adjustment for TDF when given with cobicistat (or ritonavir) might have biased the safety results between TAF and TDF during registrational trials.”

### Darunavir and cobicistat levels lower with etravirine

Overall cobicistat exposure and darunavir trough concentrations were significantly lower with coadministration of the nonnucleoside etravirine in a two-cohort open-label study.<sup>2</sup> Everyone combining darunavir/cobicistat with etravirine maintained virologic control in this 2-week study.

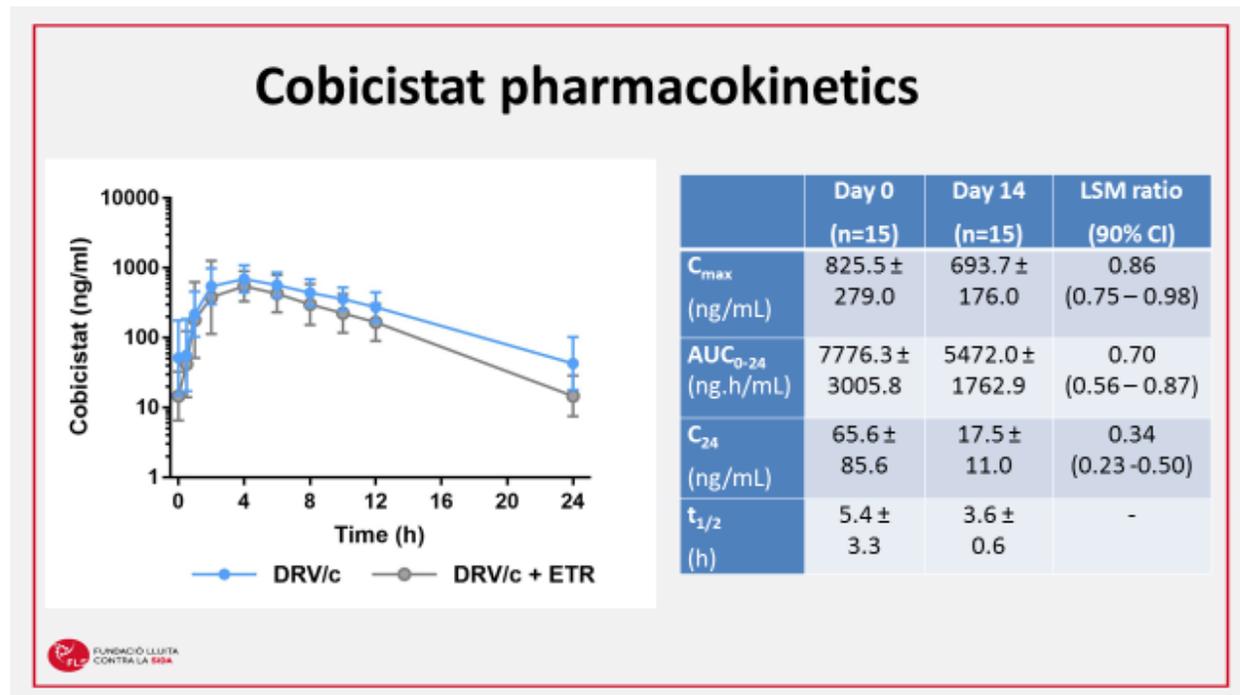
Interest has grown in nucleoside-sparing combinations, including ritonavir-boosted darunavir plus etravirine.<sup>3,4</sup> Clinicians are using a fixed-dose coformulation of darunavir/cobicistat, but data on combining that coformulation with etravirine are not available. Because cobicistat and ritonavir do not have identical boosting impacts on other medications, researchers from Barcelona’s Germans Trias i Pujol University Hospital conducted this single-center study.

The analysis involved two cohort of 15 people each, one already taking a stable regimen containing darunavir/cobicistat (800/150 mg once daily) and one taking a stable regimen based on etravirine (400 mg once daily) plus two nucleosides. While maintaining their baseline regimen, the darunavir group added etravirine on days 1

through 14 and the etravirine group added darunavir/cobicistat on days 1 through 7. The investigators obtained full pharmacokinetic profiles on days 0 and 14 in the darunavir-plus-etravirine group and on days 0 and 7 in the etravirine-plus-darunavir group. To compare the combined regimens with the baseline regimens, they used least squares mean (LSM) ratios derived from log-transformed 24-hour area under the concentration-time curve (AUC<sub>0-24</sub>), maximum concentration (C<sub>max</sub>), and trough concentration (C<sub>24</sub>).

Median ages in the darunavir and etravirine cohorts were 45.1 and 50.0 years and median body mass index 23.9 and 24.2 kg/m<sup>2</sup>. Fourteen people (93%) in the darunavir group and 12 (80%) in the etravirine group were men. All study participants maintained an undetectable viral load throughout this short study. Most adverse events were grade 1 or 2. No serious adverse events arose, and no one discontinued treatment.

Adding darunavir/cobicistat to etravirine did not affect etravirine pharmacokinetics. Adding etravirine to darunavir/cobicistat resulted in a 30% decline in cobicistat AUC<sub>0-24</sub> (LSM ratio 0.70, 90% confidence interval [CI] 0.56 to 0.87), a 14% decline in C<sub>max</sub> (LSM ratio 0.86, 90% CI 0.75 to 0.98), and a 66% decline in C<sub>24</sub> (LSM ratio 0.34, 90% CI 0.23 to 0.50) (**Figure 2**). Adding etravirine to darunavir/cobicistat lowered darunavir C<sub>24</sub> 56% (LSM ratio 0.44, 90% CI 0.33 to 0.58) but did not affect darunavir AUC<sub>0-24</sub> or C<sub>max</sub>.



**Figure 2.** In a 15-person cohort, adding etravirine to darunavir/cobicistat lowered cobicistat exposure, particularly trough concentration (C<sub>24</sub>). (Source: José Molto, Germans Trias i Pujol University Hospital, Barcelona, and colleagues.<sup>2</sup>)

On the basis of these results, the researchers suggested that “boosting darunavir with ritonavir instead of with cobicistat should be preferred” if darunavir and etravirine are combined in clinical practice.

### Similar darunavir levels in CSF with cobicistat and ritonavir

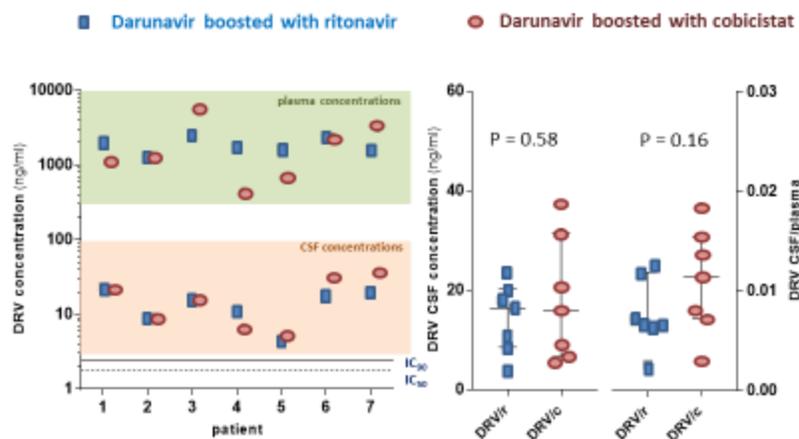
Boosting darunavir with ritonavir or cobicistat had a similar impact on cerebrospinal fluid (CSF) darunavir trough in a study of 7 adults with HIV-associated neurocognitive disorder (HAND).<sup>5</sup> All study participants maintained darunavir 50% and 90% inhibitory concentrations (IC<sub>50</sub> and IC<sub>90</sub>) with either ritonavir or cobicistat.

Researchers from the Universities of Basel and Lausanne noted that differing inhibitory profiles of ritonavir and cobicistat on drug transporters could affect distribution of antiretrovirals in sites such as the central nervous system (CNS). Previous research found that increasing concentrations of ritonavir reduce darunavir efflux by the P-gp transporter and so could improve darunavir levels in the CNS.<sup>6</sup> But compared with ritonavir, cobicistat is a weaker inhibitor of P-gp and BCRP, another efflux transporter expressed at the blood-brain barrier. The Basel-Lausanne team hypothesized that “weaker inhibition of P-gp and BCRP by cobicistat could result in less darunavir crossing the blood-brain barrier when boosted with cobicistat compared to ritonavir.”

The study included patients with HAND requiring a lumbar puncture for clinical reasons.<sup>7</sup> All were taking darunavir/ritonavir (800/100 mg once daily) or were eligible for such treatment. The researchers excluded people with conditions that might disrupt the blood-brain barrier and those taking medications that might induce or inhibit P-gp, BCRP, or CYP3A4. Participants took darunavir/ritonavir for 30 days and had lumbar puncture. Then they switched to darunavir/cobicistat (800/150 mg once daily) and had a second lumbar puncture 30 days later. The researchers collected paired plasma and cerebrospinal fluid (CSF) samples toward the end of the dosing interval. They quantified drug levels and figured CSF/plasma ratios.

Five of 7 study participants were men, 5 were Caucasian, and age ranged from 31 to 66 years. Median (interquartile range, IQR) darunavir trough concentrations in plasma were 1761 ng/mL (1614 to 2473) with ritonavir and 1275 ng/mL (657 to 3240) with cobicistat, a nonsignificant difference ( $P = 0.94$ ). Median (IQR) darunavir concentrations in CSF stood at 16.4 ng/mL (8.6 to 20.3) with ritonavir and 15.9 ng/mL (6.7 to 31.6) with cobicistat, also a nonsignificant difference ( $P = 0.58$ ) (**Figure 3**). Median (IQR) CSF/plasma ratios were 0.007 (0.006 to 0.012) with ritonavir and 0.011 (0.007 to 0.015) with cobicistat, a difference still short of statistical significance ( $P = 0.16$ ) (**Figure 3**). The researchers noted that interindividual variability in darunavir concentration was greater with cobicistat than ritonavir in both CSF and plasma.

## Darunavir concentrations in CSF and plasma



Background

Aims

Methods

Results

Discussion

**Figure 3.** Darunavir concentrations in plasma and CSF were largely similar with ritonavir and cobicistat boosting in a 7-person trial requiring two lumbar punctures. (Source: Catia Marzolini, University of Basel, and colleagues.<sup>5</sup>)

All study participants maintained darunavir CSF concentrations above the IC<sub>50</sub> and 1C<sub>90</sub>, by 9.2- and 6.7-fold with ritonavir boosting and by 8.9- and 6.5-fold with cobicistat.

The researchers concluded that “cobicistat and ritonavir give comparable effective darunavir concentrations in CSF and therefore can be used interchangeably to boost once-daily darunavir regimens.” Results of this study have been published online.<sup>8</sup>

### Cobicistat-boosted PIs raise exposure of two key statins

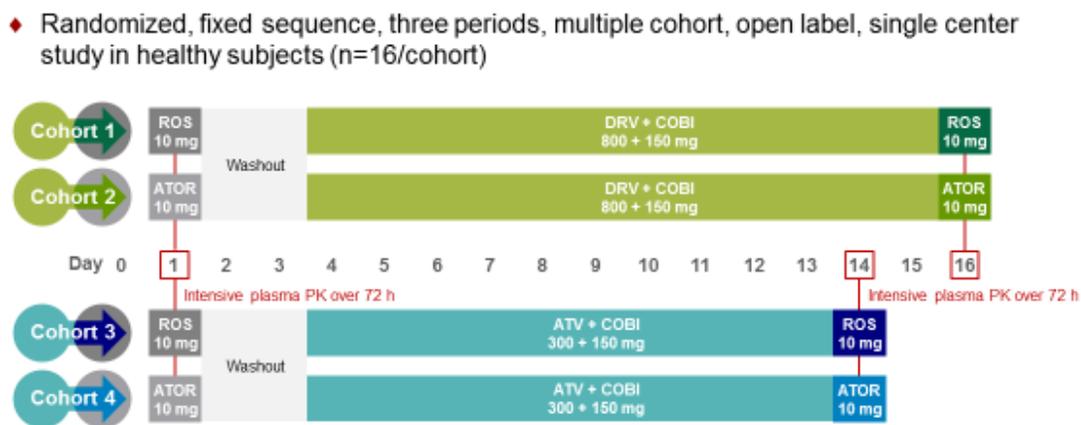
Cobicistat-boosted atazanavir and darunavir each raised concentrations of atorvastatin and rosuvastatin in a multiple-cohort study of 64 healthy volunteers.<sup>9</sup> The findings are consistent with current dosing recommendations when combining the statins with a boosted protease inhibitor (PI).

Statins see frequent use among people with HIV infection, many of whom may be taking a cobicistat-boosted antiretroviral. Cobicistat is licensed for use with the PIs atazanavir and darunavir. Atorvastatin, rosuvastatin, cobicistat, atazanavir, and darunavir share numerous metabolizing and transporter pathways:

- *Atorvastatin* and *rosuvastatin* are substrates for P-gp, BCRP, and OATP1B1/1B3.
- *Atorvastatin* is also a CYP3A substrate.
- *Cobicistat* inhibits CYP3A, P-gp, BCRP, and OATP1B1/1B3.
- *Atazanavir* inhibits CYP3A, UGT1A1, P-gp, BCRP, and OATP1B1/1B3.
- *Darunavir* inhibits CYP3A and P-gp.

To analyze potential interactions between these medications, Gilead Sciences researchers conducted a four-cohort, fixed-sequence, three-period, open-label study with 16 healthy volunteers in each cohort (**Figure 4**). On day 1 cohorts 1 and 3 received a single dose of rosuvastatin (10 mg), while cohorts 2 and 4 received a single dose of atorvastatin (10 mg) followed by a drug washout. Cohorts 1 and 2 took darunavir/cobicistat (800/150 mg daily) on days 4 through 15, adding a dose of rosuvastatin or atorvastatin on day 16. Cohorts 3 and 4 took atazanavir/cobicistat (300/150 mg daily) on days 4 through 13, adding one of the statins on day 14. Cohorts 3 and 4 took atazanavir/cobicistat (300/150 mg daily) on days 4 through 13, adding one of the statins on day 14.

## Study Design



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**Figure 4.** A four-cohort study of potential interactions between two statins and cobicistat-boosted atazanavir or darunavir used a fixed-sequence, open-label design. (Source: Joseph Custodio, Gilead Sciences, and colleagues.<sup>9</sup>)

The investigators measured drug concentrations at the end of each dosing period. To compare pharmacokinetics of statins with versus without cobicistat-boosted-PIs, they calculated geometric least-squares mean (GLSM) ratios, setting no-effect 90% confidence interval (CI) boundaries at 70% to 143%.

Ten of the 64 study participants were women, median age varied from 30 to 34 years across the four groups, and most participants were black or Hispanic. All participants completed the study. No grade 3 or 4 adverse events arose. Mild adverse events reflected well-appreciated events associated with atazanavir.

GLSM ratios for all potential drug-drug interactions assessed had 90% CIs outside the no-effect boundaries. When taken with darunavir/cobicistat, rosuvastatin area under the concentration-time curve (AUC) and maximum concentrations (C<sub>max</sub>) rose by 93% and

277%, while atorvastatin AUC and C<sub>max</sub> rose 290% and 319%. When taken with atazanavir/cobicistat, rosuvastatin AUC and C<sub>max</sub> rose by 242% and 960% and atorvastatin AUC and C<sub>max</sub> rose by 822% and 1790%.

The researchers noted that the greater magnitude of interaction between atazanavir/cobicistat and rosuvastatin or atorvastatin is explained by the potent inhibitory effect of atazanavir/cobicistat on OATP1B1/1B3 and/or P-gp/BCRP for rosuvastatin and the potent inhibitory effect of atazanavir/cobicistat on CYP3A, OATP1B1/1B3, and/or P-gp/BCRP for atorvastatin. The researchers also observed that their findings are consistent with current dosing recommendations for rosuvastatin and atorvastatin when given with boosted darunavir or atazanavir. With atazanavir/cobicistat plus atorvastatin, it is recommended to limit the atorvastatin dose to 10 mg daily while monitoring for safety. With darunavir/cobicistat plus either statin, and with atazanavir/cobicistat plus rosuvastatin, it is recommended to start with the lowest statin dose and to titrate upward until the desired response is achieved while monitoring for safety.

### **Progestin levels higher with cobicistat-boosted protease inhibitors**

Exposure of the progestin drospirenone was higher with coadministered atazanavir/cobicistat or darunavir/cobicistat in a fixed-sequence study of 36 healthy volunteers.<sup>10</sup> The finding is consistent with inhibition of CYP3A by cobicistat.

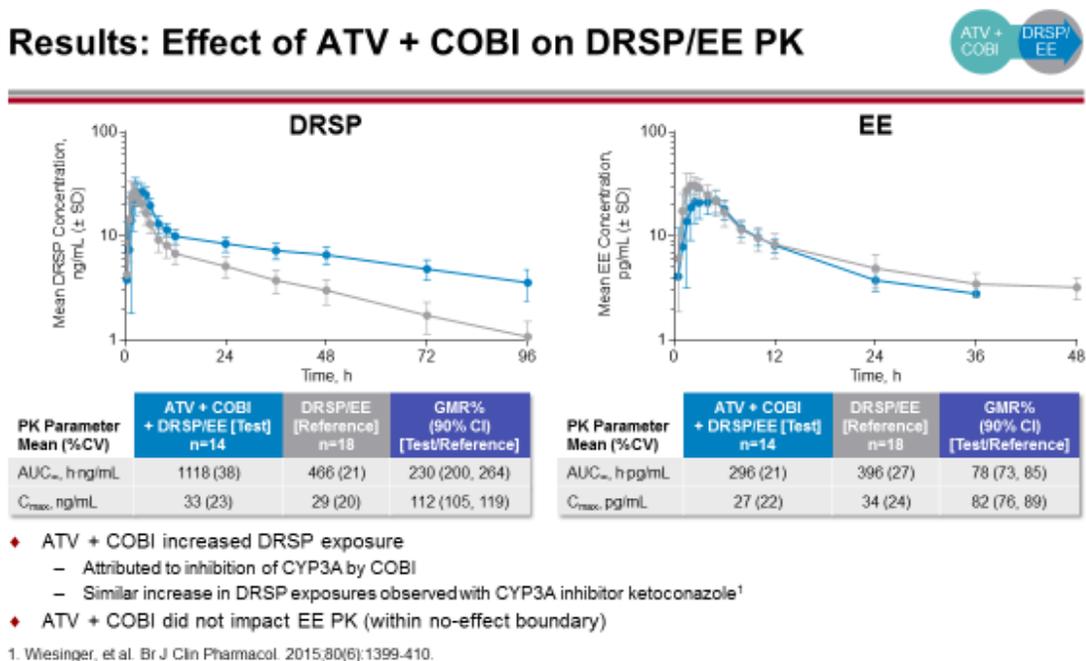
Gilead Sciences researchers who conducted this study noted that hormonal (“oral”) contraceptives are extensively metabolized by CYP enzymes, including CYP3A, CYP2C9/19, UGT, and SULT. Cobicistat, which is coformulated with the protease inhibitors (PIs) atazanavir and darunavir and the integrase inhibitor elvitegravir, is a mechanism-based inhibitor of CYP3A. Gilead investigators conducted this study to assess the impact of atazanavir/cobicistat or darunavir/cobicistat on drospirenone (3 mg) and ethinyl estradiol (20 µg), components of the oral contraceptive Yaz.<sup>11</sup>

This phase 1 open-label fixed-sequence study enrolled two cohorts, each including 18 healthy women. On day 1 women took Yaz, followed by a drug washout. On days 4 through 14 one cohort took atazanavir/cobicistat (300/150 mg daily), adding a dose of Yaz on day 14. On days 4 through 16, the other cohort took darunavir/cobicistat (800/150 mg daily), adding Yaz on day 16. Intensive PK sampling followed each Yaz administration. To compare Yaz components alone and with the boosted PIs, the researchers constructed geometric least-squares mean ratios and associated 90% confidence intervals (CI) and compared them with no-effect bounds set at 90% CIs of 70% to 143%.

Fourteen of 16 women completed the atazanavir/cobicistat study and 15 of 18 completed the darunavir/cobicistat study. The 7 women who stopped treatment all did so because of grade 1 maculopapular rash, a known adverse event associated with

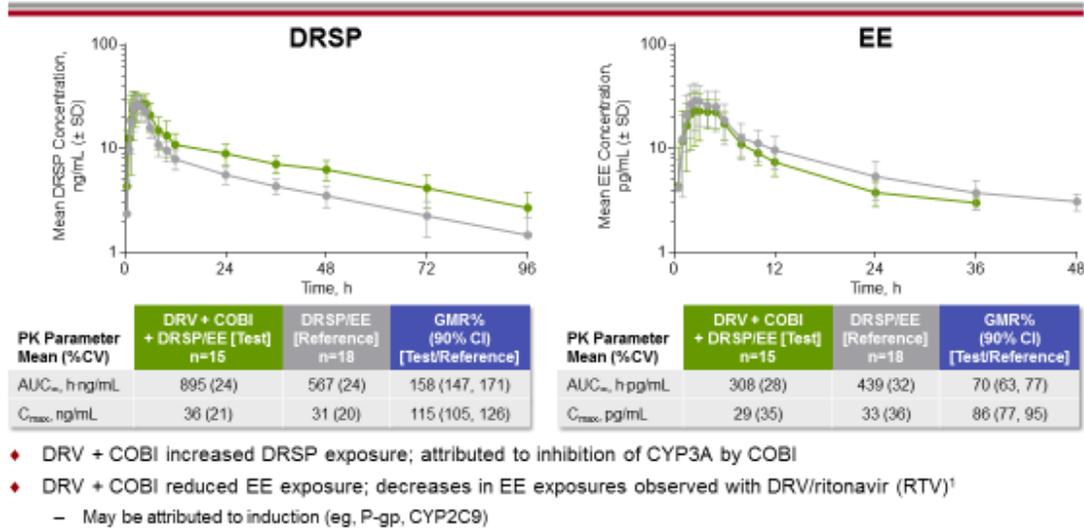
boosted PIs. Median ages in the atazanavir and darunavir groups were 30 and 28 years and median body mass index 26 kg/m<sup>2</sup> in both groups. Each cohort had a balanced make-up of whites, blacks, and Hispanics.

Drospirenone area under the concentration-time curve (AUC) was 2.3-fold higher with atazanavir/cobicistat and 1.6-fold higher with darunavir/cobicistat (**Figures 5 and 6**). These changes reflect CYP3A inhibition by cobicistat and are similar to increases in drospirenone exposure observed with the CYP3A inhibitor ketoconazole. Atazanavir/cobicistat did not affect exposure of ethinyl estradiol, while darunavir/cobicistat lowered ethinyl estradiol AUC by 30% (**Figure 6**). The impact on ethinyl estradiol may be attributed to darunavir induction of enzymes or transporters such as CYP2C9 and/or P-gp.



**Figure 5.** Coadministration of atazanavir/cobicistat increased exposure of the drospirenone component of the oral contraceptive Yaz but had no impact on the ethinyl estradiol component. (Source: Sophia Majeed, Gilead Sciences, and colleagues.<sup>10</sup>)

## Results: Effect of DRV + COBI on DRSP/EE PK



1. PREZISTA [package insert]. Titusville, NJ: Janssen Pharmaceuticals Inc; 2006.

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**Figure 6.** Coadministration of darunavir/cobicistat increased exposure of the drospirenone component of the oral contraceptive Yaz and modestly lowered exposure of the ethinyl estradiol component. (Source: Sophia Majeed, Gilead Sciences, and colleagues.<sup>10</sup>)

The drug-drug interaction results are consistent with previous findings in healthy volunteers upon coadministration of the oral contraceptive norgestimate/ethinyl estradiol and elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate. The findings are aligned with the prescribing information for cobicistat-boosted elvitegravir coformulations. Yaz prescribing information calls for clinical monitoring for hyperkalemia when giving the oral contraceptive with strong CYP3A inhibitors.<sup>11</sup> The Gilead researchers noted that this recommendation should extend to use of cobicistat-containing regimens with drospirenone-containing oral contraceptives.

## DOLUTEGRAVIR AND RILPIVIRINE

### Dolutegravir and rilpivirine exposure after switch from efavirenz or nevirapine

Concentrations of dolutegravir and rilpivirine rose steadily in the first 4 weeks after a switch from regimens containing efavirenz or nevirapine in the SWORD 1 and 2 trials.<sup>12</sup> Residual plasma concentrations of efavirenz and nevirapine fell to negligible levels in the same period.

SWORD 1 and 2 are identical trials of switching from a 3- or 4-drug regimen to a 2-drug combination of the integrase inhibitor dolutegravir and the nonnucleoside rilpivirine. Participants could switch from regimens containing a boosted protease inhibitor, an integrase inhibitor, or a nonnucleoside.

Dolutegravir depends mainly on UGT1A1 for its metabolism, with a minor contribution from CYP3A4. Rilpivirine relies primarily on CYP3A4 for its metabolism. The nonnucleosides efavirenz and nevirapine induce CYP3A4 and UGT1A1 and thus can lower concentrations of dolutegravir and rilpivirine. As part of SWORD 1 and 2, ViiV Healthcare investigators analyzed exposure of dolutegravir and rilpivirine in a subset of trial participants switching from efavirenz or nevirapine.

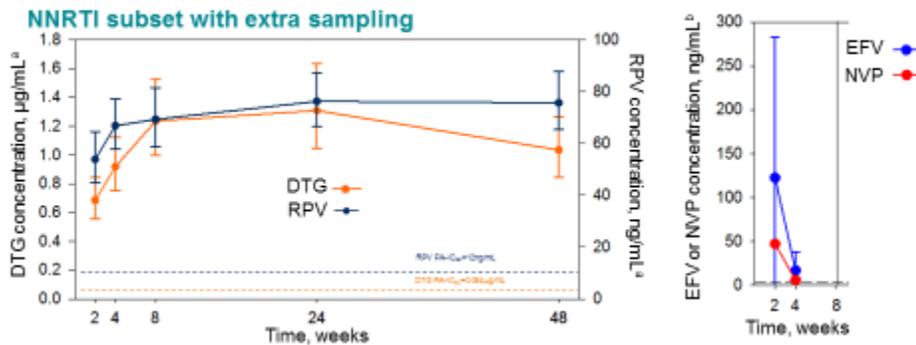
SWORD 1 and 2 randomized more than 1000 patients with a sustained viral load below 50 copies/mL on their current regimen to maintain that regimen or switch to dolutegravir/rilpivirine (50/25 mg once daily with a meal). After 48 weeks 95% of participants in both study arms maintained a viral load below 50 copies/mL, a result establishing the noninferiority of switching to dolutegravir/rilpivirine.<sup>13</sup>

All participants randomized to dolutegravir/rilpivirine had blood samples collected before dosing (C0) and at study weeks 4, 24, and 48. A subset of patients randomized to switch from efavirenz or nevirapine to dolutegravir/rilpivirine had additional predose samples at weeks 2 and 8 for dolutegravir and rilpivirine and at weeks 2 and 4 to measure residual efavirenz and nevirapine.

In the overall study population, age averaged 43 years, about 20% of participants were women, and about 20% nonwhite. Participants had taken antiretrovirals for a median of more than 50 months, and about three quarters used tenofovir disoproxil fumarate at baseline.

In the overall population C0 concentrations at weeks 4 to 48 proved comparable to previously reported levels for dolutegravir (mean 1.11 µg/mL) and rilpivirine (mean 79 ng/mL). In the nonnucleoside switch subset with extra sampling, dolutegravir C0 reached this level after 8 weeks and rilpivirine C0 reached this level after 4 weeks (**Figure 7**). Four weeks after efavirenz and nevirapine stopped, C0 of those nonnucleosides fell to negligible levels (**Figure 7**).

## PK Results: Concentrations Over Time (cont)



BQL, below quantifiable limit; DTG, dolutegravir; CI, confidence interval; EFV, efavirenz; NNRTI, non-nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PK, pharmacokinetic; RPV, rilpivirine; SD, standard deviation. <sup>a</sup>Data presented as geometric mean and 95% CI (N=54). <sup>b</sup>Data presented as mean (SD). NVP: 4/8 and 7/8 BQL at Weeks 2 and 4; EFV: 8/31 BQL at Week 4.

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18th International Workshop on Clinical Pharmacology of Antiviral Therapy, June 14-16, 2017, Chicago, IL.

**Figure 7.** After SWORD 1 and 2 participants stopped regimens including efavirenz or nevirapine, predose concentrations of dolutegravir and rilpivirine in the population with extra sampling reached levels equivalent to those in the entire study population after 4 to 8 weeks. Concentrations of efavirenz and nevirapine dropped to negligible levels 4 weeks after the nonnucleosides stopped. (Source: Kimberly Adkinson, ViiV Healthcare, and colleagues.<sup>12</sup>)

Participants in the nonnucleoside switch subset attained C<sub>0</sub> concentrations of dolutegravir and rilpivirine above the protein-adjusted 90% inhibitory concentrations for those drugs. These findings were comparable to those in (1) all trial participants who switched from efavirenz or nevirapine and (2) all participants who switched to dolutegravir and rilpivirine.

The ViiV team emphasized that efficacy results in the overall trial “demonstrate that the dolutegravir and rilpivirine exposures [after the switch from efavirenz or nevirapine] were sufficient to maintain virologic suppression.”

### Dolutegravir levels tied to shorter sleep duration in elderly

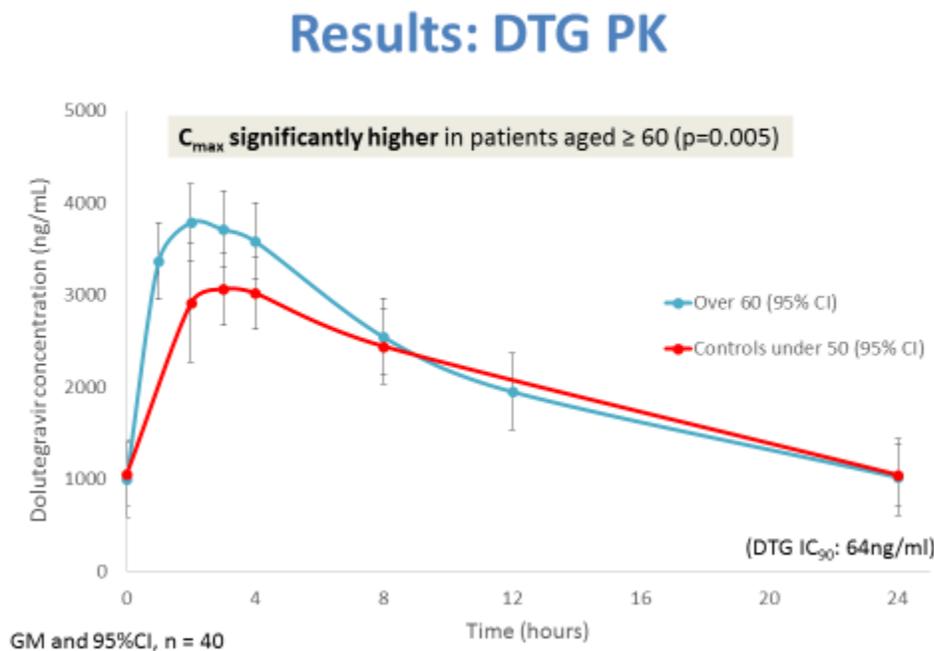
Higher dolutegravir exposure was associated with shorter sleep duration in preliminary data from HIV-positive people 60 years old or older.<sup>14</sup> This 60-or-older cohort had a higher dolutegravir maximum concentration (C<sub>max</sub>) than HIV-positive people under 50 years. But starting fixed-dose dolutegravir/abacavir/lamivudine did not affect overall sleep scores on three standard sleep tests.

In previously presented analyses, up to 5% of clinical trial participants reported central nervous system (CNS) adverse events with dolutegravir and discontinuation rates are low. In clinical practice data indicate a similar proportion of people have dolutegravir-related CNS events but few stop the drug. CNS events occur less frequently with dolutegravir than with efavirenz. Because older patients remain underrepresented in

clinical trials but constitute a growing proportion of people with HIV, researchers at London's Chelsea and Westminster Hospital and other centers conducted this prospective study.

The analysis involved HIV-positive people 60 to 64 (30%) or 65 or older (70%) with a sustained viral load below 50 copies/mL who switched to coformulated dolutegravir/abacavir/lamivudine, 43% from efavirenz regimens. On day 28 participants gave fasting samples for 24-hour pharmacokinetic analysis. Researchers compared dolutegravir findings with HIV-positive people younger than 50 years who participated in the SPRING-1 study<sup>15</sup> and also had intensive fasting pharmacokinetic monitoring. At baseline and treatment day 28, the 60-or-older group completed three sleep questionnaires: the Pittsburgh Sleep Quality Index (PSQI), the Functional Outcomes of Sleep (FOSQ) test, and the Insomnia Severity Index (ISI).

The 40 older patients had a median age of 65 years (range 60 to 78) and included 1 woman. The 16 younger controls had a median age of 37 years (range 22 to 50) and also included 1 woman. Compared with the under-50 group, older patients had a significantly higher dolutegravir C<sub>max</sub> (geometric mean 4246 versus 3402 ng/mL,  $P = 0.005$ ) (**Figure 8**).



**Figure 8.** Forty HIV patients 60 or older had a significantly higher dolutegravir C<sub>max</sub> than 16 comparison patients under 50 years old, possibly because drug absorption changes with age (Source: Marta Boffito, Chelsea and Westminster Hospital, London, and colleagues.<sup>14</sup>)

On the PSQI, global sleep scores and individuals domains did not differ significantly from baseline to day 28. Spearman correlation determined that higher dolutegravir C<sub>max</sub> and AUC were associated with shorter sleep duration on the PSQI (correlation coefficients 0.330 for C<sub>max</sub>,  $P = 0.05$ , and 0.353 for AUC,  $P = 0.03$ ).

Global and individual domain scores on the FOSQ and ISI did not differ significantly from baseline to day 28, and dolutegravir pharmacokinetics did not correlate with any changes on those two tests.

Older study participants tolerated the dolutegravir regimen well for 28 days, with no grade 3 or 4 toxicities. All participants maintained viral control throughout the study. The researchers suggested that higher dolutegravir C<sub>max</sub> in older patients may reflect changing drug absorption with age. They suggested that the association between dolutegravir exposure and sleep duration requires further investigation.

### Dolutegravir levels similar in third trimester and postpartum

Dolutegravir exposure and trough concentration (C<sub>24</sub>) proved similar in the third trimester of pregnancy and after delivery in a 5-woman multicenter analysis.<sup>16</sup> Levels of the integrase inhibitor at the end of the dosing interval remained above the 90% inhibitory concentration (IC<sub>90</sub>).

Physiologic changes during pregnancy affect the pharmacokinetics of antiretrovirals, often resulting in lower drug exposure in the third trimester than postpartum. Adequate antiretroviral concentrations are essential to maintain viral control and prevent perinatal transmission of HIV. Because data on dolutegravir pharmacokinetics during pregnancy are limited, PANNA network researchers conducted this analysis.

PANNA explores the pharmacokinetics of newly developed antiretrovirals in pregnant women.<sup>17</sup> This analysis focused on 9 pregnant women taking 50 mg of dolutegravir once daily in 4 European hospitals. Three women gave only third-trimester samples and 1 woman was excluded from the analysis. Median age stood at 30 years (range 21 to 42), median gestational age at 38 weeks (range 34 to 40), and median birth weight at 3180 g (range 2120 to 3530). The PANNA team collected samples over 24 hours at around 33 weeks gestation and again 4 to 6 weeks after delivery. They compared cord blood and maternal dolutegravir values when possible.

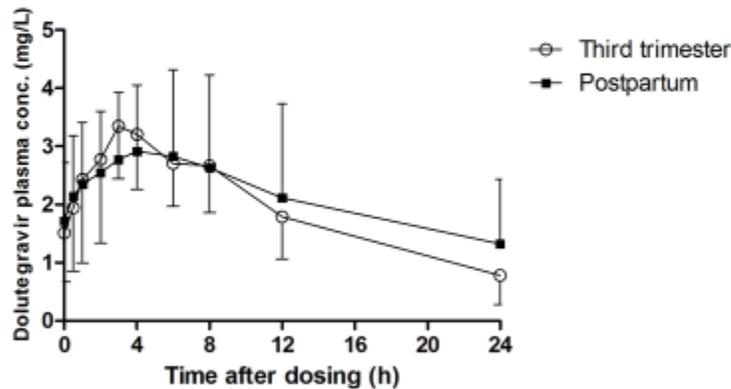
Overall dolutegravir plasma concentrations did not differ substantially between the third trimester and postpartum (**Figure 9**). Geometric mean ratios (GMR) calculated from 5 women during pregnancy and postpartum indicated similar area under the concentration-time curve (AUC) (GMR 0.95), maximum concentration (GMR 1.07), and clearance (CL/F) (GMR 1.06). Trough concentration (C<sub>24</sub>) was modestly lower in the third trimester (GMR 0.66, 90% confidence interval [CI] 0.32 to 1.36). C<sub>24</sub> remained

above the IC90 for dolutegravir in all women assessed.

These findings contrast with results for some other frequently used antiretrovirals: AUC of etravirine is higher in the third trimester than after delivery, whereas third-trimester AUCs are lower for ritonavir, darunavir, atazanavir, raltegravir, rilpivirine, tenofovir, and emtricitabine.

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## Plasma concentration vs. time curve



*Figure 9. In a 5-woman European analysis, plasma concentrations of the integrase inhibitor dolutegravir did not differ substantially between the third trimester and after delivery. (Source: Pauline Bollen, Radboud University Medical Center, Nijmegen, and colleagues.<sup>16</sup>)*

In 5 cord blood/maternal blood comparisons, the cord/maternal ratio was 1.4 for dolutegravir (90% CI 0.35 to 1.6). Previous work shows that cord/maternal ratios are also above 1.0 for emtricitabine and raltegravir but below 1.0 for tenofovir, abacavir, efavirenz, etravirine, rilpivirine, atazanavir, darunavir, and ritonavir. Because dolutegravir efficiently crosses the placenta, the PANNA team suggested that the integrase inhibitor may have potential for preexposure prophylaxis.

Seven of eight infants were not infected with HIV, while the status of 1 infant was unknown at the time of this presentation. One intrauterine fetal death occurred at 34 weeks gestation due to cholestasis pregnancy syndrome. Two serious adverse events (hospital admission to rule out preeclampsia) were not drug-related.

## INTERACTIONS INVOLVING DIRECT-ACTING ANTIVIRALS

### Glecaprevir and pibrentasvir raise exposure of statins, dabigatran

The anti-HCV direct-acting antivirals (DAAs) glecaprevir and pibrentasvir raised exposure of pravastatin, rosuvastatin, and the anticoagulant dabigantran etexilate in phase 1 studies of healthy volunteers.<sup>18</sup> Results indicate that the statins need a dose reduction with glecaprevir/pibrentasvir, while dabigantran should be given according to local guidelines on use with P-gp inhibitors when administered with glecaprevir/pibrentasvir.

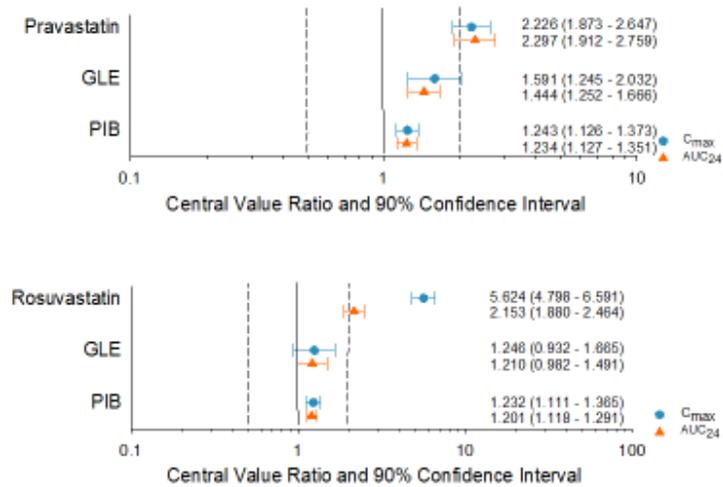
The FDA is reviewing coformulated glecaprevir/pibrentasvir as a 300/120-mg once-daily agent for all major HCV genotypes.<sup>19</sup> Glecaprevir is an NS3/4A protease inhibitor and pibrentasvir is an NS5A inhibitor. Both DAAs inhibit multiple drug transporters: P-gp, BCRP, and OATP1B1/1B3. Pravastatin is an OATP1B1/1B3 substrate, rosuvastatin is a BCRP and OATP1B1/1B3 substrate, and dabigantran etexilate is a P-gp substrate.

To characterize potential interactions between these medications, Abbvie researchers conducted phase 1 studies in 36 healthy volunteers. They evaluated pharmacokinetics with (1) 10 mg of pravastatin alone and with 400/120 mg of glecaprevir/pibrentasvir, (2) 5 mg of rosuvastatin alone and with 400/120 mg of glecaprevir/pibrentasvir, and (3) 150 mg of dabigatran etexilate alone with 300/120 mg of glecaprevir/pibrentasvir. Twelve volunteers participated in each of the three interaction analyses.

Coadministration of pravastatin with glecaprevir/pibrentasvir resulted in a 123% increase in pravastatin maximum concentration (C<sub>max</sub>) and a 130% increase in area under the concentration-time curve (AUC) (**Figure 10**). These increases in pravastatin exposure are similar to those seen previously with clarithromycin. With pravastatin, glecaprevir C<sub>max</sub> rose 59% and AUC 44% (**Figure 10**). When taken with glecaprevir/pibrentasvir, rosuvastatin C<sub>max</sub> rose 462% and AUC 115%. Increased rosuvastatin exposure with the DAAs was similar to that seen with lopinavir/ritonavir. Rosuvastatin did not affect concentrations of either DAA.

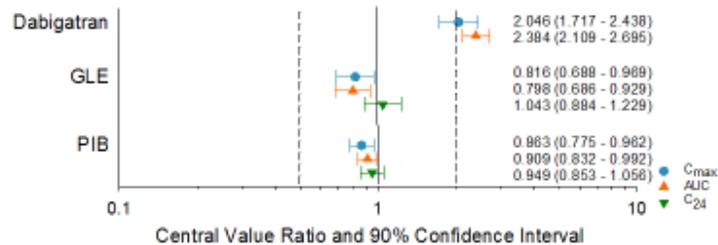
When dabigatran etexilate was taken with glecaprevir/pibrentasvir, dabigatran C<sub>max</sub> rose 105% and AUC 138% (**Figure 11**). These increases were similar to those seen with ketoconazole. Dabigatran did not affect concentrations of glecaprevir or pibrentasvir.

## Relative bioavailability of combined study drugs



**Figure 10.** Coadministration of the DAA combination glecaprevir/pibrentasvir resulted in higher concentrations of pravastatin and rosuvastatin. Glecaprevir concentrations rose modestly with pravastatin. (Source: Matthew Kosloski, Abbvie, and colleagues.<sup>18</sup>)

## Relative bioavailability of dabigatran, glecaprevir, and pibrentasvir



**Figure 11.** Coadministration of glecaprevir/pibrentasvir resulted in higher concentrations of the anticoagulant dabigatran. (Source: Matthew Kosloski, Abbvie, and colleagues.<sup>18</sup>)

On the basis of these findings, the investigators recommended a 50% pravastatin dose reduction and a maximum rosuvastatin dose of 10 mg daily with glecaprevir/pibrentasvir. They proposed that dabigatran “should be dosed per region-specific labeling on use with P-gp inhibitors” when given with glecaprevir/pibrentasvir.

In the pravastatin study all adverse events with mild and no clinically significant lab values were recorded. One participant discontinued treatment in the rosuvastatin study after a grade 2 panic attack judged unrelated to study drugs. Most adverse events were mild and no clinically significant lab findings emerged. One volunteer stopped treatment in the dabigatran study because of grade 1 chemical exposure unrelated to study drugs. All other adverse events were mild and no clinically significant lab changes occurred.

### **Platelets, PPI use predict ledipasvir exposure with decompensated cirrhosis**

Higher platelets or albumin, proton pump inhibitor (PPI) use, weight, and time after dosing predicted ledipasvir concentrations in a UK cohort of 314 patients with decompensated cirrhosis.<sup>20</sup> Overall sustained virologic response (SVR) rate was 83.1%.

The success of direct-acting antivirals (DAAs) has expanded their use to HCV patients with decompensated cirrhosis. Clinical trials<sup>21,22</sup> and cohort studies found high SVR rates with ledipasvir/sofosbuvir plus ribavirin in this population. To identify predictors of ledipasvir and sofosbuvir concentrations in patients with decompensated cirrhosis, researchers in Ireland and the UK analyzed pharmacokinetics of these DAAs in the NHS England expanded access program.

In this prospective study, researchers collected plasma samples at 3 or 4 random time points from 314 patients treated for 12 weeks with the fixed-dose coformulation of ledipasvir/sofosbuvir plus ribavirin. Researchers used a standard assay to measure concentrations of ledipasvir, sofosbuvir, and GS-331007, the major circulating metabolite of sofosbuvir.

Participants had a median age of 56 years (range 28 to 79), a median MELD score of 11, median platelet levels of 79.5 K/mL, and median albumin of 3.2 g/dL. Most participants had HCV genotype 1 (63%) or 3 (26%). Overall SVR measured 83.1% and was higher with genotype 1 (93.5%) than genotype 3 (56.6%). Geometric mean ledipasvir and GS-331007 concentrations were 213 ng/mL (90% CI 199.4 to 226.8) and 558 ng/mL (90% CI 524.9 to 592).

Multivariate analysis identified five independent predictors of ledipasvir concentrations—greater weight, longer time since dosing, higher albumin, higher platelets, and baseline PPI use (**Table 1**). But SVR rate did not differ significantly between patients with versus without baseline PPI use (82.4% and 83.6%,  $P = 0.88$ ).

**Table 1.** Independent predictors of ledipasvir concentrations with decompensated cirrhosis

Variable	$\beta$ coefficient (90% CI)	P
Weight (per 10-kg increase)	-15.3 (-21.8 to -9)	<0.0005
Time since dosing (h)	-2.18 (-4.0 to -0.31)	0.05
Albumin (per g/dL)	2.45 (0.9 to 4.0)	0.009
Platelets (per K/mL)	0.631 (0.434 to 0.828)	<0.0005
PPI use (yes vs no)	-94.0 (-115 to -72.9)	<0.0005

PPI, proton pump inhibitors.

Source: Omar Elsherif, St. James Hospital, Dublin, and colleagues.<sup>20</sup>

The researchers noted that albumin and platelet count, though not expected to directly affect ledipasvir pharmacokinetics, “may reflect an independent marker of disease activity.” Previous work linked weight to ledipasvir levels, they added, but weight was not found to be a clinically meaningful covariate for exposure of this DAA. Using these data, the researchers are developing a population-PK model to further explore the potential impact of covariates and comedications on DAA exposure in people with decompensated cirrhosis and portal hypertension.

### Higher voxilaprevir exposure with boosted antiretrovirals

Coadministering the direct-acting antiviral (DAA) voxilaprevir with a ritonavir- or cobicistat-boosted antiretrovirals resulted in higher voxilaprevir exposure in phase 1 studies of healthy volunteers, but that increase is not expected to be clinically meaningful.<sup>23</sup> The antiretrovirals assessed did not have a large impact on sofosbuvir or velpatasvir, the two other components of a once-daily fixed dose combination with voxilaprevir. And the DAAs had, at most, a modest impact on pharmacokinetics of the antiretrovirals studied.

The three-DAA coformulation of sofosbuvir/velpatasvir/voxilaprevir (400/100/100 mg once daily) is being developed for treatment of chronic HCV infection.<sup>24</sup> Gilead Sciences investigators conducted this analysis to explore potential drug-drug interactions between the three DAAs and common boosted and unboosted antiretrovirals. To do so they calculated geometric mean ratios for standard pharmacokinetic parameters with no-effect bounds set at a 90% confidence interval between 70% to 143%.

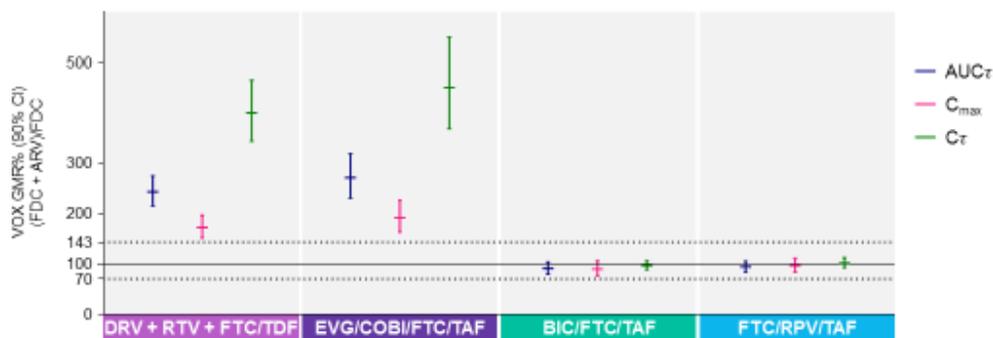
The study involved four cohorts, each including 30 healthy volunteers taking sofosbuvir/velpatasvir/voxilaprevir with or without (1) darunavir/ritonavir (800/100 mg) plus emtricitabine/tenofovir disoproxil fumarate (FTC/TDF, 200/300 mg), (2) elvitegravir/cobicistat/FTC/tenofovir alafenamide (TAF) (150/150/200/10 mg), (3) bicitgravir/FTC/TAF (50/200/25 mg), and (4) FTC/rilpivirine/TAF (200/25/25 mg). Participants took an extra 100 mg of voxilaprevir to reach exposures similar to those seen in people with HCV.

All but 4 participants completed each study; the 4 dropouts withdrew consent. There were no grade 3 or 4 adverse events, no serious adverse events, and no discontinuations due to adverse events. Grade 3 or 4 lab abnormalities developed in 7% of each of the first three cohorts and in 17% of the FTC/rilpivirine/TAF cohort. Age averaged 34 or 35 years across the four cohorts. About 20% of participants were women and about two thirds white.

Analysis of geometric mean ratios indicated that no antiretrovirals had a clinically meaningful impact on the pharmacokinetics of sofosbuvir, GS-331007 (the major circulating metabolite of sofosbuvir), or velpatasvir. Velpatasvir trough concentration rose modestly with the elvitegravir/cobicistat regimen.

Coadministration of the ritonavir- or cobicistat-boosted antiretrovirals resulted in significantly higher voxilaprevir area under the concentration-time curve, maximum concentration, and trough concentration (**Figure 12**). An exposure-safety evaluation in phase 3 trials of sofosbuvir/velpatasvir/voxilaprevir indicates that this change in voxilaprevir exposure is not clinically relevant. The two unboosted antiretroviral regimens had no impact on voxilaprevir pharmacokinetics.

## Effect of HIV ARV Regimens on VOX PK



- ◆ VOX exposure is higher with boosted ARV regimens
  - Explained by VOX being a substrate of transporters and enzymes
  - Not clinically relevant based on exposure-safety evaluation in Phase 3 SOF/VEL/VOX studies

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**Figure 12.** Taking a boosted antiretroviral regimen (darunavir/ritonavir plus FTC/TDF or elvitegravir/cobicistat/FTC/TAF) with sofosbuvir/velpatasvir/voxilaprevir resulted in higher voxilaprevir exposure, but trial data indicate this change is not clinically relevant. (Source: Kimberly Garrison, Gilead Sciences, and colleagues.<sup>23</sup>)

The DAAs had no clinically relevant impact on the pharmacokinetics of darunavir, ritonavir, elvitegravir, cobicistat, bicitgravir, or rilpivirine. When the unboosted antiretroviral regimens were taken with the DAAs, there were moderate increases in exposure of TAF (about 50% to 60%) and tenofovir (about 70% to 80%), but these changes are not considered clinically relevant. When the darunavir/ritonavir regimen was taken with the DAAs, tenofovir exposure from TDF increased about 40%, which was similar to the increase seen with boosted TDF taken with sofosbuvir/velpatasvir. The DAAs did not affect FTC pharmacokinetics.

The Gilead team concluded that findings to date support use of sofosbuvir/velpatasvir/voxilaprevir with (1) the nucleos(t)ides FTC, TAF, and TDF, (2) the nonnucleoside rilpivirine, (3) the integrase inhibitor bicitgravir and the three licensed integrase inhibitors, (4) the protease inhibitor darunavir, and (5) the boosters cobicistat and ritonavir.

### Reported rhabdomyolysis cases with DAAs plus a statin

Analysis of the FDA Adverse Event Reporting System (FAERS) yielded 14 cases of rhabdomyolysis in people taking an anti-HCV direct-acting antiviral (DAA) and a statin.<sup>25</sup>

Rhabdomyolysis remains a rare but serious statin-associated adverse event. Taking certain DAAs with a statin may raise statin concentrations and thus heighten the risk of rhabdomyolysis. FDA investigators analyzed the FAERS database to find cases of rhabdomyolysis in people taking a statin with DAAs and to determine whether there is a known mechanism for each DAA-statin interaction.

The analysis focused on DAAs currently licensed by the FDA. The investigators defined a case as “any report of a clinical diagnosis of rhabdomyolysis temporally associated with DAA therapy, with or without use of a statin.” For statin-associated cases, the FDA team assessed the potential for DAA-statin interactions. The analysis did not aim (1) to determine if the DAA regimen caused rhabdomyolysis or (2) to establish the incidence of rhabdomyolysis in patients taking a statin with DAAs.

The database search disclosed 42 rhabdomyolysis cases in patients taking a DAA, 14 (33%) of whom were also taking a statin. The FDA researchers divided the 14 DAA-statin cases into three scenarios: (1) significant increases in statin plasma concentrations are known or anticipated due to drug interactions, (2) a drug interaction resulting in an increase in statin plasma concentrations is anticipated but no specific dosing recommendation is available in prescribing information at the time of event, and (3) no significant interaction is expected based on in vitro or in vivo study results. **Table 2** lists the number of cases in each scenario and the DAAs and statins involved.

### **Table 2. Rhabdomyolysis cases in patients taking DAAs with a statin**

Scenario	n	Medications involved
1. Higher statin exposure anticipated	9	<p><i>4 cases with contraindicated combination:</i>  4: Ombitasvir/paritaprevir/ritonavir/dasabuvir and simvastatin</p> <p><i>5 cases with recommended statin dose cap:</i>  2: Simeprevir/sofosbuvir and atorvastatin  1: Ombitasvir/paritaprevir/ritonavir/dasabuvir and pravastatin  1: Daclatasvir-containing regimen and rosuvastatin  1: Simeprevir/sofosbuvir and rosuvastatin</p>
2. Higher statin exposure anticipated but no dosing advice	2	1: Ombitasvir/paritaprevir/ritonavir/dasabuvir and atorvastatin 1: Simeprevir/sofosbuvir/daclatasvir and atorvastatin
3. No significant interaction expected	3	3: Sofosbuvir/ledipasvir and atorvastatin

Source: Su-Young Choi, Food and Drug Administration, and colleagues.<sup>25</sup>

Among the 5 cases involving a statin dose cap (Scenario 1), 2 reports included the statin dose. In both cases patients were taking a statin dose recommended with their DAAs. Because the FAERS database did not include pharmacokinetic data, for Scenario 3 the investigators could not determine whether higher statin levels resulting from interactions or other factors precipitated rhabdomyolysis.

The FDA investigators also reported that many of these patients with rhabdomyolysis had at least one other factor that could raise the risk of statin-related rhabdomyolysis, such as advanced age and renal impairment. The FDA team added a note on cases involving hepatic transporter-mediated interactions with HCV protease inhibitors: The magnitude of such interactions may be higher in HCV-infected patients than in healthy volunteers because of the underlying disease (impaired liver function).

## NEW ANTIVIRALS, NEW ANTIVIRAL STRATEGIES

### Pharmacokinetics of a novel HIV maturation inhibitor in healthy adults

Four phase 1 studies of GSK2838232, an investigational HIV maturation inhibitor, yielded pharmacokinetic profiles that promise to maintain plasma concentrations of the drug above the protein-adjusted 90% inhibitory concentration (IC<sub>90</sub>) in patients with HIV.<sup>26</sup> These studies demonstrated that GSK2838232 exposure was boosted by coadministration of ritonavir in single and repeated doses.

HIV maturation inhibitors promote formation of immature viral particles by binding to the HIV Gag protein. GSK2838232 depends primarily on the CYP3A4 enzyme for clearance, and thus CYP3A4 inhibitors are expected to boost concentrations of the maturation inhibitor. Preclinical studies identified no interactions with substrates of UGT1A1, 1A3, 1A6, 1A9, 2B7, and 2B15, OAT1, OAT3, OATP1B1, OATP1B3, or OCT2. GSK2838232 has low to moderate bioavailability (6% to 40% across species), low permeability, and low solubility.

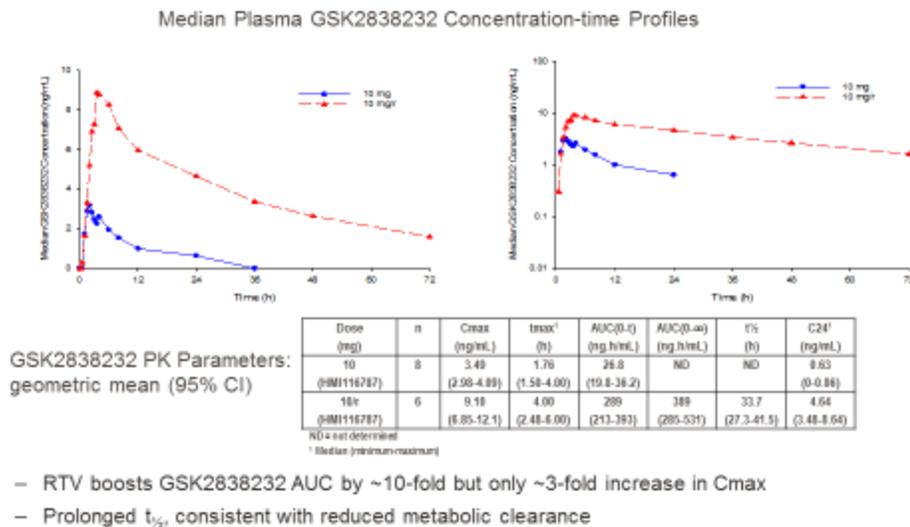
Four phase 1 dose-escalation trials in healthy volunteers (ClinicalTrials.gov identifiers NCT01802918, NCT02289482, NCT02289495, and NCT02795754) evaluated single and repeated doses of suspension and solid oral formulations of GSK2838232 with or without ritonavir boosting (100 mg oral once daily). GSK2838232 oral doses ranged from 10 to 250 mg.

The phase 1 trials enrolled 124 healthy volunteers, 9 of them women, who took GSK2838232 or placebo. Age ranged from 18 to 55 years and body mass index from 18.5 to 31.0 kg/m<sup>2</sup>. No one stopped treatment and no grade 3 or 4 lab abnormalities occurred. One volunteer had a short run of nonsustained ventricular tachycardia (NSVT) after receiving GSK2838232, which on subsequent evaluation was considered unlikely to be related to the maturation inhibitor. Participants tolerated all formulations well with or without food. There were no clinically significant changes in any safety parameters judged related to GSK2838232.

Single doses of GSK2838232 up to 200 mg yielded broadly dose-proportional concentrations through 100 mg. Analyses of these studies demonstrated lower bioavailability than preclinical studies predicted. Ritonavir at 10 mg for 12 days raised single-dose GSK2838232 area under the concentration-time curve approximately 10-fold but boosted maximum concentration only 3-fold (**Figure 13**). Prolonged terminal half-life seen in ritonavir-boosting studies is consistent with reduced metabolic clearance of the maturation inhibitor.

## GSK2838232: Boosting with RTV

RTV administered for 12 days, GSK2838232 SDD PiB administered on Day 10



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**Figure 13.** Ritonavir boosted AUC and C<sub>max</sub> of a single 10-mg oral dose of the HIV maturation inhibitor GSK2838232 by approximately 10-fold and 3-fold respectively in healthy volunteers. (Source: Mark Johnson, GlaxoSmithKline, and colleagues.<sup>26</sup>)

In a single-dose ritonavir-boosting study, GSK2838232 pharmacokinetics proved largely dose proportional. All ritonavir-boosted doses (from 50 to 250 mg) yielded GSK2838232 above-target trough concentrations. In repeat-dose studies, GSK2838232 given unboosted at a dose of 200 mg twice daily had a pharmacokinetic profile similar to that with 50 mg of ritonavir-boosted GSK2838232 once daily.

Based on analysis of these data, GSK investigators predicted that ritonavir-boosted GSK2838232 doses at or above 50 mg once daily will achieve target exposure and that unboosted GSK2838232 at higher doses may also be viable for study. A phase 2a study of 10-day monotherapy with cobicistat-boosted GSK2838232 in antiretroviral-naive adults with HIV is under way.<sup>27</sup> This proof-of-concept trial is boosting GSK2838232 with cobicistat, not ritonavir. As yet there are no pharmacokinetic data on the combination of GSK2838232 and cobicistat, although it is assumed the magnitude of GSK2838232 boosting will be similar with the two CYP3A4 inhibitors. Results of this trial will support phase 2b evaluation in 2018.

### Pharmacokinetics of investigational influenza agents in multipart study

JNJ-64155806 (AL-794), an endonuclease inhibitor of influenza A and B with activity against strains resistant to neuraminidase inhibitors, demonstrated antiviral activity at doses of 50 to 150 mg twice daily in an influenza human challenge study in healthy volunteers.<sup>28</sup> This multipart study found that JNJ-64155806 was generally well tolerated

at doses below 600 mg twice daily.

Influenza remains one of the most serious public health challenges. There are more than 1 billion cases of influenza worldwide each year, resulting in approximately 5 million cases of severe illness and up to half a million deaths. Yet no agents are licensed for hospitalized patients with influenza. JNJ-64155806 is a prodrug and is rapidly converted to ALS-033719. This investigational agent has a protein binding-adjusted 90% effective concentration (EC90) of 41 ng/mL. It is a UGT and P-gp substrate, a moderate CYP enzyme inhibitor in vitro, and a weak OATP1B1 inhibitor in vitro.

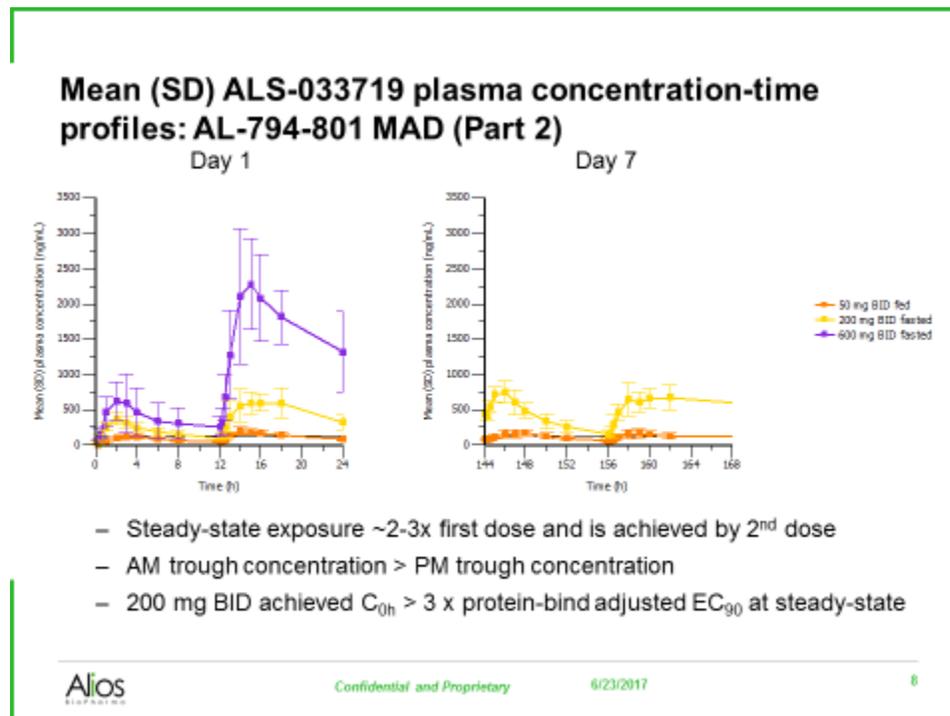
Researchers from the Janssen Pharmaceutical Companies conducted a four-part phase 1 study in healthy volunteers to assess the safety and pharmacokinetics of JNJ-64155806 (parts 1 to 3); and antiviral activity (part 4). Part 1 was a single-ascending dose (SAD) study of doses ranging from 50 to 2000 mg given fasted to 8 volunteers (6 active, 2 placebo) in each dosing cohort. Part 2 was a multiple-ascending dose (MAD) study of JNJ-64155806 at 50 mg twice daily with food or with 200 or 600 mg twice daily given fasted for 7 days to 8 volunteers (6 active, 2 placebo) in each dosing cohort. Part 3 tested a 450-mg dose with food in 8 volunteers (6 active, 2 placebo). Part 4 was an influenza challenge study involving two cohorts, each with 30 volunteers randomized to placebo or to 50 or 150 mg of JNJ-64155806 twice daily fasted for 5 days. Volunteers were inoculated with influenza virus and began treatment at day 4 regardless of PCR positivity for influenza

In study parts 1 and 3, all treatment-emergent adverse events were mild or moderate and included headache and dizziness (light-headedness). All volunteers receiving up to 1000 mg of JNJ-64155806 completed the study. There were no serious adverse events and no clinically significant lab abnormalities in these studies. In the MAD study (part 2), volunteers tolerated JNJ-64155806 well when taken at 50 mg with food or 200 mg fasted twice daily for 7 days. Volunteers did not tolerate JNJ-64155806 well when taken at 600 mg twice daily fasted: At that dose 1 volunteer developed two episodes of vasovagal syncope after the third dose, an adverse event judged related to JNJ-64155806. Dizziness affected 6 of 8 participants after the second 600-mg twice-daily dose.

In study parts 1 and 3, ALS-033719 pharmacokinetics were dose-proportional between 50 and 150 mg and less than dose-proportional between 150 and 1000 mg. A high-fat meal increased maximum concentration 3.6-fold and area under the concentration-time curve 3-fold.

In part 2, the multiple-ascending dose study, ALS-033719 reached steady-state exposure by the second dose at a concentration approximately 2 to 3 times the first-dose concentration (**Figure 14**). A dose of 200 mg twice daily achieved a predose

concentration (C<sub>0h</sub>) more than 3 times the protein-binding adjusted EC<sub>90</sub> at steady state.



**Figure 14.** A multiple-ascending dose study of the anti-influenza agent JNJ-64155806 (AL-794) showed that a dose of 200 mg twice daily achieved a trough concentration more than 3 times the protein binding-adjusted EC<sub>90</sub> at steady state. (Source: Thomas Kakuda, Alios BioPharma, and colleagues.<sup>28</sup>)

In the influenza human challenge study, volunteers tolerated JNJ-64155806 well when taken at doses that demonstrated antiviral activity, 50 to 150 mg twice daily.

The studies described here used an oral suspension. Janssen plans to develop an oral tablet and possibly an intravenous formulation.

### One- or two-drug antiretroviral regimens inhibitory in genital tract

One- or two-drug maintenance antiretroviral regimens achieved 50% inhibitory concentrations (IC<sub>50</sub>s) in the genital tract in an analysis of four minimal drug regimen strategies.<sup>29</sup> Seminal concentrations in men on minimal regimens were lower than in men taking standard triple therapy.

Interest in one- and two-drug antiretroviral maintenance regimens has grown because simpler combinations could lower toxicity, rates of drug-drug interactions, and cost. To test the potency and pharmacokinetics of one- and two-drug regimens, researchers in Orléans and Paris analyzed outcomes in patients randomized to begin one of four minimal regimens or to maintain standard triple therapy with two nucleos(t)ides (NRTIs)

plus a nonnucleoside, a boosted protease inhibitor, or an integrase inhibitor. All participants had maintained a viral load below 50 copies/mL for 12 months on their baseline regimen; they had taken standard therapy for a median of 4 years before entering this study.

1 Among patients randomized to a minimal regimen, 20 took dolutegravir monotherapy, 13 took tenofovir disoproxil fumarate/emtricitabine (TDF/FTC), 14 took unboosted atazanavir plus dolutegravir, and 11 took unboosted atazanavir plus two NRTIs. The control group included 14 patients taking dolutegravir plus abacavir/lamivudine (ABC/3TC) and 12 taking TDF/FTC plus a third antiretroviral. To measure trough concentrations after 6 months of treatment, researchers collected three sets of samples just before dosing: blood samples from everyone, semen samples from men, and vaginal lavage samples from women. They used ultrasensitive assays to measure HIV RNA and HIV DNA.

Plasma concentrations of individual antiretrovirals did not differ substantially between the minimal-regimen group and controls. Dolutegravir trough concentrations were higher when the integrase inhibitor was taken with unboosted atazanavir than when taken alone or with two NRTIs.

Vaginal trough concentrations of antiretrovirals usually did not differ significantly between the minimal-regimen group and controls, but again dolutegravir concentrations were highest with unboosted atazanavir. Median seminal trough concentrations were lower in the minimal-regimen group than in the standard-therapy controls (**Table 3**).

**Table 3.** Seminal trough concentrations with one- or two-drug regimens versus triple therapy

	Minimal-regimen median (ng/mL)	Interquartile range	Triple therapy median (ng/mL)	Interquartile range
TDF	46	7 to 315	259	17 to 380
FTC	25	12 to 337	109	54 to 392
Unboosted ATV	14	6 to 20	—	
DTG	43	13 to 119	78	27 to 116
ABC	—	—	19	15 to 23
3TC	11	—	455	160 to 760

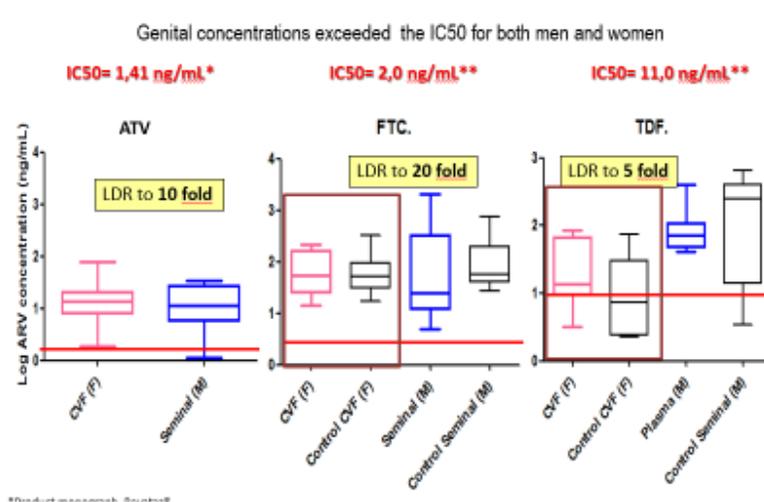
ABC, abacavir; ATV, atazanavir; DTG, dolutegravir; FTC, emtricitabine; TDF, tenofovir disoproxil fumarate; 3TC, lamivudine.

Source: Sandrine Lefevre, CHR Orléans, Orléans, and colleagues.<sup>29</sup>

However, genital concentrations in both men and women exceeded the IC50 for all individual antiretrovirals, except for abacavir levels in the triple-therapy group (median

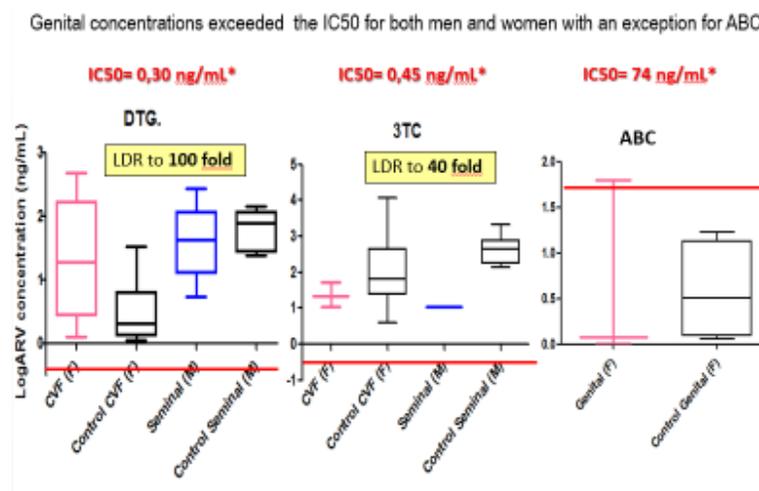
19 ng/mL) (**Figures 15 and 16**). Specifically, male and female genital concentrations were up to 10-fold higher than the 1.41 ng/mL IC<sub>50</sub> for atazanavir, up to 20-fold higher than the 2.0 ng/mL IC<sub>50</sub> for FTC, up to 5-fold higher than the 11.0 ng/mL IC<sub>50</sub> for TDF, up to 100-fold higher than the 0.30 ng/mL IC<sub>50</sub> for dolutegravir, and up to 40-fold higher than the 0.45 ng/mL IC<sub>50</sub> for 3TC.

### Genital ATV, FTC, and TNF concentrations with one- or two-drug antiretroviral regimens



**Figure 15.** Seminal and vaginal concentrations of atazanavir (ATV), emtricitabine (FTC), and tenofovir (TDF) exceeded the IC<sub>50</sub>. (Source: Sandrine Lefevre, CHR Orléans, Orléans, and colleagues.<sup>29</sup>).

### Genital DTG, 3TC, and ABC concentrations with one- or two-drug antiretroviral regimens



**Figure 16.** *Seminal and vaginal concentrations of dolutegravir (DTG) and lamivudine (3TC) but not abacavir (ABC) exceeded the IC50. CVF, cervicovaginal fluid. (Source: Sandrine Lefeuvre, CHR Orléans, Orléans, and colleagues.<sup>29</sup>).*

Preliminary virologic data indicate that two thirds of participants have undetectable HIV RNA and HIV DNA in the genital tract with ultrasensitive assays, while one third has residual viremia. The researchers aim to present full virologic results at the July 2017 International AIDS Conference in Paris.

## NOVEL ANTIVIRAL ANALYSES

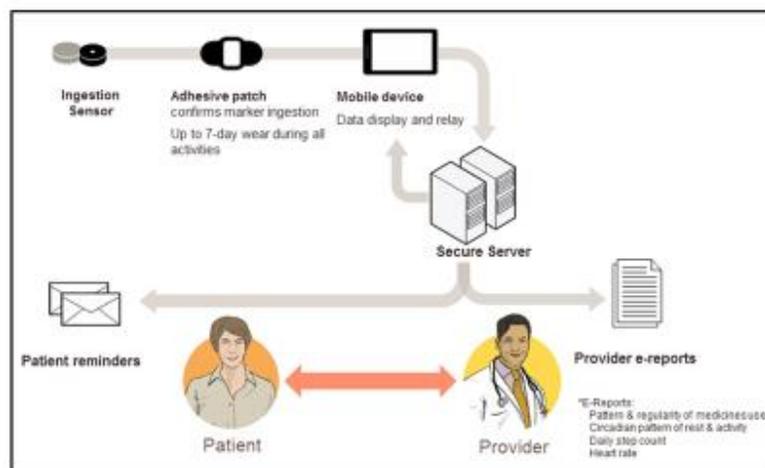
### Ingestible sensor tracks adherence in real time

A sensor chip added to a capsule containing tenofovir/emtricitabine (TDF/FTC) can track adherence in real time through a transmitting patch the user wears.<sup>30</sup> Co-encapsulating the ingestible sensor with TDF/FTC did not alter pharmacokinetics of the antiretrovirals.

Trials of TDF/FTC preexposure prophylaxis (PrEP) demonstrate the importance of steady adherence to protect users from HIV. Self-reporting and electronic pill bottle caps have their limits in gauging adherence. An FDA-cleared device may prove much more accurate and eliminate logistical challenges associated with common adherence measures, such as directly observed therapy and pill counts. The system relies on a 1 x 1 x 0.45-mm microchip that can be added to a medication capsule (**Figure 17**).

Eventually, the chip may be coformulated with the drug, but for this study the chip was added to TDF/FTC capsules. The user wears a 7-day adhesive patch that confirms chip ingestion. The patch relays ingestion data to the patient's mobile device via Bluetooth technology, which generates reports for providers and reminders for patients through a secure server.

### Drug ingestion-sensing system to track adherence



**Figure 17.** An ingestible microchip added to a medication capsule can record ingestion and relay that information via an adhesive patch worn by the user to track adherence. (Source: Nathan Hanan, University of California, San Diego, and colleagues.<sup>30</sup>)

Researchers from the University of California, San Diego and Stanford University tested the impact of the ingestible microchip on tenofovir (TFV) and FTC pharmacokinetics in 12 HIV-negative adults who took a capsule containing a Truvada tablet and the

ingestible sensor (IS-Truvada). After taking the capsule for 14 days, participants received an observed dose of IS-Truvada. They had pharmacokinetic samples drawn before dosing and 2, 4, 6, 8, and 24 hours after dosing. On day 15 participants took an observed dose of standard Truvada and had sampling 2 and 4 hours after ingestion. The researchers compared C<sub>2</sub> levels (a maximum concentration surrogate) and C<sub>4</sub> levels with IS-Truvada and standard Truvada.

Geometric mean ratios (GMR) for FTC in IS-Truvada versus standard Truvada indicated equivalence of C<sub>2</sub> (GMR 0.96, 90% confidence interval [CI] 0.87 to 1.12) and C<sub>4</sub> (GMR 0.94, 90% CI 0.90 to 1.04). For TFV in IS-Truvada versus standard Truvada, C<sub>2</sub> GMR was 1.04 (90% CI 0.89 to 1.16) and C<sub>4</sub> GMR was 0.99 (90% CI 0.87 to 1.12).

The researchers compared other pharmacokinetic values for FTC and tenofovir in IS-Truvada with values published in the literature for standard Truvada and found similar results for maximum concentration, time to maximum concentration, minimum concentration, 24-hour area under the concentration-time curve (AUC<sub>24</sub>), clearance, and terminal half-life. FTC AUC<sub>24</sub> values for IS-Truvada and standard Truvada were 10,916 and 10,700 ng\*h/mL. Respective TFV values were 2706 and 2800 ng\*h/mL.

Gilead Sciences is currently conducting dissolution studies of coencapsulated IS-Truvada. Research will also evaluate user acceptance of the transmitting patch.

### Computer modeling identifies long-acting NRTI candidates

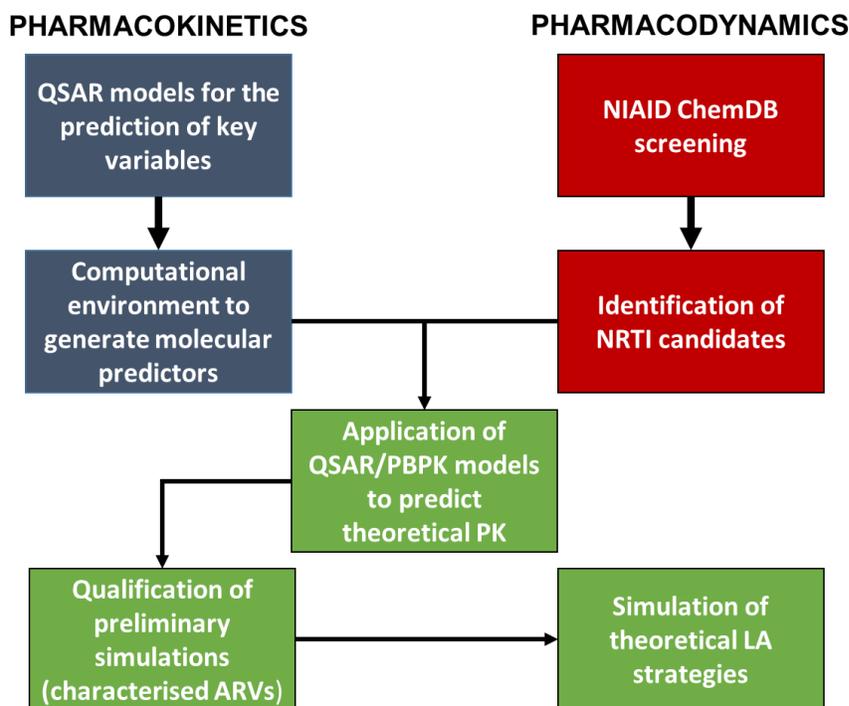
A novel in silico model incorporating pharmacokinetics with structure-activity relationship identified several nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) for possible development as monthly or quarterly antiretrovirals.<sup>31</sup>

Long-acting antiretrovirals for treatment and prevention could greatly simplify dosing to improve adherence and reduce costs. Because only a handful of long-acting antiretrovirals have entered clinical trials, researchers from the University of Liverpool aimed to identify additional candidates to help construct multidrug long-acting combinations. Because of the complexity of identifying such candidates, they explored the value of computer-based simulations in this work.

The Liverpool team began their search by culling NRTI candidates from the US Division of AIDS Anti-HIV/OI/TB Therapeutics Database (<http://chemdb.niaid.nih.gov>). They narrowed their list by selecting candidates with the highest therapeutic index (effective concentration/toxicity threshold).

To predict the pharmacokinetics of these candidates, they integrated quantitative structure-activity relationship (QSAR) modeling into physiologically based pharmacokinetic (PBPK) modeling (**Figure 18**). QSAR defines a mathematical relationship between biological activity of a molecule and its physicochemical

properties. The researchers integrated QSAR predictions of five variables into the PBPK model: blood-to-plasma ratio, fraction unbound, plasma stability, renal clearance, and volume of distribution.



**Figure 18.** Researchers aimed to identify long-acting NRTI candidates with this strategy combining quantitative structure-activity relationship (QSAR) modeling into physiologically based pharmacokinetic (PBPK) modeling. (Source: Marco Siccardi, University of Liverpool, and colleagues.<sup>31</sup>)

The researchers presented data on seven NRTI candidates, including two pyrimidine nucleosides, one pyrimidine nucleotide, two triazines, and two purine nucleosides. The purine nucleosides are EFdA (4'-ethynyl-2'-fluoro-2'-deoxyadenosine) and ECIdA (9H-Purin-6-amine). The Division of AIDS database numbers for these compounds are 343654, 105173, 343656, 168640, 108530, 113361, and 212706.

The Liverpool investigators reported four values for each compound: therapeutic index, 50% effective concentration (EC<sub>50</sub>) (ng/mL), trough concentration (ng/mL), and C<sub>trough</sub>/EC<sub>50</sub> ratio. They reported the last two values for both monthly dosing and quarterly dosing. For EFdA, for example, the therapeutic index is 1000000, EC<sub>50</sub> 0.03, C<sub>trough</sub> 73.2 for monthly dosing and 25.6 for quarterly dosing, and C<sub>trough</sub>/EC<sub>50</sub> ratio 2495.3 for monthly dosing and 873.7 for quarterly dosing.

Although the QSAR/PBPK predictions will require confirmatory experimental studies for a more precise prediction of pharmacokinetics, the researchers propose that this QSAR/PBPK approach can be used to set priorities for further research. They noted

that the already-identified candidates can now be explored through advanced reformulation strategies. The Liverpool team suggested that “this rational approach for the selection of suitable candidates may prove useful to support the development of additional long-acting formulations across multiple antiretroviral classes.”

### **Model suggests lymph node drug penetration could explain virologic failures**

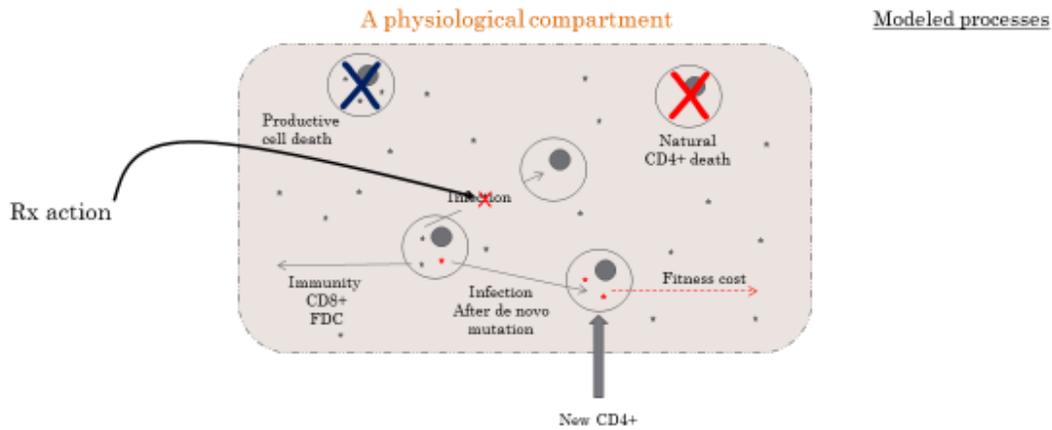
A mathematical model to predict virologic failure with efavirenz or darunavir regimens determined that limited antiretroviral lymph node penetration may account for most cases of virologic failure.<sup>32</sup> Researchers from the University of Montreal and McGill University believe the model has application in guiding treatment strategies and in drug discovery.

Clinical trial results remain the gold standard for predicting outcomes with antiretroviral therapy. But difficulties persist in predicting individual patient outcomes, the Montreal team noted, when specific regimens or sources of variability are not considered in clinical trials. Such variables may include patient-specific drug adherence, pharmacokinetics, pharmacodynamics, and immune response.

To address this problem, the researchers aimed to develop a mathematical model that predicts virologic failure by incorporating the most important processes linking antiretroviral use to viral load—not by considering every variable that may affect response. The proposed model assesses antiretroviral impact in individual physiological compartments, such as lymph nodes (**Figure 19**). Variables in this model include the number of CD4 cells susceptible to HIV infection, the number of CD4 cells producing virions, and the number of virions.

## METHODS

### MODEL OVERVIEW



Equations can describe how this system will evolve over time.

**Figure 19.** A mathematical model to predict virologic failure focuses on processes in individual physiological compartments, such as lymph nodes. (Source: Steven Sanche, University of Montreal, and colleagues.<sup>32</sup>)

To complete the model, the Montreal investigators considered two hypotheses:

1. Most cells within the host that are susceptible to infection are as exposed to drugs as **peripheral blood mononuclear cells (PBMCs)**.
2. There is at least one physiological compartment harboring a significant number of infection events that is much less exposed to the drug, and this is the **lymph node**.

All parameter values for the lymph node model are determined a priori. These values include plasma protein binding, lymph node drug penetration, viral replication rate in vivo, quasispecies variation in 50% inhibitory concentration, and a refined adherence representation.

The investigators applied the model to three regimens: efavirenz monotherapy, Atripla (efavirenz coformulated with tenofovir/emtricitabine), and darunavir/ritonavir. For efavirenz monotherapy, modeling considering hypothesis 1 predicted little to no resistance if most cells are as exposed to the drugs as PBMCs; the resulting virologic failure rate is 0%. Modeling considering hypothesis 2 predicted a failure rate of 90% with resistance in lymph nodes (indicating poor drug penetration), a prediction in better agreement with clinical observations. When compared with the observed relationship between adherence to Atripla and virologic failure, model predictions based on hypothesis 2 were also in much better agreement. Finally, hypothesis 1 could not generate virologic failure with boosted darunavir, while hypothesis 2 predicted that 15%

of patients would experience failure, closer to the reported rate (14%).

The Montreal team concluded that antiretroviral lymph node penetration may account for most cases of virologic failure with resistance. Insufficient antiretroviral concentrations in one or more compartments harboring a large number of infected CD4 cells, especially when patients deviate from their regimens, could allow viral replication of some viral strains, leading to resistance. They cautioned that this modeling approach remains limited by the availability of lymph node penetration data and by potential antiretroviral impact in other sanctuary sites.

The researchers proposed that their model may have applications in predicting virologic response for patients with differing (1) adherence patterns, (2) drug disposition, (3) viral quasispecies susceptibility to drugs, (4) mutations, and (5) viral growth rate during rebounds. They suggested the model may be adapted to predict virologic failure in specific patients, to guide clinical treatment strategies, and to aid the drug-discovery process.

#### **For 34 antivirals, 547 DDI studies and 922 label recommendations**

Analysis of FDA labels for 34 antivirals licensed from 1998 through 2015 found those drugs had undergone 547 clinical drug-drug interaction (DDI) studies contributing to 922 DDI label recommendations.<sup>33</sup> Almost 60% of label recommendations were based on clinical DDI studies.

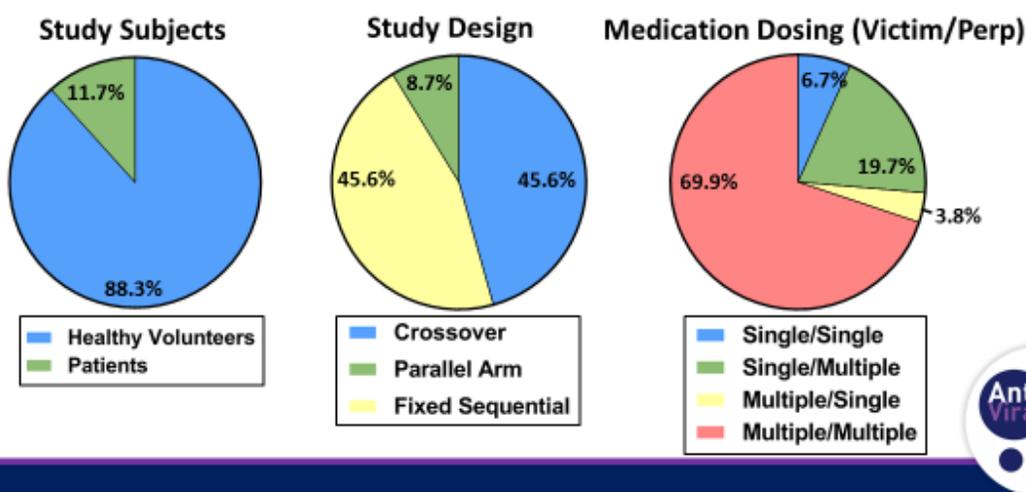
Unaddressed DDIs can lead to adverse events resulting in morbidity, mortality, and healthcare expenditures. A team from Purdue University and the FDA noted prior working showing that DDIs requiring clinical management develop in up to 41% of patients with HIV infection.<sup>34</sup> To get a better understanding of antiviral DDIs listed in FDA labels, these investigators assessed the basis for DDI recommendations for all antivirals licensed from 1998 through 2015, identified via the FDA drug database (<https://www.accessdata.fda.gov/scripts/cder/drugsatfda/>).

The researchers identified 34 approved antivirals that had 992 DDI label recommendations—27.1 recommendations per approval. For 34 approved cardiovascular agents, in contrast, there were 449 DDI label recommendations—13.2 per approval. For 37 anti-infective agents there were 363 DDI recommendations—9.8 per approval.

Among the 992 antiviral DDI label recommendations, 59.3% were based on clinical DDI studies, 39.8% on predictions based on metabolic pathways, and 0.9% on clinical experience. No recommendations were based on population pharmacokinetic models or physiologically based pharmacokinetic models. For these 992 antiviral DDI recommendations, one third (35.3%) specified no dose adjustment. The next most frequent recommendations were contraindications (20.8%) or “use with caution”

(20.6%), followed by “not recommended” (13.3%) and a dose-adjustment recommendation (10%).

## Distributions of Trial Design Elements in DDI Studies



**Figure 20.** For antivirals approved between 1998 and 2015, clinical studies that informed DDI labelling recommendations usually involved healthy volunteers, with equal proportions of studies using a parallel arm design or a fixed-sequence design. (Source: Tyler Shugg, Purdue University, and colleagues.<sup>33</sup>)

Among the 547 clinical DDI studies that informed DDI recommendations, 93% occurred before initial approval of the drug. Of these clinical DDI studies, 88.3% involved healthy volunteers and 11.7% enrolled patients with the condition for which the drug developer was seeking approval (**Figure 20**). Two thirds of these studies (65.8%) involved CYP enzymes, 37.5% drug transporters, and 28.7% both CYP enzymes and transporters. The most frequently involved enzymes or transporters were CYP3A, OATP1B1, OATP1B3, and P-gp.

Clinical DDI studies that found severe changes in drug exposure (geometric mean ratio for C<sub>max</sub> and/or AUC below 0.5 or above 2.0) informed actionable label recommendations in 77.9% of cases. Antiviral DDI studies proved more likely than studies of any other therapeutic class to have GMR changes for C<sub>max</sub> or AUC outside the 20% no-effect boundary (0.8 to 1.25).

### CYP3A induction data can predict other CYP and transporter changes

Analysis of pharmacokinetic data from a study of sofosbuvir, rifampin, carbamazepine, rifabutin, and probe drugs for CYP3A, P-gp, OATP, OATP/BCRP, CP2C9, and CYP1A2 determined that CYP3A induction data “can be leveraged to accurately predict induction of other PXR-regulated [CYP]P450s or transporters.”<sup>35</sup> As a result, Gilead Science

researchers proposed that the number of discrete induction studies needed during development of new drugs may be decreased by analyzing these induction relationships.

The direct-acting antiviral (DAA) sofosbuvir is sensitive to P-gp efflux in vivo but not to CYP3A metabolism. Carbamazepine and rifabutin are pregnane X receptor (PXR) agonists that induce CYP3A in vivo but have an incompletely understood impact on the transporter P-gp. The Gilead team conducted this study to determine whether carbamazepine or rifabutin decreases sofosbuvir exposure. They also aimed to learn whether CYP3A induction data can be interpreted to predict induction of transporters like P-gp.

Data from a rifampin dose-escalation study indicate that P-gp induction (measured using dabigatran etexilate) is always one drug-drug interaction (DDI) category (weak, moderate, strong) less than CYP3A induction (measured using midazolam). Data from this study also indicate that OATP induction and CYP2C9 induction are one DDI category less than CYP3A induction when PXR is the primary nuclear receptor being agonized. The investigators used those relationships to analyze a new pharmacokinetic study of the effect of carbamazepine or rifabutin on probe drugs and sofosbuvir.

The sofosbuvir analysis involved 44 healthy volunteers who took sofosbuvir (400 mg) plus a cocktail of CYP/transporter probe drugs on days 1 through 9, then either carbamazepine (escalated to 300 mg twice daily) on days 10 through 35 or rifabutin (300 mg once daily) on days 10 through 29. Volunteers again received sofosbuvir plus the probe cocktail on days 27 through 35 of the carbamazepine study and on days 21 through 29 of the rifabutin study. The probe drugs were dabigatran etexilate (75 mg, P-gp probe), pravastatin (20 mg, OATP probe), rosuvastatin (10 mg, OATP/BCRP probe), and midazolam (2 mg, CYP3A probe) plus tolbutamide (500 mg, CYP2C9 probe) plus caffeine (200 mg, CYP1A2 probe).

Analysis of pharmacokinetic data from these interaction studies supported the following conclusions:

- P-gp induction by carbamazepine and rifabutin is predicted by the rifabutin CYP3A-P-gp relationship.
- Carbamazepine-mediated OATP induction is underpredicted by the rifabutin CYP3A-OATP relationship, probably because of involvement of non-PXR-dependent induction.
- The effect of rifampin, carbamazepine, or rifabutin on sofosbuvir is predicted by the rifampin CYP3A-P-gp relationship.

The Gilead team proposed carbamazepine and rifabutin induction rankings for metabolizing enzymes and P-gp, as well as its inducing impact on sofosbuvir (**Table 4**).

They suggested that their findings could lead to (1) more informed label recommendations for drug transport substrates and inducers and (2) a decreased number of DDI studies during drug development by better leveraging of available data.

**Table 4.** Carbamazepine and rifabutin induction categorization

	CYP3A	P-gp	OATP	CYP2C9	CYP1A2	Sofosbuvir
CBZ	Moderate	Weak	Moderate	Weak	Weak	Weak
RBT	Moderate	Weak	None	Weak	None	Weak

Source: Justin Lutz and Brian Kirby, Gilead Sciences, and colleagues.<sup>35</sup>

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