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Jason J. Schafer, PharmD, MPH, BCPS, AAHIVP

Neha S Pandit

Agnes Cha

Emily Huesgen

Melissa Badowski

*See next page for additional authors*

## Authors

Jason J. Schafer, PharmD, MPH, BCPS, AAHIVP; Neha S Pandit; Agnes Cha; Emily Huesgen; Melissa Badowski; Elizabeth M Sherman; Jennifer Cocohoba; Ayako Shimada; and Scott W Keith

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MAJOR ARTICLE

# Incidence and Severity of Drug Interactions Before and After Switching Antiretroviral Therapy to Bictegravir/Emtricitabine/Tenofovir Alafenamide in Treatment-Experienced Patients

**Jason J. Schafer,[1] Neha S. Pandit,[2] Agnes Cha,[3,a] Emily Huesgen,[4] Melissa Badowski,[5] Elizabeth M. Sherman,[6,7] Jennifer Cocohoba,[8] Ayako Shimada,[9] and Scott W. Keith[9]**

[1]Department of Pharmacy Practice, Jefferson College of Pharmacy, Thomas Jefferson University, Philadelphia, Pennsylvania, USA, [2]Department of Pharmacy Practice and Science, University of Maryland Baltimore School of Pharmacy, Baltimore, Maryland, USA, [3]Brooklyn Hospital Center, Brooklyn, New York, USA, [4]Department of Pharmacy Practice, Indiana University Health, Indianapolis, Indianapolis, USA, [5]Section of Infectious Diseases Pharmacotherapy, Department of Pharmacy Practice, University of Illinois at Chicago, College of Pharmacy, Chicago, Illinois, USA, [6]Department of Pharmacy Practice, College of Pharmacy, Nova Southeastern University, Fort Lauderdale, Florida, USA, [7]Division of Infectious Diseases, Memorial Healthcare System, Hollywood, Florida, USA, [8]Department of Clinical Pharmacy, University of California San Francisco School of Pharmacy, San Francisco, California, USA, and [9]Division of Biostatistics, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania, USA

***Background.*** Switching antiretroviral therapy (ART) in people with HIV (PWH) can influence their risk for drug–drug interactions (DDIs). The purpose of this study was to assess changes in the incidence and severity of DDIs among PWH who switched their ART to bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF).

***Methods.*** This was a multicenter retrospective cohort study of PWH on ART and at least 1 concomitant medication (CM) who switched to BIC/FTC/TAF between 3/2018 and 6/2019. Using the University of Liverpool's HIV Drug Interaction Database, 2 DDI analyses were performed for each patient. The first assessed patients' preswitch ART regimens with their CM list. The second assessed the same CM list with BIC/FTC/TAF. Each ART-CM combination was given a score of 0 (no or potential weak interaction), 1 (potential interaction), or 2 (contraindicated interaction). A paired *t* test analyzed changes in total DDI scores following ART switches, and linear regression examined factors contributing to DDI score reductions.

***Results.*** Among 411 patients, 236 (57%) had at least 1 DDI present at baseline. On average, baseline DDI scores (SD) were 1.4 (1.8) and decreased by 1 point (95% CI, −1.1 to −0.8) after patients switched to BIC/FTC/TAF ($P < .0001$). After adjusting for demographics, baseline ART, and CM categories, switching to BIC/FTC/TAF led to significant DDI score reductions in patients receiving CMs for cardiovascular disease, neurologic/psychiatric disorders, chronic pain, inflammation, gastrointestinal/urologic conditions, and conditions requiring hormonal therapy.

***Conclusions.*** Treatment-experienced PWH eligible to switch their ART may experience significant declines in number and severity of DDIs if switched to BIC/FTC/TAF.

**Keywords.** ART; bictegravir; drug interactions; HIV; switch.

People with HIV (PWH) often have or develop other chronic medical conditions as they age and receive multiple medications in addition to their antiretroviral therapy (ART) [1]. This increases their risk for polypharmacy and its complications, including medication nonadherence, HIV treatment failure, adverse drug events, and drug–drug interactions (DDIs) [2–6]. In virally suppressed treatment-experienced PWH, switching ART can simplify treatment, improve tolerability, and limit long-term toxicity. It can also influence the presence of DDIs in those receiving concomitant medications (CMs) [7–9].

Given their efficacy, safety, and tolerability, integrase inhibitor–based regimens are preferred therapy options and are commonly used to simplify ART in treatment-experienced patients [9–11]. Among the integrase inhibitors, bictegravir has few DDIs and is available in a single-tablet regimen with tenofovir alafenamide and emtricitabine (BIC/FTC/TAF) [12]. The extent to which switching ART to BIC/FTC/TAF can influence the presence of DDIs in treatment-experienced PWH is unclear. The purpose of this study was to assess changes in the incidence and severity of DDIs after switching to BIC/FTC/TAF.

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[a]Present affiliation: Clinical Pharmacy Ambulatory Care Manager, Northwell Health, New Hyde Park, New York, USA

Correspondence: Jason J. Schafer, PharmD, MPH, Jefferson College of Pharmacy, Thomas Jefferson University, 901 Walnut Street, Suite 901 Philadelphia, Pa 19147 (jason.schafer@jefferson.edu).

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## METHODS

This was a multicenter retrospective cohort study of adult PWH on ART and at least 1 CM who switched to BIC/FTC/TAF between 3/2018 and 6/2019 in the outpatient setting. Demographic data including age, sex, and race were extracted from medical records of eligible patients, along with their medications, duration of HIV infection, duration of ART, number of previous ART regimens, preswitch HIV RNA, and their reason for switching to BIC/FTC/TAF. Institutional review board approval was obtained before data collection at each study center.

To assess the incidence and severity of DDIs with CMs before and after each patient's switch to BIC/FTC/TAF, the University of Liverpool's HIV Drug Interaction Database was used [13]. Two DDI analyses were performed for each patient. The first assessed a patient's preswitch ART regimen with the list of active medications located in their electronic medical record on the day they switched their ART. The second assessed the same CM list with BIC/FTC/TAF. Each ART-CM combination was given a numerical score that corresponded to the DDI categories listed in the University of Liverpool database. These were scores of 0 (no or potential weak interaction), 1 (potential interaction), or 2 (contraindicated interaction). Total DDI scores for each patient, both before and after switching to BIC/FTC/TAF, were then calculated.

A paired *t* test was used to analyze changes in DDI scores following ART switches, and a linear regression model was used to examine factors contributing to DDI score reductions. In addition, McNemar's test was used to analyze changes in the proportion of patients with at least 1 DDI before and after switching to BIC/FTC/TAF. Covariates in the regression model included patient demographics, viral suppression status, and baseline ART. To analyze the influence of CMs in the regression model, each medication was placed into 1 of the following categories according to its therapeutic indication: cardiovascular, antihyperglycemic, anti-inflammatory, anti-infective, chronic pain, neurologic/psychiatric, gastrointestinal/urologic, hormonal therapy, or polyvalent supplements (Table 1). All statistical analyses were performed with SAS 9.4 (SAS Institute Inc., Cary, NC, USA) at a significance level of .05.

## RESULTS

A total of 411 patients met study criteria and were included in the analysis (Table 2). The majority were African American (70.6%) and male (61.6%), with a mean age of 51 years. Patients had been living with HIV and receiving ART for a median of 14 and 10 years, respectively. The majority were receiving regimens containing either dolutegravir (37%) or elvitegravir (29.4%) plus 2 nucleoside reverse transcriptase inhibitors before switching to BIC/FTC/TAF. Most were also receiving at least 5 CMs (56.9%). The most common baseline NRTI combinations were tenofovir disoproxil fumarate or TAF plus FTC (72%) and abacavir plus lamivudine (26%). The most commonly documented reasons for switching to BIC/FTC/TAF were to improve long-term safety (23.6%), reduce regimen complexity (16.8%), and mitigate DDIs (14.1%).

Of the 411 patients analyzed, 236 (57%) had at least 1 of the 552 DDIs identified at baseline. The majority of baseline DDIs had scores of 1 (497/552, 90%). Those with scores of 2 (55/552, 10%) were most commonly the result of pharmacokinetic "boosting" agents combined with either corticosteroids (30/55, 54.5%), quetiapine (7/55, 12.7%), clopidogrel (5/55, 9.1%), or direct oral anticoagulants (3/55, 5.5%). Rilpivirine used in combination with proton pump inhibitors (7/55, 12.7%) was also common. After switching to BIC/FTC/TAF, only 136/411 (33%)

**Table 1. Concomitant Medications of Study Participants and Their Corresponding Categories**

| | |
|---|---|
| Cardiovascular | Apixaban, amiodarone, amlodipine, atenolol, atorvastatin, clopidogrel, diltiazem, digoxin, eltrombopag, hydralazine, metoprolol, nifedipine, pravastatin, rivaroxaban, rosuvastatin, simvastatin, sotolol, vorapaxar, valsartan, verapamil, warfarin |
| Antihyperglycemic | Glipizide, metformin, liraglutide, sitagliptin |
| Anti-inflammatory | Aspirin, budesonide (inhaled/nasal), celecoxib, ciclesonide (nasal), dexamethasone (systemic), diclofenac, fluticasone (inhaled/nasal), hydrocortisone oral, ibuprofen, meloxicam, mometasone (inhaled/nasal), methylprednisolone (injections), naproxen, prednisone (systemic), triamcinolone (inhaled/nasal) |
| Chronic pain | Fentanyl, hydrocodone, morphine, lidocaine, oxycodone, tizanidine |
| Anti-infective | Acyclovir, atovaquone, clindamycin, doxycycline, fluconazole, itraconazole, ketoconazole, trimethoprim/sulfamethoxazole, voriconazole, valacyclovir |
| Hormonal therapy | Calcifediol, cholecalciferol, estradiol injection, ethinyl estradiol (oral), ethinyl estradiol/norelgestromin (transdermal), norgestimate (oral), levothyroxine, testosterone |
| Neurologic/psychiatric | Alprazolam, amitriptyline, aripiprazole, bupropion, buspirone, clonazepam, diazepam, divalproex, escitalopram, fluoxetine, lurasidone, mirtazapine, nortriptyline, paroxetine, phenytoin, quetiapine, risperidone, sertraline, topiramate, trazodone, valproic acid, zolpidem |
| Gastrointestinal/urologic | Alfuzosin, antacids, finasteride, loperamide, omeprazole, pantoprazole, ranitidine, sildenafil, tamsulosin, tadalafil |
| Polyvalent cation supplements | Multivitamins, calcium supplements, iron supplements |
| Other | Hydroxyzine, methamphetamine, salmeterol |

**Table 2. Descriptive Summary of Baseline Characteristics (n = 411)**

| | | All (n = 411) |
|---|---|---|
| Site, No. (%) | University of Maryland, Baltimore | 100 (24.3) |
| | Thomas Jefferson University Hospital | 95 (23.1) |
| | The Brooklyn Hospital | 61 (14.8) |
| | Indiana University LifeCare | 60 (14.6) |
| | University of Illinois at Chicago | 40 (9.7) |
| | Memorial Healthcare System | 35 (8.5) |
| | University of California, San Francisco | 20 (4.9) |
| Age, mean (SD) | | 51.3 (12.4) |
| Gender, No. (%) | Male | 253 (61.6) |
| | Female | 151 (36.7) |
| | Transgender female | 7 (1.7) |
| Race, No. (%) | Black/African American | 290 (70.6) |
| | White | 75 (18.2) |
| | Hispanic/Latinx | 36 (8.8) |
| | Asian | 8 (1.9) |
| | Native Hawaiian/Other Pacific Islander | 2 (0.5) |
| No. of years with HIV diagnosis, median (Q1, Q3)[a] | | 14.0 (8.0, 22.0) |
| Total No. of years on ART, median (Q1, Q3)[b] | | 10.0 (6.0, 15.0) |
| No. of previous ART regimens, No. (%)[c] | 1–3 | 214 (52.1) |
| | 4–6 | 60 (14.6) |
| | ≥7 | 11 (2.7) |
| Viral suppression (HIV RNA <200 copies/mL), No. (%)[d] | Yes | 324 (78.8) |
| | No | 52 (12.7) |
| Switch reason, No. (%)[e] | Long-term safety | 97 (23.6) |
| | Complexity | 69 (16.8) |
| | Other | 66 (16.1) |
| | Drug interactions | 58 (14.1) |
| | Side effects | 45 (10.9) |
| | Not documented | 36 (8.8) |
| | Toxicity | 14 (3.4) |
| | Virologic failure | 5 (1.2) |
| | Cost | 2 (0.5) |
| Polypharmacy (≥5 concomitant medications), No. (%) | Yes | 234 (56.9) |
| | No | 177 (43.1) |
| No. of concomitant medications, median (Q1, Q3) | | 5.0 (3.0, 9.0) |
| No. of concomitant medications, No. (%) | 0 | 7 (1.7) |
| | 1–4 | 172 (41.8) |
| | 5–9 | 141 (34.3) |
| | 10–14 | 66 (16.1) |
| | 15–19 | 16 (3.9) |
| | ≥20 | 9 (2.2) |
| Baseline ART regimen, No. (%) | Dolutegravir plus 2 NRTIs | 152 (37) |
| | Elvitegravir/cobicistat plus 2 NRTIs | 121 (29.4) |
| | Boosted PI plus 2 NRTIs | 59 (14.4) |
| | Efavirenz plus 2 NRTIs | 34 (8.3) |
| | Rilpivirine plus 2 NRTIs | 29 (7.1) |
| | Nevirapine plus 2 NRTIs | 4 (1.0) |
| | Dolutegravir plus a boosted PI and 2 NRTIs | 4 (1.0) |
| | Dolutegravir plus rilpivirine | 3 (0.7) |
| | Elvitegravir/cobicistat plus a PI and 2 NRTIs | 2 (0.5) |
| | 3 NRTIs | 2 (0.5) |
| | Etravirine plus a boosted PI and 2 NRTIs | 1 (0.2) |

Abbreviations: ART, antiretroviral therapy; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

[a]Data not available for 51 subjects.

[b]Data not available for 144 subjects.

[c]Data not available for 126 subjects.

[d]Data not available for 35 subjects.

[e]Data not available for 19 subjects.

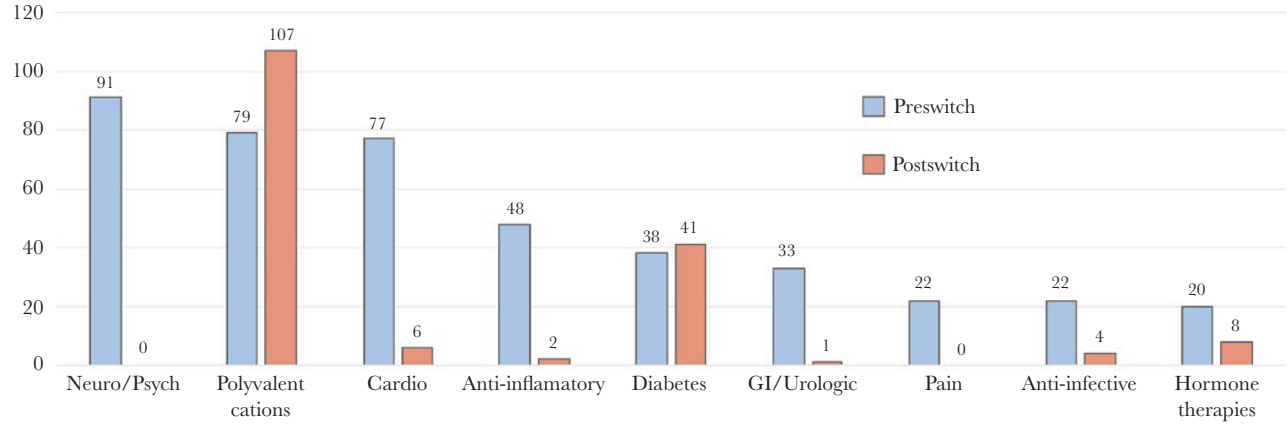


**Figure 1.** Subjects with at least 1 DDI between their ART and selected CM categories pre- and postswitch. Abbreviations: ART, antiretroviral therapy; CM, concomitant medication; DDI, drug–drug interaction; GI, gastrointestinal.

patients continued to have at least 1 DDI ($P < .0001$). Declines in DDIs were observed for nearly all CM categories (Figure 1). The total number of DDIs declined to 188, almost all of which had a score of 1 (187/188, 99.5%); these were most commonly the result of BIC/FTC/TAF used in combination with either polyvalent cation supplements (125/188, 66.5%) or metformin (45/188, 23.9%).

In terms of total DDI scores, patients had a median score (interquartile range) of 1 (0–2) or an average (SD) of 1.4 (1.8) at baseline and experienced a 1-point reduction (95% CI, –1.1 to –0.8) after switching to BIC/FTC/TAF ($P < .0001$). In the regression model, DDI score reductions were not associated with patient demographics, viral suppression status, or baseline ART, but were significantly associated with patient CMs (Table 3). For instance, patients receiving cardiovascular medications experienced an average DDI score reduction of 1.42 (95% CI, –1.64 to –1.19; $P < .0001$) after switching to BIC/FTC/TAF. Similar score reductions were associated with neurologic/psychiatric medications, gastrointestinal/urologic medications, hormonal therapies, and medications for chronic pain. The largest score reductions were associated with anti-inflammatory medications (–1.9; 95% CI, –2.14 to –1.65; $P < .0001$). The only CMs that were not associated with DDI score reductions were polyvalent cation supplements and medications for diabetes.

**Table 3. Linear Regression for the Difference of DI Scores (Post–Pre; n = 376[a])**

| Variable | Estimate | 95% CI | *P* Value |
|---|---|---|---|
| Intercept (ref: age 51 y and Black/AA) | 0.38 | (0.01 to 0.75) | **.05** |
| Age (per year) | 0.00 | (0.00 to 0.01) | .13 |
| White | –0.17 | (–0.36 to 0.02) | .08 |
| Other race (Hispanic/Latino, Asian, Native Hawaiian/other Pacific Islander) | 0.05 | (–0.18 to 0.29) | .66 |
| Viral suppression (yes) | –0.17 | (–0.38 to 0.04) | .11 |
| Dolutegravir-based ART (yes) | –0.18 | (–0.50 to 0.15) | .28 |
| Elvitegravir-based ART (yes) | 0.00 | (–0.34 to 0.34) | .00 |
| NNRTI-based ART (yes) | 0.23 | (–0.11 to 0.57) | .19 |
| PI-based ART (yes) | –0.03 | (–0.37 to 0.32) | .89 |
| Interactions between the patient's ART and cardiovascular medications at baseline (yes) | –1.42 | (–1.64 to –1.19) | **<.0001** |
| Interactions between the patient's ART and hyperglycemic medications at baseline (yes) | 0.02 | (–0.23 to 0.28) | .85 |
| Interactions between the patient's ART and anti-inflammatory medications at baseline (yes) | –1.90 | (–2.14 to –1.65) | **<.0001** |
| Interactions between the patient's ART and pain medications at baseline (yes) | –1.49 | (–1.85 to –1.13) | **<.0001** |
| Interactions between the patient's ART and anti-infectives at baseline (yes) | –1.05 | (–1.38 to –0.72) | **<.0001** |
| Interactions between the patient's ART and hormonal therapies at baseline (yes) | –0.82 | (–1.16 to –0.48) | **<.0001** |
| Interactions between the patient's ART and neurologic and psychiatric medications at baseline (yes) | –1.52 | (–1.72 to –1.32) | **<.0001** |
| Interactions between the patient's ART and gastrointestinal and urologic medications at baseline (yes) | –1.51 | (–1.79 to –1.24) | **<.0001** |
| Interactions between the patient's ART and polyvalent supplements at baseline (yes) | –0.02 | (–0.21 to 0.17) | .82 |
| Interactions between the patient's ART and other medications at baseline (yes) | –0.86 | (–1.27 to –0.45) | **<.0001** |

Abbreviations: ART, antiretroviral therapy; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

P < .05 is considered significant.

[a]This analysis was performed for all patients who had evidence of their viral suppression status (yes or no) at the time of their ART switch.

## DISCUSSION

We observed significant declines in the incidence and severity of DDIs among treatment-experienced PWH who switched their ART to BIC/FTC/TAF. Importantly, these declines were significantly associated with a patient's CMs rather than their demographics, viral suppression status, or baseline ART. DDI declines also occurred among CMs representing a broad range of comorbid conditions. This is important because PWH have a disproportionate risk for developing multiple medical conditions, experiencing polypharmacy, and incurring DDIs [1–6, 14].

The majority of subjects in this study were experiencing polypharmacy and receiving CMs for conditions common to patients aging with HIV [15]. These included cardiovascular disease, chronic pain, gastrointestinal diseases, and urologic disorders. Consistent with prior studies, CMs for these conditions were common sources of DDIs for patients at baseline in our study [14, 16, 17]. DDI declines were associated with CMs in these medication categories when patients switched to BIC/FTC/TAF. These DDI declines might have been more substantial in an elderly patient population, because as age progresses, polypharmacy and drug interactions among PWH increase substantially [14]. In addition, patients in this study were also frequently receiving CMs for conditions common to all PWH such as neurologic disease, psychiatric illness, co-infections, and conditions requiring hormonal therapy. When patients switched to BIC/FTC/TAF, DDI declines were also associated with CMs in these medication categories. The only CM categories not associated with DDI declines were diabetes and polyvalent cation supplements. This finding may have been expected, as most subjects were on dolutegravir or elvitegravir at baseline, which also interact with metformin and supplements containing polyvalent cations. Overall, these findings suggest that if patients are able to switch their ART to BIC/FTC/TAF, they may experience significant declines in DDIs when they are also receiving CMs for medical conditions common to all PWH.

In terms of DDI severity, corticosteroids were the most common source of contraindicated DDIs for patients at baseline. These interactions were the result of corticosteroids used in combination with pharmacokinetic boosting agents such as ritonavir and cobicistat. Pharmacokinetic boosting agents are strong cytochrome P450 inhibitors that can elevate corticosteroid concentrations, leading to adrenal suppression and Cushing's syndrome [18]. Boosting agents also led to contraindicated DDIs in this study with certain antithrombotic and antipsychotic medications by inhibiting their cytochrome P450 metabolism. In prior studies, these types of contraindicated interactions increased a person's risk for experiencing significant toxicity requiring hospitalization [19, 20]. Because BIC/FTC/TAF is an unboosted regimen, switching not only reduced the total number of DDIs for patients in this study, but also removed nearly all contraindicated DDIs that may otherwise have resulted in patient harm.

The low incidence of contraindicated DDIs with BIC/FTC/TAF was also recently demonstrated in a study of nearly 5000 German PWH [21]. Investigators in this study also utilized the University of Liverpool Drug Interaction Database to evaluate potential DDIs among patients receiving BIC/FTC/TAF and at least 1 CM. Overall, the incidence of DDIs was low, with several common medication classes posing no risk for DDIs with BIC/FTC/TAF including anti-ulcerants, antirheumatics, and lipid-lowering agents. Similar to our study, contraindicated combinations with BIC/FTC/TAF in the German cohort were rare (<0.25%) and the result of metabolism-inducing medicines such as carbamazepine, oxcarbazepine, and rifampicin in the German cohort and phenytoin in our analysis. Overall, both studies demonstrate that there is a low potential for DDIs between BIC/FTC/TAF and CMs including contraindicated combinations. Unique to our study, however, is the finding that a substantial number of DDIs can be avoided and contraindicated combinations can be nearly eliminated if treatment-experienced patients can switch their ART to BIC/FTC/TAF from their current regimen.

Current treatment guidelines recommend switching a patient's ART regimen when feasible in order to mitigate DDIs, as well as reduce treatment complexity, improve tolerability, limit long-term toxicity, and reduce costs [7–9]. However, it should be noted that switching ART can also lead to new adverse events and even virologic breakthrough in treatment-experienced patients. Furthermore, switching to or from a boosted ART regimen may require dosing adjustments for a patient's CMs. Some subjects in this study were switched to mitigate DDIs; however, the majority switched for other reasons including safety, tolerability, and regimen simplification. While prior studies have demonstrated that regimen simplification can reduce a patient's risk for DDIs, the results of this study suggest that DDI reductions may occur regardless of the reasons for switching a patient's regimen [22].

This study has several limitations. First, our analysis only included patients who switched to BIC/FTC/TAF. However, it should be noted that BIC and dolutegravir have nearly identical drug interaction profiles, and similar DDI reductions would have occurred if patients in this study had switched their baseline regimens to dolutegravir/FTC/TAF. Moreover, there are specific DDI situations when a dolutegravir-based regimen may be preferred to BIC/FTC/TAF (ie, concomitant rifamycins) that were not captured in this study. Second, our assessment of DDIs using the University of Liverpool's HIV Drug Interaction Database is only reflective of the study's time period. Changes in the tool's identification and assessment of DDI severity since this study was conducted are possible. Furthermore, the clinical relevance of each DDI identified in this study was not evaluated by the

investigators, and it is possible that separate DDIs with the same scores could differ considerably in their clinical relevance. Also, as a retrospective cohort study, we relied on the accuracy and completeness of medical records, but omissions or inaccuracies could have influenced the results. For example, we were unable to collect patients' nonprescription medications consistently, which may have resulted in an underestimation of DDIs. We were also unable to assess patient adherence to CMs, which may have resulted in an overestimation of DDIs. We also placed CMs into groups for our analysis, which limited our ability to investigate DDI changes for individual CMs following switches to BIC/FTC/TAF. In addition, dosing adjustments made to offset DDIs were not considered within our analysis. Lastly, our cohort was predominantly African American and male from large, academic, and urban medical centers in the United States. As a result, the findings may not be generalizable to patients living in rural settings or those living outside of the United States.

## CONCLUSIONS

Treatment-experienced PWH who are receiving CMs and are eligible to switch their ART may experience significant declines in the number and severity of DDIs if their regimen is switched to BIC/FTC/TAF. This may be particularly important for patients experiencing polypharmacy and those receiving CMs for conditions common to patients aging with HIV.


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***Patient consent.*** Institutional review board approval was obtained before data collection at each participating study center. This study did not include factors necessitating patient consent.

***Author contributions.*** Study concept and design: J.J.S. Acquisition, analysis, or interpretation of data: J.J.S., N.S.P., A.C., E.H., M.B., E.S., J.C. Statistical analysis: A.S. and S.W.K. Drafting of the manuscript: J.J.S. Critical review and revision of the manuscript: J.J.S., N.S.P., A.C., E.H., M.B., E.S., J.C., A.S., and S.W.K.

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