Dolutegravir – a review of the pharmacology, efficacy, and safety in the treatment of HIV

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Abstract: Dolutegravir is the newest integrase strand transfer inhibitor to be approved for the treatment of human immunodeficiency virus (HIV) infection. Dolutegravir is equivalent or superior to existing treatment regimens in both treatment-naïve and treatment-experienced patients including those with previous raltegravir or elvitegravir failure. The consistent efficacy coupled with excellent tolerability and infrequent drug–drug interactions makes the co-formulation of dolutegravir with two nucleotide reverse-transcriptase inhibitors an attractive treatment option. This review summarizes the pharmacokinetics, adverse event profile, and efficacy of dolutegravir in the treatment of HIV.

Keywords: patient-reported outcomes, integrase inhibitor, antiretroviral therapy

Introduction

Since the approval of zidovudine in 1987, there has been an increasing number of antiretroviral agents developed targeting the human immunodeficiency virus (HIV). The current antiretroviral classes include the nucleoside and nucleotide reverse-transcriptase inhibitors (NRTIs), non-nucleoside reverse-transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), entry inhibitors, and integrase strand transfer inhibitors (INSTIs).1,2 Increasingly, co-formulations are constructed with the goal of enhancing adherence, thereby ensuring the continual HIV suppression necessary to avoid the development of resistance.3 Antiretroviral therapy has lengthened the average life span of HIV-infected individuals to approach that of the general population while concurrently increasing the burden of comorbidities.4,5 Accordingly, there is an increasing need for agents with few drug–drug interactions, reduced toxicity, high genetic barrier to resistance, low pill burden, and decreased cost.

With the incremental improvement in viral load suppression and the expanding antiretroviral armamentarium, opportunistic infections and HIV-related mortality have significantly declined precluding their use as measures of efficacy as impossibly large sample sizes would be required to detect statistically and clinically important differences.6 This leaves targeted surrogate outcomes as the markers of efficacy and, given the number of randomized clinical trials assessing antiretrovirals, it is necessary to standardize these to allow for appropriate comparisons. As such, the US Food and Drug Administration (FDA) Snapshot algorithm is commonly used to evaluate for effectiveness along with a comparable mechanism for classifying adverse events.7,8

INSTIs, the newest class of antiretrovirals, act by preventing HIV DNA from incorporating into the host T-lymphocyte genome, limiting virus propagation. Raltegravir, requiring twice-daily dosing, and elvitegravir, requiring concurrent cobicistat, were the first to be approved.9–13 Dolutegravir, the most recent INSTI, can be taken once
daily and has been co-formulated into a single-tablet regimen (STR) with abacavir and lamivudine that was recently granted FDA approval.\textsuperscript{14} Currently, dolutegravir, with either abacavir–lamivudine or tenofovir–emtricitabine, is included among the preferred initial antiretroviral regimens.\textsuperscript{1,15}

The purpose of this review is to summarize the evidence pertaining to dolutegravir, focusing on the rationale for combination therapy.

**Pharmacology**

Dolutegravir acts by impairing the function of the HIV integrase-DNA complex to which it was chemically synthesized to bind.\textsuperscript{16} It is rapidly absorbed, achieving maximal blood concentration hours after ingestion and, with a terminal half-life of 12 hours, requires once-daily administration without pharmacological enhancement.\textsuperscript{17–19} There is minimal urinary excretion as it is metabolized predominantly through hepatic glucuronidation by UDP-glucuronosyltransferase 1A1.\textsuperscript{17,20} Given the low renal elimination, reduced renal function does not significantly alter the pharmacokinetics of dolutegravir.\textsuperscript{21} Whether this extends to patients receiving renal replacement therapy is unknown. Similarly, there is a dearth of evidence evaluating the impact of impaired hepatic function on the activity of dolutegravir. In a small comparison of those with Child-Pugh class B cirrhosis to healthy controls, the only difference was an increase in the unbound concentration of dolutegravir, the clinical significance of which is likely minimal as more than 99% remained in the active protein-bound form.\textsuperscript{22} Evidence of the wide distribution of dolutegravir comes from its detection in human colorectal tissue, cerebrospinal fluid, seminal fluid, cervicovaginal fluid, and vaginal tissue at concentrations above that expected to confer continued antiviral efficacy.\textsuperscript{23–25}

Drug–drug interactions with dolutegravir are minimal as it has little ability to alter drug-metabolizing enzymes. There are no interactions or dose adjustments required when combined with the NRTI class, as bioequivalence was observed when dolutegravir and abacavir–lamivudine, administered separately, were compared to a co-formulated single tablet.\textsuperscript{26–28} Among the NNRTI class, both efavirenz and etravirine significantly lower dolutegravir levels and should be avoided unless etravirine is administered with ritonavir, which reverses this reduction.\textsuperscript{29,30} There is no interaction between rilpivirine and dolutegravir.\textsuperscript{31} The PIs darunavir, lopinavir, fosamprenavir, and atazanavir, irrespective of ritonavir coadministration, can be safely used with dolutegravir.\textsuperscript{32–34} Tipranavir, however, reduces the plasma concentration of dolutegravir and caution should be exercised with coadministration.\textsuperscript{30} Interactions between dolutegravir and cobicistat – currently being evaluated as an alternative pharmacokinetic enhancer to ritonavir – are unclear and require further investigation.

Coinfection with hepatitis C and tuberculosis frequently occur, and the lengthy treatment regimens consisting of multiple agents make interactions with antiretrovirals inevitable. While there are no interactions between dolutegravir and boceprevir or telaprevir, the explosion of new antiviral agents active against hepatitis C will require pharmacokinetic studies to establish the feasibility of concurrent administration.\textsuperscript{35} Given the mechanism of metabolism of dolutegravir and with no clinically significant interactions between it and grazoprevir with elbasvir, it is expected that concurrent use with the direct acting agents against hepatitis C should not impact drug levels, but clinical data are lacking.\textsuperscript{15,36} As for tuberculosis therapy, rifampin lowers the concentration of dolutegravir, which can be offset by increasing the frequency of dolutegravir (50 mg twice daily) or substituting rifabutin as no adjustments are required.\textsuperscript{37}

Outside of antimicrobial agents, dolutegravir has few drug–drug interactions. There does not appear to be a significant interaction between dolutegravir and oral contraceptive pills or proton pump inhibitors.\textsuperscript{38,39} Antacids, however, can attenuate the effectiveness of dolutegravir, which should be taken 2 hours prior to or 6 hours following the ingestion of an antacid.\textsuperscript{39} Such a schedule should likewise be followed if dolutegravir is taken with cations such as iron and calcium, although these interactions can be avoided when ingested with a moderately fatty meal.\textsuperscript{40} Dolutegravir alters the pharmacokinetics of metformin, possibly enhancing gastrointestinal upset.\textsuperscript{41} In the absence of mineral supplements, dolutegravir can be taken with or without food.\textsuperscript{42}

**Dolutegravir efficacy**

**Antiretroviral-naïve patients**

Dose response studies determined 50 mg of dolutegravir as the most efficacious, with similar side effects as lower daily doses.\textsuperscript{43,44} In a blinded study, SPRING-2, comparing raltegravir against dolutegravir with either abacavir–lamivudine or tenofovir–emtricitabine, once-daily dolutegravir was noninferior, with 88% and 85%, respectively, achieving viral load suppression.\textsuperscript{45} This effect diminished slightly, but noninferiority persisted to 96 weeks.\textsuperscript{46} Failure to achieve virologic suppression was entirely due to discontinuation of dolutegravir for reasons other than the development of resistance, which was not observed. Against darunavir–ritonavir in the open-label FLAMINGO study,\textsuperscript{47} dolutegravir
led to virologic suppression in 90% of patients at 48 weeks compared with 83% in the darunavir–ritonavir group, which was predominantly the result of discontinuation due to adverse events, but also some improvement in efficacy above 100,000 copies per milliliter. The open-label nature of FLAMINGO could have led to biases in discontinuation rates.47 Similar to SPRING-2, the effect waned slightly, but remained statistically significant at 96 weeks.48 In SINGLE, a randomized placebo-controlled study comparing dolutegravir with abacavir–lamivudine against tenofovir–emtricitabine–efavirenz, viral load suppression occurred in 88% and 81% at 48 weeks, respectively.26 The superiority of dolutegravir with abacavir–lamivudine persisted at 144 weeks.29 The benefit was driven almost entirely by increased discontinuations due to adverse events associated with efavirenz. The unique aspect of SINGLE resides with controlling backbone agents as the aforementioned randomized trials entrusted backbone selection to study investigators. When all Phase III randomized trials were amalgamated, subgroup analysis did not find that patient age, backbone, or pretreatment viral load impacted effectiveness.50,51 Dolutegravir has been compared against PIs, NNRTIs, and INSTIs in treatment-naïve patients with consistent efficacy despite varying study populations (Table 1).

Antiretroviral-experienced patients

With the trend toward early initiation of antiretrovirals, the requirement for lifetime use, and myriad ways HIV escapes drug suppression, the proportion of treatment-experienced patients are naturally expected to rise.52 SAILING, a randomized trial of patients with resistance to at least two antiretroviral classes yet who were INSTI-naïve, compared raltegravir to dolutegravir with optimally constructed backbones. After 48 weeks, virologic suppression was observed in 71% in the dolutegravir cohort and 64% in the raltegravir cohort. The superiority of the dolutegravir regimen was observed irrespective of the background regimen, and resistance mutations were less likely to develop with dolutegravir.53 The biologic plausibility for the incremental benefit of dolutegravir over raltegravir is the slower dissociation from the HIV-1 integrase-DNA complex and the reduced interindividual pharmacokinetic variability.17,54

The VIKING trials assessed the utility of dolutegravir in populations with previous INSTI failure. In VIKING, patients with raltegravir resistance either by genotype analysis or treatment failure received dolutegravir once or twice daily for 10 days followed by optimization of the background regimen. After 24 weeks, almost twice as many subjects had an undetectable viral load in the twice-daily group (75% to 41%).55 In VIKING-3, patients with historical or current evidence of resistance to either raltegravir or elvitegravir by genotype or phenotype testing were given dolutegravir twice daily for 7 days before optimizing the background regimen. After 24 weeks, 69% achieved virologic suppression.56 VIKING-4 prospectively studied a heavily treatment-experienced cohort comparing a 7-day run-in period of dolutegravir or placebo followed by both groups receiving dolutegravir and an individually optimized background regimen. After 24 and 48 weeks, viral load suppression occurred in 47% and 40%, respectively.57 In an open-label cohort of heavily treatment-experienced HIV-2-infected patients, dolutegravir led to an undetectable viral load in 38%.58 Cumulatively, these studies support the use of twice-daily dolutegravir among those with raltegravir or elvitegravir failure (Table 2). Success with the sequential use of dolutegravir following INSTI failure is predicated on the presence of at least two active backbone agents and reduced development of INSTI resistance mutations. Thus, patients should stop a failing raltegravir- or elvitegravir-containing regimen as soon as possible to avoid the accumulation of mutations potentially compromising subsequent use of dolutegravir.

STR with dolutegravir

The bioequivalence of the co-formulated tablet leaves little doubt as to the potential efficacy of an STR containing dolutegravir.28 Given that there have been no published studies of dolutegravir as an STR and the consistent underrepresentation of women in the aforementioned trials, the Antiretroviral Therapy in Naïve Women (ARIA) trial was conducted, and the results are forthcoming. ARIA will compare the dolutegravir–abacavir–lamivudine STR against atazanavir–ritonavir with tenofovir–emtricitabine in treatment-naïve women.59 Further studies will address the feasibility of switching to the dolutegravir–abacavir–lamivudine STR from either an INSTI-free regimen or from nevirapine with abacavir–lamivudine.60,61

Safety of dolutegravir

Adverse events

Amalgamating the adverse event profiles accrued from the randomized controlled trials of dolutegravir provides a robust evidence base. The total incidence of adverse effects approaches 90%, but this liberal estimate consists of predominantly mild reactions that largely remit with time and may not entirely be drug related. Common adverse events include headache, nausea, and diarrhea, but the proportion with severe reactions (grade III or IV) is 1%.62 In SINGLE, as compared to SPRING and SAILING, the...
Table 1 Randomized trials of dolutegravir in treatment-naïve HIV-1-positive patients

<table>
<thead>
<tr>
<th>Trial</th>
<th>Antiretrovirals</th>
<th>Backbone</th>
<th>Outcomes&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Serious adverse events</th>
<th>Protocol-defined virologic failure&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Mutations due to INSTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPRING-1&lt;sup&gt;43&lt;/sup&gt;</td>
<td>DTG 10 mg (n=53)</td>
<td>TDF–FTC (67%)</td>
<td>DTG 10 mg 91%</td>
<td>DTG 10 mg 6%</td>
<td>DTG 10 mg 4%</td>
<td>DTG 10 mg</td>
</tr>
<tr>
<td>SPRING-1&lt;sup&gt;43&lt;/sup&gt;</td>
<td>DTG 25 mg (n=51)</td>
<td>ABC–3TC (33%)</td>
<td>DTG 25 mg 88%</td>
<td>DTG 25 mg 2%</td>
<td>DTG 25 mg 4%</td>
<td>NRTI: M184V</td>
</tr>
<tr>
<td>SPRING-1&lt;sup&gt;43&lt;/sup&gt;</td>
<td>DTG 50 mg (n=51)</td>
<td>efV (n=50)</td>
<td>DTG 50 mg 90%</td>
<td>DTG 50 mg 8%</td>
<td>DTG 50 mg 0%</td>
<td>DTG 50 mg, DTG 50 mg, efV</td>
</tr>
<tr>
<td>SPRING-2&lt;sup&gt;45&lt;/sup&gt;</td>
<td>DTG (n=411)</td>
<td>TDF–FTC (59%)</td>
<td>DTG 88%</td>
<td>DTG 0.7%</td>
<td>DTG 5%</td>
<td>None</td>
</tr>
<tr>
<td>SPRING-2&lt;sup&gt;45&lt;/sup&gt;</td>
<td>RAL (n=411)</td>
<td>ABC–3TC (41%)</td>
<td>RAL 85%</td>
<td>RAL 1%</td>
<td>RAL 7%</td>
<td>None</td>
</tr>
<tr>
<td>SINGLE&lt;sup&gt;26&lt;/sup&gt;</td>
<td>DTG–ABC–3TC (n=414)</td>
<td>Not applicable</td>
<td>DTG–ABC–3TC 88%</td>
<td>DTG–ABC–3TC 1%</td>
<td>DTG–ABC–3TC 4%</td>
<td>NRTI: A62V, K65R, K70E, and M184V</td>
</tr>
<tr>
<td>SINGLE&lt;sup&gt;26&lt;/sup&gt;</td>
<td>EFV–TDF–FTC (n=419)</td>
<td></td>
<td>EFV–TDF–FTC 81%</td>
<td>EFV–TDF–FTC 2%</td>
<td>EFV–TDF–FTC 4%</td>
<td>NRTI: M184I</td>
</tr>
<tr>
<td>FLAMINGO&lt;sup&gt;47&lt;/sup&gt;</td>
<td>DTG (n=242)</td>
<td>TDF–FTC (67%)</td>
<td>DTG 90%</td>
<td>DTG 1%</td>
<td>DTG 1%</td>
<td>None</td>
</tr>
<tr>
<td>FLAMINGO&lt;sup&gt;47&lt;/sup&gt;</td>
<td>DRV/R (n=242)</td>
<td>ABC–3TC (33%)</td>
<td>DRV/R 83%</td>
<td>DRV/R 1%</td>
<td>No INSTI, PI, NRTI mutations</td>
<td></td>
</tr>
</tbody>
</table>

Notes: <sup>a</sup>Percentage of cohort achieving HIV RNA <50 copies/mL at 48 weeks. <sup>b</sup>Virologic failure defined in SINGLE and SPRING-2 as two HIV RNA levels >50 copies/mL on or after 24 weeks; in FLAMINGO as two HIV RNA levels >200 copies/mL on or after 24 weeks; in SPRING-1 as one HIV RNA level >400 copies/mL on or after 24 weeks or decrease less than 1.0 log<sub>10</sub> copies/mL by week 4.

Abbreviations: DTG, dolutegravir; EFV, efavirenz; RAL, raltegravir; TDF, tenofovir; ABC, abacavir; 3TC, lamivudine; FTC, emtricitabine; DRV/R, darunavir/ritonavir; INSTI, integrase strand transfer inhibitor; NRTI, nucleoside and nucleotide reverse-transcriptase inhibitors; PI, protease inhibitor.
Table 2 Trials of dolutegravir in treatment-experienced HIV-1-positive patients

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>Antiretrovirals</th>
<th>Outcomes*</th>
<th>Emergent DTG resistance mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAILING**</td>
<td>Resistance to ≥1 drug in ≥2 classes</td>
<td>DTG (n=354) RAL</td>
<td>At 48 weeks</td>
<td>DTG 71% RAL 64% R263R (FC 1.12)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(n=361)</td>
<td>DTG daily</td>
<td>DTG daily 41% DTG daily 75%</td>
</tr>
<tr>
<td>VIKING**</td>
<td>RAL resistance and ≥1 drug in ≥3 classes</td>
<td>DTG daily (n=27)</td>
<td>At 24 weeks</td>
<td>DTG twice daily 75%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DTG twice daily (n=24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VIKING-3**</td>
<td>RAL/ELV resistance and ≥1 drug in ≥3 classes</td>
<td>DTG twice daily (n=183)</td>
<td>At 24 weeks</td>
<td>DTG 69%</td>
</tr>
<tr>
<td>VIKING-4**</td>
<td>RAL/ELV resistance and ≥1 drug in ≥2 classes</td>
<td>DTG twice daily (n=30)</td>
<td>At 24 weeks</td>
<td>DTG 47%</td>
</tr>
</tbody>
</table>

Abbreviations: RAL, raltegravir; DTG, dolutegravir; ELV, elvitegravir; FC, fold change in phenotype resistance; max, maximum.

prevalence of insomnia was higher, which may be related to the specific study questionnaire that had not been employed in the previous trials. In a meta-analysis, there were significantly fewer adverse events with dolutegravir as compared to atazanavir–ritonavir, lopinavir–ritonavir, and efavirenz, while no differences between darunavir–ritonavir, elvitegravir–cobicistat, raltegravir, and rilpivirine were observed. Furthermore, adverse events ascribed to dolutegravir infrequently led to treatment cessation, occurring in less than 2%, comparable to raltegravir and lower than efavirenz and PI-based regimens. When compared to raltegravir in treatment-experienced patients, there was no difference in the overall frequency of adverse events nor in the frequency of adverse events leading to drug discontinuation. Dolutegravir has not been associated with an increase in cardiovascular risk. 

Further proof of the tolerability of dolutegravir is the similar side effect profile observed when given twice daily, even among those with advanced immunosuppression. With respect to biochemical perturbations due to dolutegravir, the most consistently observed is creatinine elevation. This typically occurs within a week of initiation followed by a plateau at an average increase of 11 mmol/L. This rise is mediated through inhibition of the renal transporter OCT-2, but the reduced creatinine secretion does not translate into a lower glomerular filtration rate. Elevations in transaminases occur in 5%, are generally mild, and occur at a similar rate as with raltegravir, darunavir–ritonavir, and efavirenz. In the limited number of patients with hepatitis B or C coinfection, the incidence of transaminase elevation rises to 16%, most likely reflecting immune reconstitution, and is lower than that observed with raltegravir and efavirenz, but higher than that with darunavir–ritonavir. Elevation in total cholesterol, low-density lipoprotein, and triglycerides observed with PIs is absent with dolutegravir. Creatine kinase elevations are common, largely asymptomatic, and mild, with only 5% being grade III or IV in severity. Hypersensitivity reactions were extremely uncommon, occurring in less than 1%, and tend to occur shortly after treatment initiation.

Special populations

There is a paucity of information regarding the use of dolutegravir in pediatric and pregnant populations. In animal studies, dolutegravir crosses the placenta, but this had no impact on fetal development in rats and rabbits despite
exposure to supratherapeutic doses, resulting in an FDA class B classification.\textsuperscript{65} Ongoing clinical trials evaluating dolutegravir in treatment-experienced children and pregnant women will clarify the safety and efficacy of dolutegravir in these populations.\textsuperscript{66,67} In the interim, dolutegravir is not recommended in pregnancy unless alternative agents are unavailable.

**Resistance profile**

Another advantage of dolutegravir relates to the barrier to resistance. When analyzing those experiencing virologic failure while on dolutegravir as first-line therapy, no resistance mutations were discovered.\textsuperscript{68} This contrasts with the four of 281 patients who developed raltegravir resistance in STARTMRKK at 5 years and one of 411 patients in SPRING-2 at 96 weeks.\textsuperscript{15,45} In comparison, at week 144, elvitegravir-resistant virus was observed in nine of 348 patients and six of 353 patients in studies comparing it to efavirenz and atazanavir–ritonavir, respectively.\textsuperscript{69,70} It is unclear as to whether the resistance barrier to dolutegravir is similar to or surpasses that of PIs, as virologic failure due to resistance was not observed in FLAMINGO.\textsuperscript{47}

Dolutegravir has induced mutations within the integrase enzyme, but these are infrequent and have minimal effect clinically. Dolutegravir can select for a R263K mutation that attenuates its activity, but not to an extent that allows for viral rebound.\textsuperscript{71} Continual dolutegravir selection pressure allows for the development of sequential mutations, generally in the same R263K pathway, but again these do not substantially impact antiviral activity and may in fact confer reduced HIV replication fitness.\textsuperscript{52,72–75}

It is important to note that the randomized clinical trials evaluating dolutegravir test for resistance upon detection of viral rebound, which often differs from clinical practice, where patients can remain on failing regimens for longer before genotype analysis is undertaken. This allows for additional selection pressure and may serve to increase the incidence of dolutegravir resistance. Given that adherence may be less optimal outside the rigor of clinical trials, over time the increasing use of dolutegravir may result in the emergence of novel mutations. Recently, a patient with known N155H, S119R, and E157Q mutations who achieved suppression with dolutegravir experienced virologic rebound conferred by novel mutations, T97A and S147G.\textsuperscript{76} This further confirms the importance of modifying a failing regimen urgently to avoid the accumulation of mutations that may compromise therapy.\textsuperscript{77}

**Patient-reported outcomes**

Not captured in the randomized trials of dolutegravir are subjective measures of a patient’s health – termed “patient-reported outcomes”. A number of assessment tools have been evaluated, principally among those receiving NNRTI- or PI-based regimens, but none are sufficiently robust for widespread adoption.\textsuperscript{79} When these infrequently ascertained measures are assessed, as in SINGLE, dolutegravir is not inferior to tenofovir–emtricitabine–efavirenz.\textsuperscript{26}

Maximizing adherence to antiretroviral treatment is vital and became even more important following the recognition that multiple antiretrovirals with varying mechanisms of action were required for continual HIV suppression.\textsuperscript{79,80} Strategies to improve adherence, including reducing pill burden to simplify regimens, should translate into improved quality of life.\textsuperscript{81} As an added benefit, co-formulated STRs, when compared to the component antivirals taken separately, may potentially reduce the development of resistance mutations.\textsuperscript{82–86} Furthermore, an initial highly successful regimen obviates the need to switch therapy, which may result in experiencing new side effects that negatively impact quality of life.\textsuperscript{87,88} As the initial antiretroviral regimen predicts successful long-term virologic suppression, selecting the correct therapy is critically important.\textsuperscript{89}

**Conclusion**

Dolutegravir, the newest INSTI, is an effective antiretroviral agent for both treatment-naïve and treatment-experienced patients infected with HIV. This is driven by effective virologic suppression, good tolerability, infrequent drug–drug interactions, and once-daily administration. Co-formulation of dolutegravir with abacavir–lamivudine maximizes adherence and should be considered among the initial options for the treatment-naïve. In the treatment-experienced, including those with INSTI resistance, dolutegravir remains effective when taken twice daily. Future studies will hopefully extend the effectiveness to populations underrepresented in current clinical trials. Perhaps the most novel aspect of dolutegravir is the high barrier to resistance, which may have important public health implications by reducing the development, and subsequent transmission, of resistance mutations.

**Disclosure**

Sharon L Walmsley has served on advisory boards, spoken at Continuing Medical Education-related events, and conducted clinical trials with Viiv, Bristol Meyers Squibb, Abbvie, Janssen Pharmaceuticals, Gilead, and Merck and Co.
Incorporate. The authors report no other conflicts of interest in this work.

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