




# Dolutegravir And Lamivudine Combination For The Treatment Of HIV-1 Infection

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**Abstract:** There have been remarkable advances in drug development for the treatment of HIV-1 infection. From the co-formulation of combination antiretroviral therapy (cART) into single-tablet regimens to the development of long-acting antiretroviral (ARV) drug formulations, the treatment of HIV has and will become much more tolerable and less complicated for patients. In addition, and appropriately, there is a focus on reducing short- and long-term toxicities of treatment while maintaining robust efficacy. One of such approaches includes 2-drug regimen constructs that contain and retain effective ARV compounds while excluding components that have relatively unfavorable toxicity profiles. The first-ever 2-drug regimen approved for the treatment of HIV-1 infection for treatment-naïve people living with HIV (PLWH), consisting of the integrase inhibitor dolutegravir (DTG) and the nucleoside reverse transcriptase inhibitor (NRTI) lamivudine (3TC), is reviewed in this paper. The chemical composition and properties, pharmacokinetic and pharmacodynamics profile, and clinical trial data on efficacy and safety of DTG/3TC are presented. An expert opinion aims to highlight important considerations for the use of DTG/3TC in the context of existing and emerging ARV options.

**Keywords:** dolutegravir, lamivudine, combination antiretroviral therapy

## Introduction

Remarkable advancements have occurred in the development of combination antiretroviral therapy (cART) for the treatment of HIV infection since the approval of the first antiretroviral agent, zidovudine, in 1987. Since then, more potent, effective and better tolerated treatment regimens which require less frequent dosing and/or that are co-formulated into single-tablet regimens (STRs) have revolutionized the treatment of HIV and led to significant gains in life expectancy among people living with HIV (PLWH).

The current treatment paradigm, supported by guidelines developed by reputable organizations including the US Department for Health and Human Services (DHHS) and the International AIDS Society (IAS), includes initiating HIV treatment with two nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) in combination with either an integrase strand transfer inhibitor (INSTI), a protease inhibitor (PI) or a non-nucleotide reverse transcriptase inhibitor (NNRTI) with INSTIs being the preferred drug class and others reserved as alternative agents for certain clinical situations. Sustained and durable suppression of viral replication is now possible with such treatment combinations when taken consistently and the repertoire now includes more than 10 STRs.<sup>1-4</sup>

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Given the expanded treatment options, regimen selection by HIV care providers include considerations such as dosing frequency, food requirement, drug–drug interaction (DDI) potential, short- and long-term toxicities as well as costs of what is expected to be life-long treatment. These considerations and regimen characteristics are also important for drug development and inform what drugs and treatment strategies should be advanced for clinical use.

One approach to simplifying treatment and limiting its associated toxicities is the use of dual ARV (treatment) regimens (DTRs) that have been evaluated in multiple studies for both initial and maintenance therapy for PLWH.<sup>5–8</sup> Results of these studies have shown variable efficacy but some of these regimen constructs have been associated with an increased risk for treatment-emergent drug resistance as well as decreased efficacy in individuals with high viral loads and/or low CD4 counts.<sup>9–11</sup> One regimen that has shown satisfactory efficacy and subsequently received approval by the US Food and Drug Administration (FDA) is dolutegravir/rilpivirine but is only for use for maintenance of virologic suppression in treatment-experienced patients.<sup>12</sup>

Studies in treatment-naïve individuals have been performed comparing 2-drug to 3-drug regimens. An open-label randomized study involving 757 treatment-naïve patients comparing ritonavir(r)-boosted lopinavir (LPV/r) or efavirenz (EFV), each in combination with two NRTIs (standard of care [SOC]) to the NRTI-sparing combination -EFV/LPV/r, found that the efficacy of dual therapy was similar to the EFV/2 NRTIs arm but was associated with more treatment-emergent resistance.<sup>6,13–16</sup> Another study showed that the 2-drug combination of LPV and 3TC had similar efficacy but superior tolerability compared to LPV/2 NRTIs among ARV-naïve patients.<sup>17</sup>

Similarly, dolutegravir (DTG) in combination with 3TC (DTG/3TC) has been extensively studied as a 2-drug regimen with favorable characteristics such as excellent tolerability (both drugs) and high resistance barrier (DTG). It is the first 2-drug STR approved as initial therapy for PLWH and is marketed as DOVATO<sup>®</sup> (GlaxoSmithKline, Research Triangle Park, NC, USA).<sup>18,19</sup> This review will include an overview of the chemistry, pharmacodynamic and pharmacokinetic properties, clinical trials data and drug–drug interactions of DTG/3TC.

## Overview Of The Market

Over the past two decades, the paradigm of cART has been the use of 3-drug regimens as initial therapy for the

treatment of HIV-1 infection. DTG/3TC enters a competitive market of over 50 approved medications many of which are co-formulated products. However, DTG/3TC is only the second approved 2-drug STR but holds the distinction of being the first one approved for treatment-naïve PLWH.<sup>20</sup>

## Introduction To Compound

DTG/3TC is a two-drug combination of DTG, an INSTI and 3TC, an NRTI, and is approved as a complete regimen for the treatment of HIV-1 infection in ARV-naïve adults with no genotypic resistance to the individual ARV components.<sup>21</sup>

## Chemistry

### Dolutegravir/Lamivudine (DTG/3TC) STR

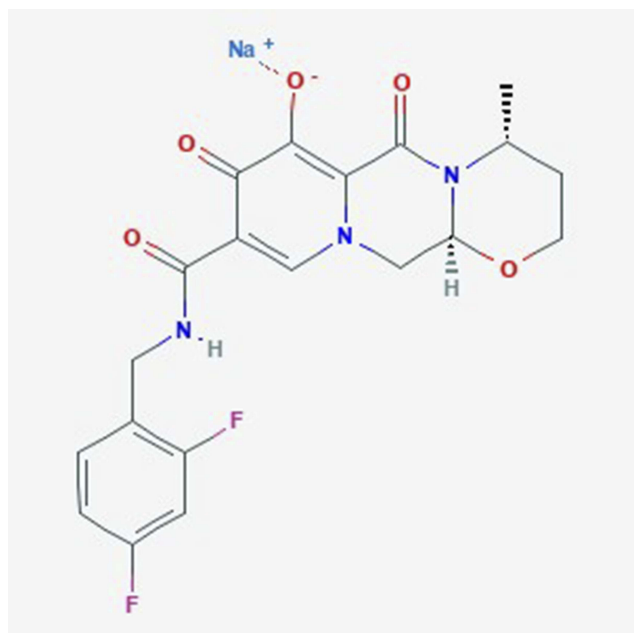
The single tablet contains 300 mg of lamivudine and 50 mg of dolutegravir (equivalent to 52.6 mg dolutegravir sodium) as active ingredients. Inactive ingredients include povidone K29/32, sodium starch glycolate, sodium stearyl fumarate magnesium stearate, mannitol and microcrystalline cellulose, as well as hypromellose, polyethylene glycol, titanium dioxide in the tablet's coat. The tablet is formulated for oral administration.<sup>19</sup>

### Dolutegravir (DTG)

DTG sodium is monocarboxylic acid amide and an organic heterocyclic compound with a chemical formula –sodium(4R,12aS)-9-{[(2,4-difluorophenyl)methyl]carbamoyl}-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2Hpyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazin-7-olate (Figure 1). It has a sodium moiety with the molecular formula – C<sub>20</sub>H<sub>18</sub>F<sub>2</sub>N<sub>3</sub>NaO<sub>5</sub> with an exact mass of 441.36 g/mol. It is light yellow to white powder in appearance and is slightly water soluble.<sup>21,22</sup>

### Pharmacodynamics

DTG is a potent integrase inhibitor that employs divalent cations (Mg<sup>2+</sup>) to couple with the enzymatic active site of the viral integrase. Its structure allows DTG to penetrate the active and recently vacated enzymatic pocket where it binds farther in than prior drugs in its class. This provides a more stable and lasting bond compared to other precursor integrase inhibitors such that its dissociation constant (mean dissociation constant 2.7 x 10<sup>-6</sup> s<sup>-1</sup>) is slower compared to either raltegravir (RAL) or elvitegravir (EVG) – 22 and 71 x 10<sup>-6</sup> s<sup>-1</sup>, respectively. It also has a



**Figure 1** DTG molecular structure (adapted from PubChem).<sup>22</sup>

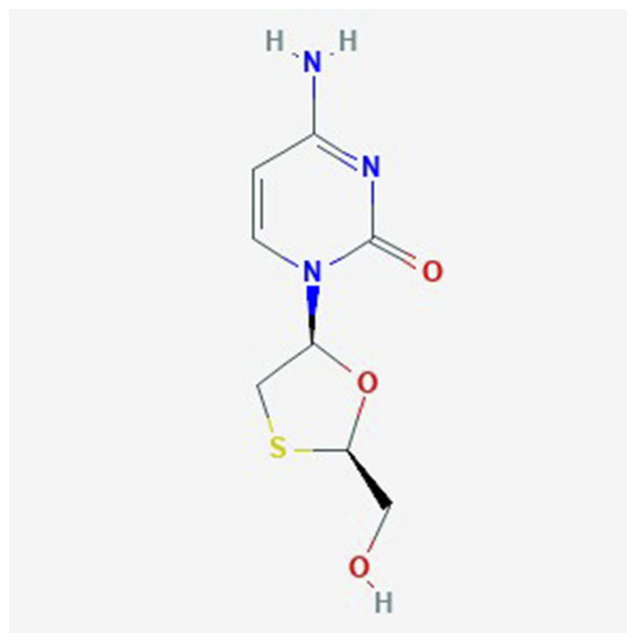
lower half-maximal inhibitory concentration (IC<sub>50</sub>) for HIV-1 of 1.6 nM compared to 3.3 and 6 nM for RAL and EVG, respectively.<sup>23,24</sup>

### Pharmacokinetics

Following ingestion, DTG peaks in 2–3 hrs. Low-, medium- and high-fat meals increase DTG's AUC by 33%, 41% and 66%, respectively. The median time to maximal concentration (T<sub>max</sub>) is 2.5 hrs. It is tightly protein bound (99%) in plasma and has a medium volume of distribution of 17 L. Its elimination half-life is about 14 hrs which allows for once-daily dosing. DTG is excreted mainly via feces (64%) and urine (31%). DTG is metabolized by UGT1A1 (major pathway) and CYP 3A (minor pathway) but does not inhibit UGT1A1 or inhibit or induce any CYP enzymes, therefore possesses a limited drug–drug interaction profile. However, it is a substrate of BCRP, P-gp, UGT1A3 and UGT1A9.<sup>25</sup>

### Lamivudine (3TC)

Lamivudine is a cytidine analogue with a chemical formula (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one, formulated as a sulfur salt (Figure 2). Its molecular formula is C<sub>8</sub>H<sub>11</sub>N<sub>3</sub>O<sub>3</sub>S with an exact mass of 229.3 g/mol. It appears as an off-white to white crystal that is water soluble with a melting point of 160–162°C.<sup>26</sup>



**Figure 2** 3TC molecular structure (adapted from PubChem).<sup>27</sup>

### Pharmacodynamics

3TC competitively inhibits HIV-1 reverse transcriptase by incorporation of its active tri-phosphorylated form into the viral DNA producing chain termination. It has excellent activity against HIV-1 and HIV-2 virus with an EC<sub>50</sub> value of 120 nM for HIV-1 and HIV-2 in cell lines including PBMCs and monocytes. 3TC has activity against hepatitis B virus, although monotherapy is associated with the rapid development of resistance.<sup>28,29</sup>

### Pharmacokinetics

Following oral ingestion, 3TC is rapidly absorbed with excellent bioavailability (87% approximately) that is not significantly impacted by meal intake and with a T<sub>max</sub> of 1 hr. It distributes mainly to the extravascular spaces with a peak time of approximately 3.2 hrs and a volume of distribution of 96 L. Its half-life of 13–19 hrs allows for once-daily dosing. 3TC does not undergo hepatic metabolism and is excreted primarily through the kidneys, hence dose adjustments are required in the setting of compromised renal function. 3TC exhibits linear pharmacokinetics, achieving steady state by day 15 of administration.<sup>29–33</sup>

## Clinical Efficacy

### Initial Therapy

The DTG/3TC combination was first evaluated for efficacy, safety and tolerability in the proof-of-concept PADDLE study conducted in Argentina (see Table 1). Twenty ARV-

Table 1 Summary Of Clinical Trials – DTG/3TC For Treatment-Naive Individuals

Authors	Title	Study Design	Subjects on DTG/3TC vs 3-Drug Regimen	HIV RNA < 50 Copies Per mL, DTG/3TC vs 3-Drug Regimen (% FDA Snapshot)	Mean CD4 Count Increase (cells/ $\mu$ L)	Discontinuation Due To AEs DTG/3TC vs 3-Drug Regimen (%)	Virologic Failure (%)	Treatment Emergent Resistance, DTG/3TC vs 3-Drug Regimen
Cahn et al <sup>34</sup>	PADDLE	Proof of concept (Phase I)	20/NA	90(48 week)	267	0	5	None
Taiwo et al <sup>35</sup>	ACTG A5353	Phase II	120/NA	90(24 week)	NA	0	<1%	M184V and R263R/K in 1 subject
Cahn et al <sup>36</sup>	GEMINI 1 and 2	Phase III	719/722	91(48 week)	NA	1/2	2/3 (virologic non-response)	None

naive subjects with HIV-1 RNA < 100,000 copies/mL, CD4 cell counts > 200 cells/mm<sup>3</sup>, no known genotypic resistance to lamivudine and with negative hepatitis B surface antigen (HBsAg) at screening were enrolled. Median age was 34 years and 19 subjects were male. The primary endpoint was the proportion of subjects with HIV-1 RNA below 50 copies/mL at week 48. All enrolled participants completed 48 weeks on the study except 1 patient (who committed suicide).<sup>34</sup>

On intention to treat analysis, 90% achieved the primary endpoint by week 48 (per protocol viral suppression rate was 95%) and this included 3/4 subjects who were later found to have a baseline viral load >100,000 copies/mL. Rapid decline in viral loads was observed with all subjects having a VL < 50copies/mL by week 8. The sole subject who later experienced virologic failure re-suppressed without any change in therapy off-study at week 48. Median CD4 cell count change was by 267 cells/mm<sup>3</sup> from baseline. Treatment was well-tolerated overall, and adherence was reported to be 100% by self-report and confirmed by pill counts.

ACTG5353 was a multicenter Phase II single-arm study of DTG/3TC combination for ARV treatment-naive individuals with HIV VLs between 1000 and 500,000 copies/mL with no CD4 count restrictions and no major resistance mutations to NRTIs, NNRTIs or INSTIs. Enrolled subjects (120) had a median age of 30 years were predominantly male (87%) with racial/ethnic composition including blacks (40%), Hispanics (28%) and Asians (2%). Thirty-one per cent of subjects had HIV VLs >100,000 copies/mL. Median baseline CD4 count was 387 cells/mm<sup>3</sup>. The primary endpoint was the proportion of subjects with VL < 50 copies per mL at week 24 using the FDA snapshot algorithm. Secondary measures included safety and tolerability assessments, change in CD4 cell count, emergence of resistance and efficacy evaluation by baseline viral load (< or > 100,000 copies/mL). DTG levels were also measured to assess for its relationship to the study outcomes.

The primary study outcome was achieved in 90% (108/120) of subjects. Results were comparable regardless of baseline viral load. Five (4%) had virologic non-success and 7 (6%) had no virologic data in the analysis window. Virologic failure in 3 subjects occurred after initial viral suppression and was thought to have been the result of suboptimal adherence as evidenced by DTG serum levels (<5ng/mL at 1 or more time points). The M184V (NRTI resistance) and R263R/K (INSTI resistance) mutations developed in 1 subject. Overall, the DTG/3TC regimen was well-tolerated with no study discontinuation due to

adverse events. Self-reported adherence was high with 90% of subjects reporting perfect adherence.<sup>35</sup>

Two identical multinational randomized, double-blind, non-inferiority Phase III studies conducted in 192 centers in 21 countries (GEMINI-1 and GEMINI-2) evaluated DTG/3TC compared to DTG/tenofovir disoproxil fumarate (TDF)/Emtricitabine (FTC) for treatment of ARV-naïve individuals (see Table 1). Enrolled participants had to have HIV VL <500,000 copies/mL, and no major mutations conferring resistance to NRTIs, NNRTIs or PIs. Women of childbearing potential who were on approved contraception modalities were also enrolled. A total of 1441 participants were randomized 1:1 to either study arm (719 in 2-drug and 722 in 3-drug regimen groups but with 3 and 5 individuals in each group not receiving a single dose of drug, respectively). Demographics and baseline clinical characteristics were similar among the groups studied, median age was 33 years, participants were predominantly male (85%) and white (68%). Most subjects had baseline had viral loads <100,000 copies per mL (80%) and CD4 counts >200 cell/mm<sup>3</sup> (92%).

The primary endpoint was the proportion of participants with VL < 50 copies per mL at week 48 using the FDA snapshot algorithm with the objective to show non-inferior virologic efficacy with a margin of -10%. Secondary endpoints included proportion of subjects achieving VL < 50 copies per mL at week 24, time in weeks to achieve VL < 50 copies per mL and change in CD4 cell count from baseline to week 48. Safety endpoints included incidence and severity of adverse events and proportion of participants discontinuing treatment due to safety events. Renal and bone biomarkers were assessed at baseline, week 24 and week 48.

In GEMINI-1, the primary endpoint in the-intention-to-treat-exposed subjects was 90% (320 of 356) in the 2-drug group and 93% (332 of 358) in the 3-drug group. Similarly, in GEMINI-2, 93% (335 of 360) in the 2-drug group and 94% (337–359) in the 3-drug group achieved the primary endpoint. Median time to viral suppression was impressive and observed to be 29 days. Both studies met pre-set non-inferiority criteria for virologic efficacy. On combined analysis, virologic non-response (defined by Snapshot analysis as  $\geq 50$  copies per mL at week 48) was seen in 3% (20 of 716) in the 2-drug group and 2% (13 of 717) in the 3-drug group.

Ten individuals (<1%) met criteria for virological withdrawal (6 in the 2-drug regimen group and 4 in the 3-drug regimen group). Virologic withdrawal was met if a second

and consecutive VL met any of the following: decrease in baseline of less than 1 log<sup>10</sup>, unless level was <200 by week 12; VL > 200 copies/mL at or after week 24; or rebound (VL > 200 after level was <200 copies/mL). Genotypic and phenotypic resistance testing did not reveal any reverse transcriptase or integrase mutations in these subjects.

Overall, the combined results in GEMINI 1 and 2 trials were similar among individuals with higher (>100,000 copies per mL) and lower viral loads ( $\leq 100,000$  copies per mL). Similar virologic response was also seen for individuals with CD4 counts >200 cells/mm<sup>3</sup> (93% in both groups). Less virologic response occurred in those with CD4 < 200 cells/mm<sup>3</sup> (79% in 2-drug and 93% in 3-drug regimens), but was thought to be unrelated to efficacy of the treatment regimens or treatment failure. Safety outcomes were similar across both treatment groups as were changes in health quality of life assessment (EQ-5D-5L health utility scale).<sup>36</sup> Results of safety outcomes are detailed in the section below.

## Safety And Toxicity Of DTG/3TC In Phase III Trials

In the combined GEMINI studies, adverse events (AEs) were reported in 76% (543 of 716) of subjects in the two-drug regimen and 81% (579 of 717) of subjects in the 3-drug group (see Table 2); safety and tolerability were comparable between treatment groups. Drug-related AEs were numerically lower in the 2-drug group and was attributable to less drug-related grade 1 nausea. Most adverse effects were considered non-serious and commonly included headache, diarrhea and nasopharyngitis. Adverse effects leading to study discontinuation and any serious event were similar between the two study groups. Neuropsychiatric AEs related to suicidal ideation or behavior occurred in 2% of each group. Two deaths occurred, one in each study group, but investigators thought they were unrelated to study drugs.

Regarding secondary outcomes, changes in biomarkers related to renal and bone safety favored the 2-drug regimen group. On the other hand, significantly lower elevations in lipids were observed in the 3-drug arm (see Tables 3 and 4). All these findings are consistent with the addition of TDF in the 3-drug treatment arm with its known effects on the kidneys, bone and cholesterol. Health-related quality of life scores was similar and high at baseline for both groups and remained high at week 48.

**Table 2** Select Adverse Effects Reported From Phase III Trials At Week 48

Adverse Effects	DTG/ 3TC (%)	3-Drug Regimen (%)
<b>Any adverse effect</b>		
Headache	10	10
Diarrhea	9	11
Nasopharyngitis	8	11
Upper respiratory tract infection	8	6
Pharyngitis	5	4
Back pain	5	4
Nausea	4	7
Insomnia	4	6
<b>Drug-related adverse effect</b>	18	24
<b>Serious adverse events</b>	7	8
<b>Drug related serious adverse events</b>	1	1
<b>Adverse events leading to discontinuation of treatment or withdrawal from study</b>	2	2
<b>Discontinuation due to drug-related adverse events</b>	1	1

**Table 3** Changes In Renal Biomarkers In GEMINI Trials

Parameters	Two-Drug Regimen	Three-Drug Regimen	P-value
Mean change in serum creatinine (mmol/mL)	+10.4	+13.5	0.0001
GFR from creatinine CKD-EPI (mL/min per 1.73 mm <sup>3</sup> )	-12.1	-15.5	0.0001
Protein creatinine ratio of week 48 to baseline (g/mol)	+0.87	+1.03	0.0001

**Table 4** Changes In Lipid Profiles In GEMINI Studies

Adjusted Mean Change (mmol/L)	Two-Drug Regimen	Three-Drug Regimen	P-value
Total cholesterol	+0.32	-0.15	0.0001
HDL cholesterol	+0.15	+0.02	0.0001
LDL cholesterol	+0.17	-0.14	0.0001
Triglycerides	+0.03	-0.08	0.0457
Ratio of total cholesterol to HDL cholesterol	-0.12	-0.24	0.0182

## Unique Safety And Toxicity Considerations

### DTG

#### Use In Pregnancy

A National Institute of health-funded observational surveillance study of outcomes at birth among pregnant women on cART in Botswana identified a possible increased risk of neural tube defects when DTG is taken at the time of conception.<sup>37-39</sup> Treatment guidelines have since been updated to reflect this safety concern such that the risks and benefits of treatment with DTG should be shared between women of childbearing potential and their providers.<sup>40</sup>

#### Changes In Serum Creatinine

DTG may cause minimal increases in serum creatinine by inhibition of renal transporter OCT-2. The increase is typically seen within the first 4 weeks of use but does not reflect a true decline in glomerular filtration rate (GFR) or renal function.<sup>41</sup>

### 3TC

#### Resistance Barrier And Mutation

3TC has broad activity against HIV-1 and HIV-2 virus. Resistance develops when there is a substitution of methionine for valine at amino-acid position 184 (M184V or M184I) of the reverse transcriptase *pol* gene of HIV-1. The mutation is easily selected for and appears days after exposure to 3TC monotherapy or with suboptimal adherence to regimens containing the medication. However, the M184V/I mutation reduces HIV replication and overall viral fitness; hence good clinical outcomes may still be observed for patients with 3TC-resistant strains of HIV-1 that continue 3TC treatment in combination with other regimens particularly those that include tenofovir to which such strains may be hypersusceptible.<sup>38,42,43</sup>

#### Hepatitis B

As 3TC has antiviral activity against hepatitis B virus (HBV), severe acute exacerbation of hepatitis may occur in HBV/HIV co-infected patients who have used 3TC-containing regimens and discontinue it. Therefore, close monitoring of such individuals is warranted.<sup>44</sup>

## Drug Interactions

### Dolutegravir (DTG)

Compared to other classes of ARV agents, INSTIs have a low potential for drug interactions. Nonetheless, DTG has several important drug interactions to consider.

The absorption of DTG is significantly impaired by co-administration with divalent or trivalent cations such as iron, calcium, aluminum, and magnesium. Such interactions can be minimized if DTG is taken 2 hrs before or 6 hrs after ingestion of medications or substances that contain these agents. Drugs that induce CYP3A4 and the transporters UGT1A1 and P-glycoprotein will reduce DTG levels. These include rifampin, carbamazepine and EFV so these should not be co-administered with DTG (dosed daily). In cases where co-administration with rifampicin and carbamazepine is necessary (see section on dosing), the dosing frequency of DTG should be increased to twice-a-day to overcome the interaction.

On the other hand, the pharmacokinetics of metformin and dofetilide are altered when given with DTG with resultant increased levels of both drugs. The recommendation is to limit the dosing of metformin to a total daily dose of 1 g only with concurrent use. The use of dofetilide with DTG is contraindicated.<sup>45</sup>

### Lamivudine (3TC)

3TC is associated with limited significant drug interactions. Sorbitol-containing products can result in dose-dependent decreases in C<sub>max</sub> and AUC of 3TC when co-administered. Such products should therefore be avoided for patients on 3TC.<sup>46</sup>

### Regulatory Affairs

DOVATO received approval by the US FDA on April 8, 2019 for the treatment of HIV-1 infection in ARV-naïve adults with no known viral mutations associated with resistance to the individual components.

On July 3, 2019, the European Medicines Agency (EMA) granted marketing authorization to DOVATO for the treatment of HIV-1 infection in ARV-naïve adults and adolescents above 12 years of age weighing at least 40kg, with no known or suspected resistance to the integrase inhibitor class or 3TC.

Further applications are pending worldwide.

### Dosing Routes

DTG/3TC is to be taken as a single tablet once daily by oral route with or without food. As a fixed-dose tablet, it is not recommended for use in patients with creatinine clearance less than 50mL/min. If given with carbamazepine or rifampin (see drug interaction section), an additional dose of 50mg of DTG (as a single agent) should be taken 12 hrs from the first dose of DTG/3TC.<sup>20</sup>

### Conclusion And Expert Opinion

DTG/3TC represents an effective NRTI drug-sparing option with demonstrated efficacy as initial therapy for the treatment of HIV-1 infection. Studies evaluating DTG/3TC for maintenance of virologic suppression for treatment-experienced patients are ongoing, and the expectation is that it will be just as successful as the combination of DTG/rilpivirine (RPV) that holds the distinction of being the first approved 2-drug regimen for maintenance therapy.

Both DTG and 3TC, as have been described in the earlier sections of this article, are potent antiretroviral compounds that both have favorable tolerability profiles and limited drug interaction potential. Reassuringly, clinical trials have shown that the regimen works well for individuals with high viral loads (100,000–500,000 copies/mL) and low CD4 counts (<200 cells/mm<sup>3</sup>) and that the concerns about treatment-emergent viral resistance for treatment failures are unwarranted as even where resistance to 3TC develops, resistance to DTG remains very rare due to its high resistance barrier. Treatment providers, however, may be wary of offering DTG/3TC to patients who are likely to be poorly or sub-optimally adherent to treatment.

It is important to note that certain categories of patients were either underrepresented or excluded in the late-phase clinical trials of DTG/3TC including women, individuals with very high viral loads (>500,000 copies/mL) – an important consideration for “test and treat” strategies, children less than 12 years of age or weighing <40kg, individuals with hepatitis B co-infection, those with resistance mutations to NRTI and/or INSTI class of ARVs and those with renal insufficiency (GFR<50mL/min). This impacts the generalizability of the prelicensure studies and highlight some populations for which more data are needed to justify its use. In addition, with emerging data suggestive of birth (neural tube) defects occurring at a low but significantly higher rate among pregnant women exposed to DTG compared to other comparator antiretroviral agents and the rate among the general population, there is lingering concern about its use for women of childbearing potential.<sup>39,40,47</sup> Similarly, neuropsychiatric side effects occurring as both short-term and long-term complications have also been reported with DTG exposure, including exacerbation of depressive disorders with suicides are a consideration for prescribing providers.<sup>48</sup>

By excluding the NRTIs – abacavir (ABC) and tenofovir (TDF or TAF), DTG/3TC excludes compounds that have been associated with long-term toxicities including cardiovascular disease, renal and bone toxicity. However, the exclusion of tenofovir (specifically TDF) also confers weaknesses on the DTG/3TC combination such that it is not a preferred regimen for HIV/HBV co-infected patients as 3TC is quite resistance prone and the favorable effect of TDF on lowering lipids (cholesterol) is lost.

Of note, INSTI resistance was not tested in GEMINI studies though the product label of DTG/3TC states that its use is only indicated in those without known INSTI mutations. This is not likely to be relevant in clinical practice as the prevalence of transmitted (pre-treatment) INSTI resistance remains extremely low (1.2%).<sup>49</sup>

Economic considerations are worth highlighting as well. The availability of generic 3TC enables DTG/3TC to enter the ARV market with a reduced price that is approximately 26% less than that of bictegravir/TAF/FTC and almost 35% less than the price of DRV/cobicistat, co-formulated with TAF/FTC. This may have a favorable impact on utilization and inclusion of this drug on treatment formularies.<sup>20</sup>

In the near future, with the anticipated emergence of long-acting ARV formulations, the era of the daily dosed STR as the preferred treatment approach may be experiencing the beginning of its end. Till that occurs, however, the approval of an effective and well-tolerated 2-drug STR for ARV-naïve PLWH is certainly a game-changer and welcome development.

## Disclosure

The authors report no conflicts of interest in this work.

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