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Expert Opinion on Pharmacotherapy

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ieop20

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To cite this article: Brandon L Christensen & Darrell HS Tan (2022): An up-to-date evaluation of dolutegravir/abacavir/lamivudine for the treatment of HIV, Expert Opinion on Pharmacotherapy, DOI: 10.1080/14656566.2022.2029409

To link to this article: https://doi.org/10.1080/14656566.2022.2029409

Published online: 24 Jan 2022.

EXPERT OPINION ON PHARMACOTHERAPY
https://doi.org/10.1080/14656566.2022.2029409

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DRUG EVALUATION

An up-to-date evaluation of dolutegravir/abacavir/lamivudine for the treatment of HIV

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ABSTRACT

Introduction: There are more than 30 agents available for the treatment of HIV with guidelines shifting toward integrase strand transfer inhibitors (INSTIs) as part of first line therapy. The fixed dose combination of dolutegravir (DTG), abacavir (ABC), and lamivudine (3TC) is a convenient, well tolerated, and highly effective option for treating HIV infection and remains a first line therapy across several prominent guidelines.

Areas covered: In this drug evaluation, the authors provide a comprehensive overview of DTG/ABC/3TC for the treatment of HIV including the pharmacokinetics, pharmacodynamics, efficacy, safety, and tolerability. The authors also provide the reader with their expert perspectives on this particular treatment strategy.

Expert opinion: While DTG/ABC/3TC remains a valuable HIV treatment option, newer combination regimens have entered the market. Bictegravir with tenofovir alafenamide and emtricitabine offers the benefit of same day initiation and efficacy in hepatitis B co-infection, while new two-drug regimens enhance the simplicity of HIV treatment. Continued study is required into the mechanisms and optimal management strategies for weight gain for many regimens, including DTG/ABC/3TC.

ARTICLE HISTORY
Received 31 August 2021
Accepted 11 January 2022

KEYWORDS
Antiretroviral; abacavir; dolutegravir; HIV; integrase strand transfer inhibitors; INSTI; lamivudine

1. Introduction

Treatments for human immunodeficiency virus (HIV) have improved dramatically in recent years, with a growing focus on improving tolerability, facilitating adherence, and optimizing quality of life for people living with HIV. The single-tablet combination of dolutegravir (DTG), abacavir (ABC), and lamivudine (3TC)[1] is a highly effective regimen that remains a preferred first-line treatment option in the American Department of Health and Human Services (DHHS)[2] and European AIDS Clinical Society guidelines[3] and an alternative first-line treatment in the International AIDS Society-USA guidelines [4].

2. Review of the compound

2.1. Overview of market

Worldwide, there are >30 antiretroviral medications available. Effective HIV treatment typically requires three of these agents in combination, usually including two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI), or integrase strand transfer inhibitor (INSTI). Additional classes include fusion inhibitors, CCR5 antagonist, and CD4 lymphocyte post-attachment inhibitors. INSTI-based regimens now dominate guidelines, based on their rapid reduction in viral load, excellent tolerability, low pill burden, and clinical efficacy

2.2. Introduction to compound

DTG entered the market in the early 2010s as the first once-daily, non-boosted agent in its class. The original INSTI, raltegravir (RAL), requires twice daily dosing [5] (extended release formulations available), and the second available INSTI, elvitegravir (EVG), requires pharmacokinetic boosting with cobicistat [6]. As a second generation INSTI, DTG generally maintains activity against viruses in which resistance has emerged to the earlier INSTIs [7]. Newer INSTIs include bictegravir (BIC), which is available as a fixed-dose combination with tenofovir alafenamide (TAF) and emtricitabine (FTC) and cabotegravir (CAB), which is available as the first long-acting injectable antiretroviral in combination with long-acting rilpivirine (RPV) [8,9].

ABC and 3TC are NRTIs usually dosed once daily and form the backbone of several regimens [10,11]. ABC/3TC was associated with a shorter time to virologic failure and first adverse event than TDF/FTC in those with high baseline viral load (HIV RNA>100,000 copies/mL) when used in combination with either the NNRTI efavirenz or the PI atazanavir/ritonavir [12]. However, these results have not consistently been reproducible with no difference noted in a subsequent observational study, prior to the use of INSTIs [13].

2.3. Chemistry

The combination tablet contains dolutegravir sodium 50 mg, abacavir sulfate 600 mg, and lamivudine 300 mg [1]. DTG inhibits

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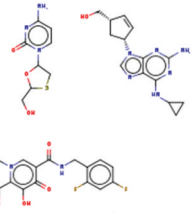
HIV replication by binding to the integrase enzyme, prior to integration, preventing the transfer of HIV viral DNA into the host DNA [14,15]. ABC is converted to carbovir triphosphate while 3TC is converted into lamivudine triphosphate. These metabolites compete with deoxyguanosine triphosphate and deoxycytidine triphosphate, respectively, for integration into the HIV viral DNA ending the DNA growth and inhibiting reverse transcription [11,16] (Box 1).

2.4. Pharmacodynamics

DTG has demonstrated good in vitro integrase inhibition activity and dissociates more slowly from the integrase enzyme than RAL or EVG (dissociative half-lives of 71, 8.8, and 2.7 h, respectively) [18]. In the first phase IIa trial using 50 mg daily, DTG was shown to have potent anti-HIV activity with a 2.5 log_{10} decrease in viral load at 10 days and higher levels of antiretroviral activity at higher doses of DTG [19].

Box 1. Drug summary.

Drug name	Dolutegravir/abacavir/lamivudine
Phase	Launched
Indication	HIV/AIDS infection
Pharmacology description	HIV integrase inhibitor Nucleoside reverse transcriptase inhibitor
Route of administration	Oral, swallowed
Chemical structure	
Pivotal trial(s)	[30–35, 37–40 and 17]

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ABC and 3TC have demonstrated good in vitro antiviral activity individually with additive effects in combination [20]. Both in vitro and in vivo, ABC selects for the reverse transcriptase mutations K65R, L74V, Y115F, and M184V while lamivudine selects for M184V/I [11,21]. The first and most frequent mutation to emerge when ABC/3TC is used in failing regimens is M184V/I, which confers high-level resistance to 3TC and FTC, and low-level resistance to ABC and didanosine (ddI). K65R, L74V, and Y115F individually cause 3–4 fold resistance to ABC [22].

Initial studies into the resistance pattern for DTG found no highly resistant mutants after 112 days during passage experiments [7]. These findings contrast with those for RAL and EVG, which have moderate barriers to resistance and are associated with the integrase mutations Q148 and N155 [23]. The N155 mutation confers low level resistance to DTG while Q148 imparts high level resistance only when several other secondary mutations are present [23,24].

In vivo, DTG has rarely been associated with treatment-emergent resistance both in INSTI-naïve and experienced patients, often in association with poor adherence, drug-drug interactions, high baseline viral load, and active opportunistic infections [25]. Resistance is typically via R263K, which imparts low level (~2-fold) resistance and a considerable viral fitness cost [23]. In non-type B viruses, DTG has selected for G118R at virologic failure, which imparts a > 5-fold reduction in DTG susceptibility [23,24]. Treatment-emerging DTG resistance is also rare in the pediatric population, even in the setting of virologic failure, provided DTG is paired with at least one other active antiretroviral [26].

2.5. Pharmacokinetics and metabolism

In a phase IIa study, DTG was readily absorbed, with maximum concentrations detected 1.5–2 h after administration (average half-life of 11–12 h) [19]. Steady state was achieved after 7 days, with a negative correlation between DTG concentration and viral load [19].

The oral bioavailability of DTG/ABC/3TC is >80% with the average time to maximum concentration being 2–3 h for DTG, 1.5 h for ABC, and 1 h for 3TC. The combination tablet can be taken with or without food [1]. DTG is highly protein bound (98.9%), ABC is moderately protein bound (~50%), and lamivudine, which has linear kinetics, has low protein binding (<36%) [1].

DTG is metabolized by three mechanisms including glucuronidation by UGT1A1, oxidation by CYP3A4, and through a sequential oxidative defluorination and glutathione conjunction [27]. Most is excreted in the stool (mean 64.0%) followed by the urine (mean 31.6%) [27]. ABC is predominantly metabolized hepatically through alcohol dehydrogenase and glucuronidation, with metabolites excreted in the urine; 2% is renally eliminated as unchanged compound. 3TC is excreted unchanged in urine, with minimal hepatic metabolism (<10%) [1]. Overall, DTG/ABC/3TC is associated with relatively few clinically significant drug-drug interactions, driven primarily by the DTG component (Table 2).

2.6. Clinical efficacy

Numerous clinical trials have demonstrated the efficacy, safety, and tolerability of DTG/ABC/3TC. For reasons described below, trial criteria required participants to be HLA-B*5701 negative, hepatitis B negative, and to have no significant resistance to agents within the regimen.

In the dose-ranging, phase IIb trial SPRING-1, participants were randomized 1:1:1:1 to DTG 10 mg, 25 mg, 50 mg, or efavirenz 600 mg in combination with TDF/3TC or ABC/3TC. Across all DTG doses, the proportion of participants with viral suppression to <50 copies/mL was >88% at 16 weeks, with the highest efficacy demonstrated at 50 mg (Table 1)[29].

Multiple phase III randomized controlled trials have demonstrated the efficacy of DTG in combination with ABC/3TC in treatment-naïve patients, compared to the leading comparator INSTI-, NNRTI-, and PI-based regimens at the time of trial conduct. In SPRING-2, DTG was non-inferior to RAL when used in combination with the investigator's choice of either ABC/3TC or TDF/FTC [30]. In SINGLE, DTG/ABC/3TC demonstrated superiority over EFV/TDF/FTC, with higher proportions of

Table 1. Summary of key clinical trials.

Trial	Population	Study Arms	Results
Treatment-naïve patients			
SPRING-1 [17] (Phase IIb)	• ≥18 years old • Treatment naïve HIV-1 • HIV viral load >1000 copies/mL • CD4 > 200 cells/uL	DTG 10, 25, 50 mg with • TDF/3TC • ABC/3TC EFZ 600 mg with • TDF/3TC • ABC/3TC	Virologic suppression (<50 copies/mL) at 96 weeks (proportion of participants in each group): • DTG 50 mg 88% • DTG 25 mg 78% • DTG 10 mg 79% • EFV 72%
SPRING-2 [30] (Phase III)	• ≥18 years old • Treatment naïve HIV-1 • HIV viral load >1000 copies/mL	DTG with • TDF/FTC • ABC/3TC RAL with • TDF/FTC • ABC/3TC	Virologic suppression (<50 copies/mL) non-inferior DTG 81% vs. RAL 76% at 96 weeks Adjusted difference 4.5% (95% CI −1.1–10.0)
SINGLE [31,32] (Phase III)	• ≥18 years old • Treatment naïve HIV-1 • HIV viral load >1000 copies/mL • HLA-B*5701 negative • No resistance to any study agents	• DTG/ABC/3TC • EFZ/TDF/3TC	Virologic suppression (<50 copies/mL) superior at • 48 weeks 88% vs. 81% (p = 0.003) • 96 weeks 80% vs. 72% (p = 0.006) • 144 weeks 71% vs 63% (p = 0.01) CD4 count significantly higher in DTG/ABC/3TC at 48 weeks (59 cells/mm3 95% CI 33–84, p < 0.001) Virologic response rate faster in DTG/ABC/3TC group (28 vs. 84 days, p < 0.001)
FLAMINGO [33,34] (Phase IIIb)	• ≥18 years old • Treatment naïve HIV-1 • HIV viral load >1000 copies/mL • No resistance to NRTIs or PIs	DTG with • TDF/FTC • ABC/3TC DRV/r with • TDF/FTC • ABC/3TC	Virologic suppression (<50 copies/mL) superior at 96 weeks DTG 80% vs. DRV/r 68% (p = 0.002) Adjusted difference 12.4 (95% CI 4.7–20.2)
BIC/TAF/FTC vs. DTG/ABC/3TC [35] (Phase III)	• ≥18 years old • Treatment naïve HIV-1 • HBV and HLA-B*5701 negative	• BIC/TAF/FTC • DTG/ABC/3TC	Virologic suppression (<50 copies/mL) non-inferior in BIC 88% vs. DTG 90% at 96 weeks Adjusted difference of −1.9 (95% CI −6.9–3.1)
SAILING [37] (Phase III)	• ≥18 years old • Treatment experienced • INSTI-inexperienced • Resistance to 2 or more classes • 1–2 fully active background agents • HIV viral load >400 copies/mL on two consecutive readings or >1000 copies/mL once	DTG with investigator selected background therapy vs. RAL with investigator selected background therapy	Virologic suppression (<50 copies/mL) superior in DTG 71% vs. RAL 64% at 48 weeks Adjusted difference 7.4 (95%CI0.7–14.2, p = 0.03) Significantly fewer treatment emergent resistance in DTG 1% vs. RAL 5% (p = 0.03)
Treatment-experienced patients			
VIKING [38] (Phase IIb)	• ≥18 years old • HIV viral load >1000 copies/mL • Current or past RAL treatment failure	DTG 50 mg daily while continuing failing regimen for 10 days then suggested switch to optimized regimen (Cohort I) vs. DTG 50 mg twice daily while continuing failing regimen for 10 days then mandated switch to optimized regimen (Cohort II)	Multivariable adjusted reduction in HIV viral load significantly higher at 24 weeks in cohort II (mean adjusted treatment difference, −0.32 log_{10} copies/mL; −1.76 vs. −1.45 log_{10} copies/mL, p = 0.017)
VIKING-3 [39]	• ≥18 years old • HIV viral load >500 copies/mL • Evidence of resistance to RAL and/or EVG and 2 other classes	Single arm of DTG 50 mg BID monotherapy for 7 days with addition of optimized background regimen from day 8	Mean change in baseline viral load was −1.43 log10 copies/mL (95% CI −1.50 to −1.34 log 10 copies/mL, p < 0.001) Virologic suppression (<50 copies/mL) achieved in 69% (95% CI 62–76%) at 24 weeks
DAWNING [40] (Phase IIIb)	• ≥18 years old • During 6 months treatment with one NNRTI plus two NRTIs had virologic failure • PI and INISTI naïve	• DTG with investigator chosen dual NRTI backbone • LPV/r with investigator chosen dual NRTI backbone	Virologic suppression (<50 copies/mL) superior in DTG 84% vs. LPV/r 70% at 48 weeks. Adjusted difference 13.8 (95%CI 7.3–20.3 p < 0.0001)

participants achieving VL<50 copies/mL at 48, 96, and 144 weeks, a shorter time to viral suppression, higher CD4 count increases at each time point, and no treatment emergent resistance mutations to INSTI or NRTIs in the DTG group (Table 1)[31,32]. Superior virologic efficacy was also seen in FLAMINGO comparing DTG to DRV/r, both in combination with the investigator's choice of either ABC/3TC or TDF/FTC at both 48 and 96 weeks (Table 1)[33,34].

More recently, a phase III trial compared DTG/ABC/3TC to the newer fixed-dose combination INSTI regimen BIC/TAF/FTC as initial treatment of HIV and showed non-inferiority between these two regimens at weeks 96 and 144 (Table 1) with no new treatment-related drug resistance in either arm and less gastrointestinal side effects with BIC/TAF/FTC [35,36]. Together, these trials demonstrate the excellent efficacy of DTG/ABC/3TC as initial therapy for HIV, compared to leading INSTI-, NNRTI-, or PI-based regimens.

High virologic efficacy has also been demonstrated for DTG-based regimens among treatment-experienced patients, though not always in combination with ABC/3TC. The SAILING trial compared DTG 50 mg once daily against RAL 400 mg twice daily, both in combination with an optimized background regimen, among INSTI-naïve patients with resistance to ≥2 other antiretroviral classes and found superiority of DTG in achieving VL<50 copies/mL at week 48 [37]. In the phase IIb VIKING trial, treatment-experienced participants with virologic failure on RAL and genotypic evidence of RAL resistance were randomized to DTG 50 mg once or twice daily, together with an optimized background regimen. While both groups experienced clinically meaningful reductions in HIV RNA, a significantly larger reduction was seen in the twice daily group (Table 1)[38]. Subsequently, the single-arm VIKING-3 study found DTG 50 mg twice daily together with an optimized background regimen was associated with virologic suppression to VL<50 copies/mL in 69% of participants by week 24 [39]. In DAWNING, treatment-experienced patients with evidence of previous virologic failure on NNRTI-based regimens had a higher rate of virologic suppression to VL<50 copies/mL with DTG compared to LPV/r, in combination with two NRTIs, at 48 weeks, strengthening this regimen's use in salvage therapy (Table 1)[40]. Notably, only 2% of participants received ABC/3TC as their NRTI backbone. DTG or DTG/ABC/3TC may thus be useful in highly treatment-experienced patients, although additional agents (including a second dose of DTG for INSTI-experienced patients) will generally be needed.

A recent 4101-person cohort study assessing the real-world effectiveness of DTG-based regimens showed only 7% virologic failure at 96 weeks with no differences by sex, HIV treatment status or ethnicity [41].

2.7. Safety and tolerability

The most common side effects of DTG/ABC/3TC include nausea (11–24%), diarrhea (6–16%), insomnia (10%), and headache (6–16%), which accounted for a small amount of treatment discontinuation in clinical trials [32,35,42].

Weight gain is common following initiation of antiretroviral therapy and is partially explained by 'return to health' (restoration of weight previously lost due to uncontrolled HIV replication). INSTIs have been shown to cause significantly more weight gain than PIs and particularly NNRTIs [43]. The weight gain associated with INSTIs could be explained by rapid virologic response with these regimens [44]. Within the INSTI class, DTG, BIC, and RAL have been shown to cause more weight gain than EVG/c, hypothesized to be a result of better adherence and/or GI side effects with cobicistat [43,45,46]. One proposed mechanism for DTG-associated weight gain has been its inhibition of α-melanocyte-stimulating hormone's interaction with human

Table 2. Select drug-drug interactions of dolutegravir [1,28].

Mechanism	Interacting drugs	Outcome	Clinical management
Metabolism of DTG by UGT1A1, CYP3A	Inducers of UGT1A1/CYP3A: antiretrovirals • Efavirenz, Etravirine • Tipranavir/ritonavir, • Fosamprenavir/ritonavir Antibiotics • Rifampin Anticonvulsants • Phenytoin • Carbamazepine • Phenobarbital Herbals • St. John's Wart	Reduce DTG concentrations	Consider increasing DTG component to twice daily
Cationic binding of DTG	• Antacids – Magnesium or aluminum containing • Iron supplements • Calcium supplements	Direct binding reducing absorption of DTG	Take DTG 2 hours before or 6 hours after culprit drug
Inhibition of OCT2, MATE1 transporters by DTG	• Metformin	Increase metformin concentrations	Consider decreasing metformin dosage

Abbreviations: organic cation transporter 2 (OCT2), multidrug and toxin extrusion 1 (MATE1), dolutegravir (DTG), UDP glucuronosyltransferase 1 family, polypeptide A1 (UGT1A1). cytochrome P450 3A4 (CYP3A4)

recombinant melanocortin 4 (MC4R), the absence of which is associated with obesity [47]. There is disproportionate weight gain in women over men, and blacks over non-blacks [43]. The management of this weight gain remains unclear, with diet and exercise as the mainstay of treatment. Whether switching regimens can mitigate ART-related weight gain is unknown.

DTG may be associated with higher rates of neuropsychiatric side effects including headache, insomnia, and dizziness [42]. However, the literature on its relationship with HIV-associated neurocognitive disorder (HAND) remains mixed. Rates of discontinuation due to neuropsychiatric side effects in the SINGLE, FLAMINGO, and SPRING-II trials were not different than comparator regimens. In one case series, increased suicidal ideation was noted after starting DTG but an association has not been established [48]. There is evidence showing higher rates of DTG discontinuation in women over men (HR = 2.64 95%CI = 1.23–5.65), with note that additional study is needed given the predominance of men in the original trials [49]. Evidence for this is furthered by an analysis showing women had higher rates of INSTI discontinuation for any adverse event compared to men [50]. One study exploring the neuropsychiatric effects of switching from DTG/ABC/3TC to EVG/COBI/FTC/TAF showed improvement in patient reported symptoms, neuropsychiatric adverse events, and neurocognitive status [41]. Moreover, there is some evidence that longer duration of INSTI exposure, particularly DTG, is associated with poor neurocognitive performance [51]; however, literature remains limited.

An unplanned analysis from the Botswana Harvard AIDS Institute Partnership Tsepamo birth outcomes surveillance study demonstrated higher rates of neural tube defects (NTD) among infants born to mothers who had used DTG, as opposed to EFV, at the time of conception [52]. Further analysis initially supported this assertion with 3 per 1000 deliveries in those on DTG at conception vs. 1 per 10,000 deliveries in those on alternative ART having NTD [53,54]. Studies in mice demonstrated a non-dose-dependent, 2-fold higher risk of NTD on therapeutic DTG [55] while another in zebrafish embryos showed supratherapeutic DTG levels produced toxicity (including morphologic and cardiac) which could be ameliorated by folic acid supplementation [56]. More recently, however, the difference in the prevalence of NTDs between DTG-based and other regimens was found to no longer be statistically significant [57], estimated at 0.19% versus 0.11% respectively (prevalence difference: 0.09% (95%CI = −0.03% to 0.30%). Of note, the NRTI backbone for all these analyses was TDF/FTC, and a signal was not seen among infants born to women initiating DTG during pregnancy. Recent DHHS guidelines thus suggest pregnancy testing before commencing DTG and include DTG-containing regimens, such as DTG/ABC/3TC, among the recommended options in individuals wishing to become pregnant [2].

Although not a true adverse event, serum creatinine elevations are seen with DTG, usually in the first 4 weeks. These increases are attributed to blockage of creatinine secretion by the renal organic cation transporter 2 [31,58]. Usually the rise is modest (10.2–13.4 umol/L) and not thought to reflect glomerular filtration, similar to other medications such as cobicistat [59].

ABC hypersensitivity reaction was seen in 5–8% of individuals before baseline HLA-B*5701 testing became routinely recommended in HIV care [20]. Reactions include fever, gastrointestinal upset, fatigue, malaise, and rash [20], which may become life-threatening if patients are rechallenged with the drug. As such, guidelines suggest routinely testing for this allele at baseline and avoiding ABC entirely in those who test positive. There is mixed evidence around the cardiac safety of ABC with several competing findings to date. The D:A:D study found current or recent use of ABC was associated with higher rates of myocardial infarction [19,60]. However, a large FDA meta-analysis found no association between ABC and myocardial infarction [61].

3TC is well tolerated with no major adverse effects for most patients. Guidelines suggest dose adjustments for those with creatinine clearance under 50 mL/min; however, studies have demonstrated safety across various stages of kidney disease, including dialysis [2,62].

2.8. Regulatory affairs

DTG/ABC/3TC is approved by major regulatory bodies including the Food and Drug Administration, European Medicines Agency, and Health Canada and is available in >65 countries [63].

3. Conclusion

DTG/ABC/3TC remains an effective, safe, and well-tolerated antiretroviral regimen, with non-inferior or even superior virologic efficacy compared to NNRTI-, PI-, and first-generation INSTI-based regimens among treatment-naïve patients, and excellent efficacy in salvage therapy. When compared to fixed dose combinations containing first generation INSTIs, DTG/ABC/3TC has the advantages of being dosed once daily, non-boosted, and having a higher genetic barrier to resistance. DTG/ABC/3TC remains a first-line treatment choice for treatment-naïve individuals and has non-inferior virologic efficacy compared to the other leading fixed-tablet INSTI combination, BIC/TAF/3TC.

4. Expert opinion

DTG/ABC/3TC was a ground-breaking regimen when first introduced, outperforming leading alternative regimens for HIV treatment. In the future, DTG/ABC/3TC's place in the guidelines may be diminished with the emergence of newer regimens including BIC/FTC/TAF and with the fundamental shift seen with two-drug regimens. The relative advantage of these newer options include same-day initiation of therapy in the newly diagnosed, given that DTG/ABC/3TC requires a negative HLA-B*5701 test prior to commencement. Furthermore, DTG/ABC/3TC is not suitable for HBV co-infected individuals, since the NRTI backbone is less active against hepatitis B than tenofovir plus either 3TC or FTC.

DTG/ABC/3TC may have a role in resource limited and other settings where BIC-based regimens may not yet be available, but HLA-B*5701 testing is. Additionally, this regimen may remain a suitable option in pregnancy compared to BIC-

based regimens, where sufficient data have yet to emerge. However, surveillance and mechanistic research is ongoing regarding the evolving relationship between DTG and NTDs [56].

The GEMINI trials have shifted the narrative on HIV treatment by demonstrating that DTG/3TC is non-inferior to DTG/TDF/FTC as initial therapy in treatment-naïve individuals with viral loads <500,000 copies/mL, with 86.0% vs. 89.5% achieving virologic suppression at 96 weeks (adjusted difference = −3.4%, 95% CI = −6.7, 0.0007) and no identified resistance to NRTI, PI, or NNRTI [64]. More recently, TANGO showed that a switch to DTG/3TC was non-inferior to remaining on a TAF-based regimen at 48 weeks in maintaining viral suppression [65]. Together, these data diminish the primacy of DTG/ABC/3TC in treatment-naïve and switch settings, given that DTG/3TC is associated with excellent efficacy while eliminating the costs, toxicity risks, and HLA*B-5701 testing requirements of ABC.

The role of DTG/ABC/3TC in initial therapy is being further eroded by the emergence of long-acting injectable CAB/RPV, whose 8-weekly injection schedule now offers the convenience of a completely pill-free regimen. However, given that the pivotal trials of CAB/RPV employed DTG/ABC/3TC for the induction phase of therapy in treatment-naïve patients [8,9], DTG/ABC/3TC could be a useful 'fallback' regimen for patients who start but subsequently discontinue injectable therapy.

The continued development of two-drug and long-acting regimens is expected to further simplify antiretroviral therapy, although DTG and DTG/ABC/3TC may continue to be useful components of therapy for individuals with treatment experience. This is in large part because DTG-based regimens demonstrate a high genetic barrier to resistance, with little treatment-emergent resistance [35,64,66–68]. Recent data have even suggested the efficacy of DTG/ABC/3TC in those whose virus harbors M184V/I mutations, which impart 3TC and FTC resistance and decreased ABC susceptibility. In a pooled analysis of patients from five observational cohorts followed for a median of 288.5 days, the risk of virologic failure among individuals switched to DTG/ABC/3TC did not differ between those with and without this mutation in a propensity score weighted analysis (HR = 1.27,95%CI = 0.35,4.59) [69]. Similarly, in the ART-PRO study of dual DTG/3TC therapy, there were no cases of virologic failure at 96 weeks among participants with prior 3TC or FTC treatment but no 3TC resistance-associated mutations (RAMs) on baseline proviral DNA population sequencing, despite 51% having such RAMs on prior viral RNA genotyping and 71% having them on next generation sequencing [70]. Although further study is required in this context to show long-term efficacy, these data provide reassurance regarding the use of this regimen in settings or clinical circumstances where access to comprehensive resistance data are lacking.

Several questions remain unanswered regarding DTG/ABC/3TC including the mechanism and mitigation strategies for weight gain. Furthermore, direct comparisons of DTG and BIC with respect to weight gain are needed.

DTG/ABC/3TC remains an excellent choice in the treatment of HIV, although innovative new regimens continue to emerge with less toxicity, simplicity of initiation, and alternative routes of administration.

Declaration of interest

DHS Tan's institution has received investigator-initiated research grants from AbbVie, Gilead Sciences, and ViiV Healthcare. DHS Tan is also a Site Principal Investigator for clinical trials sponsored by GlaxoSmithKline. Furthermore, DHS Tan is supported by a Tier 2 Canada Research Chair in HIV Prevention and STI Research. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Funding

This manuscript has not been funded.

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Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

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