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REVIEW

HIV Treatment with the Two-Drug Regimen Dolutegravir Plus Lamivudine in Real-world Clinical Practice: A Systematic Literature Review

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ABSTRACT

The two-drug regimen dolutegravir plus lamivudine demonstrated durable efficacy for up to 3 years in phase III studies and a high barrier to resistance in treatment-naive and virologically suppressed people with HIV (PWH). This systematic literature review summarizes real-world evidence evaluating effectiveness and safety of dolutegravir plus lamivudine. We searched Ovid MEDLINE®, Embase®, PubMed, Cochrane

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library, and relevant international conference proceedings from 2013 to 2020. Qualitative synthesis of virologic suppression at Week 48, treatment-emergent resistance, discontinuation rates, and comorbidities was undertaken, with no statistical analyses conducted. Linked publications and potential for duplication in reporting of outcomes for cohorts and populations were identified, and the publication reporting the highest number of PWH receiving dolutegravir plus lamivudine was included in the analysis. Thirty-four studies reporting on cohorts of PWH not suspected to be linked or to include duplicate data receiving dolutegravir plus lamivudine were identified ($N = 5017$). Of 3744 virologically suppressed PWH who switched to dolutegravir plus lamivudine, 603 (16%) reported history of virologic failure. Nineteen studies included effectiveness data ($n = 3558$), four of which included data from treatment-naive PWH ($n = 69$). In studies with > 100 PWH, high rates of virologic suppression (Week 48, 97–100%) were maintained with dolutegravir plus lamivudine, with low rates of virologic failure (0–3.3 per 100 person-years of follow-up); one instance of emergent integrase strand transfer inhibitor resistance was reported in a complex treatment-experienced individual. Rates of discontinuation due to adverse events were low and consistent with previously observed trial data. Dolutegravir plus lamivudine minimally impacted renal function and had minimal impact on or improved lipid profiles and bone mineral density. This systematic review demonstrates that effectiveness and safety of doutegravir plus lamivudine in clinical practice support data from randomized controlled trials with regard to high rates of virologic response, low rates of discontinuation, and a high barrier to resistance.

Keywords: Dolutegravir; Dual therapy; HIV-1 infection; Lamivudine; Real-world

Key Points

The two-drug regimen dolutegravir plus lamivudine has demonstrated durable efficacy and a high barrier to resistance in phase III clinical trials with data up to 3 years, and this review summarizes data on the effectiveness and safety of dolutegravir plus lamivudine in real-world settings.

Virologic suppression was achieved and maintained with dolutegravir plus lamivudine in a wide variety of people with HIV-1, including those simplifying from a three-drug regimen.

Rates of virologic failure were low in virologically suppressed individuals who switched to dolutegravir plus lamivudine, and rates of discontinuation due to adverse events were low and consistent with previously observed trial data.

Results from this systematic literature review demonstrate that real-world effectiveness and safety of dolutegravir plus lamivudine in clinical practice support data from randomized controlled trials regarding high rates of virologic response, low rates of discontinuation due to adverse events, and a high barrier to resistance.

INTRODUCTION

Recommended antiretroviral therapy (ART) regimens historically included a core agent such as a non-nucleoside reverse transcriptase inhibitor (NNRTI), boosted protease inhibitor (PI), or integrase strand transfer inhibitor (INSTI) plus 2 nucleoside reverse transcriptase inhibitors (NRTIs) [1]. These three-drug regimens (3DRs) have been successful at improving life expectancy for people with HIV (PWH) to near that of the general population [2]. Therefore,

PWH are living longer and consequently will likely remain on ART for decades, in the continued absence of a cure. Antiretroviral therapy may contribute to comorbidities associated with aging, including renal, liver, or cardiovascular disease; osteoporosis; and metabolic disorders including diabetes and dyslipidemia [3–6]. Therefore, two-drug regimens (2DRs) have been investigated as a means of reducing the number of antiretroviral agents needed in a complete ART regimen. To be successful, a 2DR should include at least one antiretroviral agent with high potency and a high barrier to resistance [7]. Protease inhibitors were included in early investigations of 2DRs because of their high barrier to resistance and non-inferior efficacy to 3DRs [8–10]; however, long-term treatment with PIs is associated with cardiovascular and cerebrovascular disease as well as adverse metabolic effects including dyslipidemia and insulin resistance [11]. In addition, pharmacokinetic enhancements required with boosted PIs can lead to complex drug-drug interactions [12, 13]; thus, the need for a well-tolerated, unboosted, potent 2DR with a high barrier to resistance remains.

The INSTI dolutegravir has a high barrier to resistance and has demonstrated high potency for inhibition of HIV-1 in phase III studies [14–16], making it well suited for use in a 2DR. Treatment with dolutegravir in combination with lamivudine in ART-naive participants through 144 weeks demonstrated long-term non-inferior efficacy vs. dolutegravir plus tenofovir disoproxil fumarate/emtricitabine in the phase III GEMINI-1 and -2 studies [17]. Treatment with dolutegravir plus lamivudine and dolutegravir plus tenofovir disoproxil fumarate/emtricitabine led to similar rapid declines in plasma HIV-1 RNA regardless of baseline viral load, similar discontinuation rates, and few instances of participants meeting confirmed virologic withdrawal criteria and only one case of resistance in a participant with reported non-adherence on dolutegravir plus lamivudine [17–19]. Additionally, switching to the fixed-dose combination dolutegravir/lamivudine in adults with HIV-1 suppressed on a three- or four-drug tenofovir alafenamide-based regimen demonstrated good safety with non-inferior efficacy compared with continuing on a tenofovir alafenamide-based regimen in the phase III TANGO study, with no confirmed virologic withdrawals or observed resistance through 144 weeks in the dolutegravir/lamivudine treatment group [20]. These data led to the marketing authorization (starting in 2019) of the fixed-dose combination of dolutegravir/lamivudine as a once-daily, single-tablet 2DR by the US Food and Drug Administration (FDA) [21], European Medicines Agency [22], Australian Therapeutic Goods Administration [23], and Japanese Ministry of Health, Labour and Welfare [24]. In addition, dolutegravir/lamivudine is included as a recommended or preferred first-line regimen and a switch option for virologically suppressed PWH in major international guidelines [1, 25, 26].

Overall, approximately 1100 participants received dolutegravir plus lamivudine in the phase III GEMINI-1 and -2 and TANGO clinical studies [19, 27]. Real-world evidence can provide data in populations that may be underrepresented in clinical trials—including women, older PWH, PWH from diverse racial backgrounds, and PWH with comorbidities—and can aid understanding of the generalizability of the effectiveness and safety results from these clinical studies to a more diverse population as is treated in clinical practice. Published data from PWH using dolutegravir plus lamivudine in real-world settings are available, and there is accumulating evidence for the effectiveness of this 2DR in clinical practice. The objective of this systematic literature review was to identify and summarize real-world evidence in published literature from January 1, 2013, to December 31, 2020, regarding the effectiveness, safety, and barrier to resistance of dolutegravir plus lamivudine.

METHODS

Search Strategy

A systematic literature review of Ovid MEDLINE®, Embase®, PubMed, and Cochrane Central Register of Controlled Trials databases was conducted on December 31, 2020, to identify

real-world observational studies of dolutegravir plus lamivudine in PWH. In addition, relevant conference proceedings (listed in Fig. 1) were manually searched. Key terms included in the search strings were related to HIV, study types typically associated with real-world evidence (Embase and MEDLINE searches only), and dolutegravir (full search strategies are reported in Table S1 in Supplementary Material).

Eligibility Criteria

Eligible studies were articles and conference presentations on the 2DR dolutegravir plus lamivudine (either dosed separately or as a fixed-dose combination) in PWH in non-interventional and observational studies. Eligibility assessment was independently reviewed by two reviewers. Any discrepancies between the decisions of the two reviewers at either stage of screening were resolved by a third independent reviewer. Titles and abstracts were screened during the initial stage, and then full-text articles were screened during the second stage. Only articles with publication dates from January 1, 2013, through December 31, 2020, were included; studies with < 10 PWH, case reports, reviews, and editorials were excluded as were preclinical, in vitro, animal, or controlled studies.

Linked publications were identified based on trial identifiers in addition to reporting of population, sites, and study period. Studies were also reviewed to assess whether there was potential duplication in reporting of outcomes for cohorts and populations. If duplication of cohort/population was suspected, the publication reporting the highest number of PWH receiving dolutegravir plus lamivudine, the overarching study, was included in the analysis.

Data Extraction

Data were extracted from eligible studies using a list of data outputs that was determined before the extraction. If more than one publication was identified as describing a single trial (linked publication), the data were compiled into a single entry in the data extraction table to avoid double counting PWH and studies. Information was extracted from each included study on (1) number of PWH receiving dolutegravir plus lamivudine; (2) prior ART experience; (3) previous treatment regimens and duration of ART; (4) baseline resistance; (5) baseline demographic characteristics; (6) effectiveness outcomes; (7) virologic failure; (8) treatment-emergent resistance; (9) treatment discontinuations; and (10) lipid, renal, and bone mineral density (BMD) outcomes. To determine the quality of eligible observational studies, a single reviewer assessed the extent of loss to follow-up as well as the methods of selecting PWH, assessing effectiveness outcomes, and handling missing data using the Downs and Black checklist [28]. All information was extracted from the published material; there were no instances of personal communication with the author to confirm or retrieve data.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

Of the 2657 records identified through database search using Ovid MEDLINE, Embase, PubMed, and Cochrane Library databases and conference information, 240 were removed as duplicates and 761 studies remained after the screen of the title and abstract and were further screened for the full-text article. Of these, 367 articles and 186 conference abstracts (reporting data on dolutegravir-based regimens) were screened for data evaluating dolutegravir dual therapy (n = 141). Seventy-three of the 141 publications met the inclusion criteria for reporting data on dolutegravir plus lamivudine and included 34 cohorts not suspected to be linked or to include duplicate data (Fig. 1). Quality measures assessing the risk of bias within these studies are presented in Table S2 in Supplementary Material.

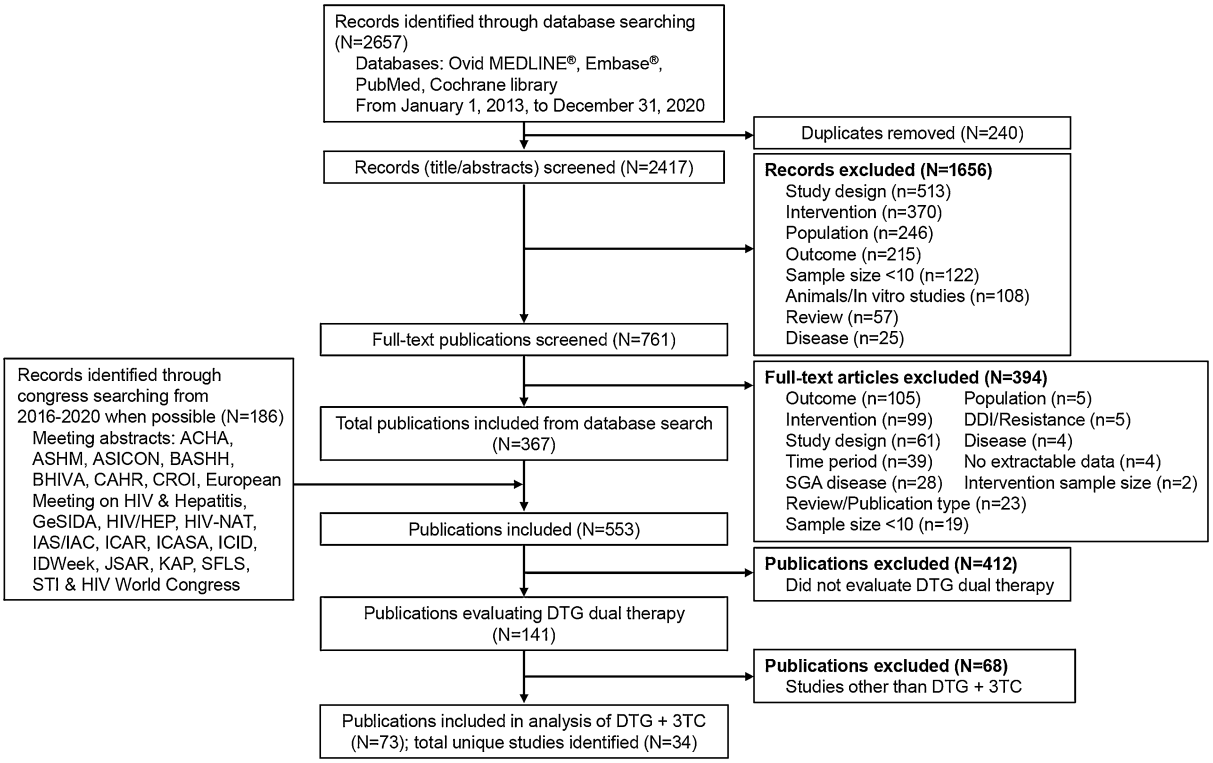

Fig. 1 Flow diagram of literature search for systematic review. *ACHA* Asian Conference on Hepatitis and AIDS, *ASHM* Australasian HIV & AIDS Conference, *ASICON* National Conference of AIDS Society of India, *BASHH* British Association for Sexual Health and HIV, *BHIVA* British HIV Association, *CAHR* Canadian Conference on HIV/AIDS Research, *CROI* Conference on Retroviruses and Opportunistic Infections, *DDI* drug-drug interaction, *DTG* dolutegravir, *GeSIDA* Grupo de Estudio del SIDA-SEIMC, *HIV/HEP* HIV & Hepatitis in the Americas, *HIV-NAT* The HIV Netherlands Australia Thailand Research Collaboration, *IAS/IAC* International AIDS Society/International AIDS Conference, *ICAR* International Conference on Antiviral Research, *ICASA* International Conference on AIDS and STIs in Africa, *ICID* International Congress on Infectious Diseases, *JSAR* Japanese Society for AIDS Research, *KAP* Kenya Association of Physicians, *SFLS* Société Française De Lutte Contre Le Sida, *SGA* small for gestational age, *STI* sexually transmitted infection, *3TC* lamivudine

Baseline Characteristics

This analysis included 5017 PWH who were reported to be using dolutegravir plus lamivudine. In 20 studies that reported data for sex, the majority of PWH treated with dolutegravir plus lamivudine were male (range, 60-97%) [29–48]. In five of seven studies with reported racial demographics, ≥ 90% of PWH were identified as White [30, 32, 33, 42, 43, 46, 47]. In the other two studies, one population was 29% White, 45% Black, and 27% Hispanic [42] and the other population was 52% White, 35% Black, and 13% Asian [43]. Median ages ranged from 34.0 to 60.5 years among the 17 studies that reported median age [29–37, 39, 41, 42, 44, 45, 47, 48]. Among studies clearly reporting treatment history, 4474 individuals switched from another regimen, and 73 were treatment naive (effectiveness was reported in 3489 and 69 PWH, respectively). Those who switched from another regimen had extensive ART experience ranging from 1.3 to 17.9 years in studies that reported prior ART duration [29, 30, 32–36, 38, 41, 42, 44, 46–49]. This analysis includes 1251 individuals who switched to dolutegravir plus lamivudine with no prior virologic failure and no known resistance where reported across eight studies

[29, 34, 43, 47, 50–53]. Previous virologic failure was reported for 603 PWH in 9 studies [29, 30, 34, 35, 41, 43, 45, 46, 48]. Baseline substitutions associated with ART resistance were reported in 286/1668 (17%) PWH with available baseline genotype data [30, 31, 34, 35, 40, 45, 48, 54–56]. Among studies that reported information on prior regimens (n = 1958), many PWH switched to dolutegravir plus lamivudine from 3DRs (n = 1718; 88%) [29, 35, 42, 43, 48, 49, 54, 57]. Primary reasons for switching to dolutegravir plus lamivudine included toxicity of the previous regimen [48, 52], avoidance of drug interactions [36, 48, 52, 53], treatment regimen simplification [34, 48, 52, 58], and comorbidities (including cardiovascular, renal, and bone disease) [34, 53, 58]. Of the comorbidities reported at baseline, bone, hypertension, liver, and metabolic comorbidities were most prevalent (Table 1) [32]. In 3 studies (n = 1028) that reported baseline prevalence of PWH with hepatitis B virus (HBV) coinfection who were treated with dolutegravir plus lamivudine, 19 were reported to have a positive hepatitis B surface antigen test or chronic HBV infection at baseline [29, 34, 40].

Virologic Effectiveness of Dolutegravir Plus Lamivudine in Real-world Settings

Four studies investigated the on-treatment effectiveness of dolutegravir plus lamivudine in 69 treatment-naive PWH (Table S3 in Supplementary Material) [31, 40, 43, 44]. In one study, after 4 weeks of dolutegravir plus lamivudine therapy, all 17 PWH with available data had HIV-1 RNA < 200 copies/ml [40]. At Week 8, two studies reported 89% (8/9) and 100% (4/4) of PWH with HIV-1 RNA < 50 copies/ml, respectively [31, 43]. In the former study, all seven PWH with follow-up and five with 48 weeks of follow-up achieved HIV-1 RNA < 50 copies/ml [31]. After 6 months, one study reported 90% (19/21) of PWH achieving HIV-1 RNA < 50 copies/ml; one (5%) individual had HIV-1 RNA ≥ 200 copies/ml, but none discontinued because of virologic failure [44]. One individual was reported to have baseline D232N INSTI mutation and had undetectable viral load at last follow-up (8 weeks) [31].

The way that effectiveness outcomes in virologically suppressed PWH were assessed varied among studies included in this analysis. Outcomes included proportion of PWH achieving virologic suppression (plasma HIV-1 RNA < 50 copies/ml) [32, 52], estimated probability of maintaining virologic suppression [30, 48, 59–61], and absence of virologic failure [62] or estimated probability of remaining free of virologic failure [63–65], defined as two consecutive viral loads ≥ 50 copies/ml or a single viral load ≥ 1000 copies/ml. Virologic effectiveness observed across five cohorts with ≥ 100 suppressed switch PWH (n = 2224) ranged from 97% to 100% at Week 48 (Fig. 2) [29, 30, 32, 48, 52] and 92% to 100% at Week 96 [29, 30, 32, 48]; virologic failures per 100 person-years of follow-up (PYFU) ranged from 0 to 3.3 at Week 48 (Fig. 2).

In the only study that reported effectiveness data specifically in PWH with reported history of virologic failure regardless of the presence of M184I/V, detection of HIV-1 RNA ≥ 50 copies/ml occurred in 1.4–1.9 events per 100 PYFU in 194 PWH with previous virologic failure and 0.5–1.0 events per 100 PYFU in 772 PWH without previous virologic failure [29]. In several cohorts that included virologically suppressed PWH with historic M184I/V substitution (n = 154) before treatment switch to dolutegravir plus lamivudine, five PWH experienced virologic failure (3%; Table 2), and none of the five had treatment-emergent resistance-associated INSTI substitution at virologic failure [30, 33, 45, 48, 52, 55, 66].

Treatment-Emergent Resistance

Documented resistance-associated substitutions were detected in two individuals treated with dolutegravir plus lamivudine with accompanying baseline genotypic data among all studies in which effectiveness was evaluated and regardless of prior ART experience (n = 3558; < 1%; Fig. S1 in Supplementary Material) [48, 52]. In one individual who was virologically suppressed at time of switch to dolutegravir plus

Table 1 Characteristics of studies with ≥ 100 PWH who switched to DTG + 3TC reporting effectiveness outcomes at week 48

Source	Study type	PWH receiving DTG + 3TC, *n*	Inclusion criteria	Time on cART, median, years	PWH switching from 3DR, *n* (%)	Previous virologic failures, *n* (%)	Baseline comorbidities, *n* (%)	PWH with available genotype at baseline (*n*)	Baseline resistance substitutions in PWH with available genotype at baseline, *n* (%)	Effectiveness outcome at Week 48
Gagliardini (2020) [29]	Multicenter, retrospective	966	VL < 50 c/ml	8.4 years	NR	194 (20)	HCV, 172 (18) HBsAg, 15 (2)	NR	NR	Viral rebound (confirmed VL ≥ 50 c/ml)
Galizzi (2020) [48]	Single-center, observational, retrospective	307	VL < 50 c/ml	15.2 years	NR	134 (44)	HCV, 79 (26)	NR	NR	Estimated probability of maintaining VL < 50 c/ml
Hidalgo-Tenorio (2019) [52]	Multicenter, observational, retrospective	177	Treated ≥ 6 months with ART with VL < 50 c/ml, ≤ 1 viral blip for ≥ 6 months before study, and no history of VF; no documented resistance to study drugs; no HBV coinfection treated with tenofovir	13 years	Total, 116 (66)	0	HCV, 17 (10)	90	4 (4) had M184V substitutions	VL < 50 c/ml (ITT)
Baldin et al. (2019) [30]	Multicenter, retrospective, observational	556	Treated ≥ 6 months with ART with VL < 50 c/ml; HBsAg negative	11.5 years	2 NRTIs + NNRTI, 141 (26); 2 NRTIs + PI or bPI, 77 (14); 2 NRTIs + INSTI, 89 (16); total, 307 (55)	226 (41)	HCV, 125 (23)	451	45 (8) had M184V substitutions	Estimated probability of maintaining VL < 50 c/ml
Maggiolo (2018) [32]	Multicenter, prospective	218	HBsAg negative; absence of M184V substitution; VL < 50 c/ml for > 6 months	10.2 years	NR	NR	Bone, 75 (34); hypertension, 67 (31); liver, 53 (24); metabolic, 46 (21); CNS 40 (18); diabetes, 27 (12); cardiovascular, 27 (12); renal 24 (11); GI tract, 16 (7); neoplastic, 14 (6); pulmonary, 6 (3)	NR	NR	VL < 50 c/ml

Duplicate studies have been removed

ART antiretroviral therapy, *bPI* boosted PI, *cART* current ART, *c/ml* copies/ml, *CNS* central nervous system, *DTG* dolutegravir, *GI* gastrointestinal, *HBsAg* hepatitis B surface antigen, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *INSTI* integrase strand transfer inhibitor, *ITT* intention to treat, *NNRTI* non-nucleoside reverse transcriptase inhibitor, *NR* not reported, *NRTI* nucleoside reverse transcriptase inhibitor, *PI* protease inhibitor, *PWH* people with HIV, *RPV* rilpivirine, *3TC* lamivudine, *VF* virologic failure, *VL* viral load

lamivudine and whose history of previous virologic failure was unreported, NRTI resistance-associated substitution M41M/L was detected at virologic failure but not before starting dolutegravir plus lamivudine. No INSTI substitutions were detected, and HIV-1 RNA levels were 65 and 107 copies/ml at virologic failure [48]. The other individual had a viral load of 229 copies/ml and no previous history of virologic failure or documented resistance-associated mutations when switching from raltegravir plus abacavir/lamivudine to dolutegravir plus lamivudine. At virologic failure, the S147G integrase substitution was detected (HIV-1 RNA 1123–8899 copies/ml), and virologic suppression was achieved after adding boosted darunavir to the existing dolutegravir plus lamivudine regimen (HIV-1 RNA 131 copies/ml) [52].

In a separate retrospective study analyzing ten PWH with no previous history of virologic failure who experienced virologic failure after dolutegravir plus lamivudine use, two had M184V/I at failure and one had E138A. However, there were no historic resistance data available to inform whether these were present before use of the 2DR [67].

Rate of Discontinuations with Dolutegravir Plus Lamivudine

In studies with available safety data regardless of ART experience, discontinuations occurred in 2–20% of the cohorts [30, 32, 33, 36, 41, 43, 44, 48, 52, 68], and in the five studies with available safety data and ≥ 100 PWH, discontinuations due to adverse events (AEs) or treatment intolerance/toxicity occurred in 2% to 8% (Fig. S2 in Supplementary Material) [30, 32, 39, 44, 52]. The most commonly reported reasons for discontinuation due to AEs/toxicity included neuropsychiatric, gastrointestinal and hepatic, and renal events. Neuropsychiatric AEs led to treatment discontinuations in 1% to 3% of PWH (Fig. S2 in Supplementary Material) [30, 32, 39, 52]. Neuropsychiatric outcomes resulting in discontinuation of dolutegravir plus lamivudine included insomnia, anxiety, headache, mood disorders, and sudden onset of nightmares [30, 32, 52]. Although no HBV flares were reported and a modest increase in liver enzymes occurred in one PWH, that individual did not discontinue treatment [34].

Renal Outcomes in PWH Receiving Dolutegravir Plus Lamivudine

Six studies (all in virologically suppressed PWH) switching to dolutegravir plus lamivudine assessed serum creatinine levels and estimated glomerular filtration rate (eGFR) measured by creatinine clearance (Table 3) [34, 36, 42, 52, 69, 70]. Although increases in serum creatinine [52, 69] and decreases in eGFR [36, 70] were reported, changes were minimal and generally not considered to be clinically significant.

Lipid Outcomes in PWH Switching to Dolutegravir Plus Lamivudine

Of five studies reporting lipid outcomes (all in virologically suppressed PWH), two reported no statistically significant changes from baseline in lipid parameters [34, 36], and three reported significant improvements from baseline (Table 3). Overall, switching to dolutegravir plus lamivudine was associated with reductions in total cholesterol and triglycerides [30, 69]; increases in high-density lipoprotein cholesterol was observed in two of three studies [30, 52, 69]. Two studies reported that switching to dolutegravir plus lamivudine from a PI- or INSTI-based regimen was associated with more pronounced improvement in total cholesterol and/or triglycerides [30], whereas previous tenofovir disoproxil fumarate use was predictive of an increase in total cholesterol or triglyceride levels after switching to dolutegravir plus lamivudine [60, 64]. However, other studies found that pre-switch regimens were not predictive of changes in lipid profiles after switching to dolutegravir plus lamivudine [52, 59].

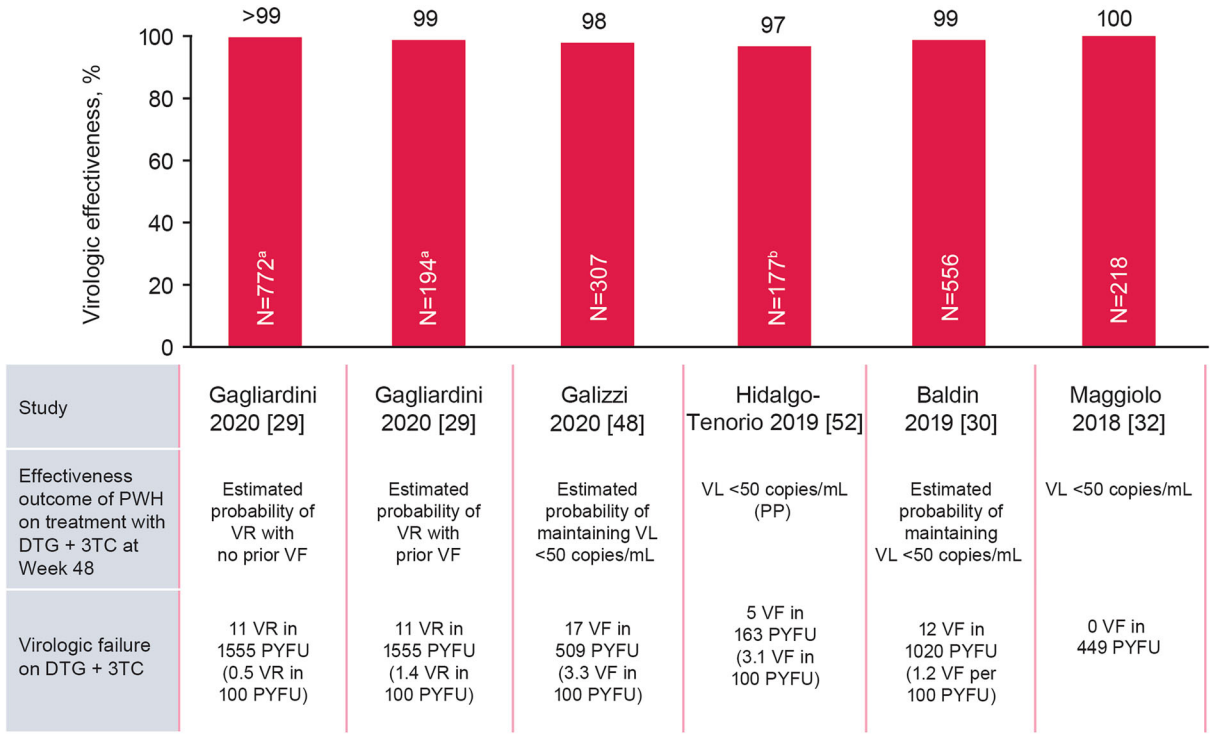

Fig. 2 Proportion of PWH in switch cohorts treated with DTG + 3TC reporting effectiveness at Week 48. Data included for studies with N ≥ 100. Duplicate studies have been removed. *DTG* dolutegravir, *PP* per protocol, *PWH* people with HIV, *PYFU* person-years of follow-up, *3TC* lamivudine, *VF* virologic failure, *VL* viral load, *VR* virologic rebound. [a]*N* = 772 PWH with no prior VF; *N* = 194 PWH with ≥ 1 prior VF. [b]*N* is for overall population and includes 6 PWH who were not suppressed at baseline

Bone Health

Three studies (all in virologically suppressed PWH) examined the effect of dolutegravir plus lamivudine on BMD (Table S4 in Supplementary Material) [71–73]. Two of these studies reported significant improvements from baseline in spine BMD at Week 48 (mean increase from baseline in lumbar spine BMD, + 0.03 g/cm^2; $P = 0.001$) [71] or Week 96 (percentage increase from baseline in spine BMD, 3.2; $P < 0.001$) [72], and the third reported no difference compared with baseline [73]. One study found that length of exposure to tenofovir disoproxil fumarate in pre-switch regimens was a negative predictor of BMD improvement [71].

DISCUSSION

In this systematic literature search of real-world studies, dolutegravir plus lamivudine has been observed to be prescribed for 5017 PWH with a wide spectrum of ART experience, including 603 who experienced previous virologic failure before switching to dolutegravir plus lamivudine. Overall, high rates of virologic suppression were maintained with dolutegravir plus lamivudine regardless of prior virologic failure, with high proportions of PWH achieving specified effectiveness outcomes at Weeks 48 and 96. In addition, rates of virologic failure were low in virologically suppressed PWH who switched to dolutegravir plus lamivudine, though history of previous virologic failure was associated with a modest increase in virologic failure, consistent with previous analyses showing that prior virologic failure is a significant risk factor

Table 2 PWH with M184V treated with DTG + 3TC in real-world studies

Cohort or study	Study type	Study population	PWH on DTG + 3TC, *N*	M184V					Definition of VF
				PWH with M184V/I, *n*	M184V detection method	Time point	PWH maintaining/achieving virologic effectiveness, *n* or %[a]	PWH with VF, *n*	
DOLULAM[b] (France) [33, 55]	Single-center, observational, prospective	Virologically suppressed; heavily treatment experienced	27	17	Historical RNA, 8; Sanger DNA, 2; NGS, 7	2 years	17	0	2 confirmed VL > 50 c/ml
DOLAMA[b] (Spain) [52]	Multicenter, observational, retrospective	Virologically suppressed	177	4[c]	BL genotypic test	48 week	3	1	2 confirmed VL > 50 c/ml
ODOACRE[d] (Italy) [30]	Multicenter, observational, retrospective	Virologically suppressed	556	45	NR	48 week	NR	2	2 confirmed VL ≥ 50 c/ml or single VL ≥ 1000 c/ml
ARCA (Italy) [66]	Retrospective, observational	Virologically suppressed	126	21	Historical RNA	1 years	NR for M184V; 95% and 96% estimated probability of remaining free of VF in PWH with M184V (n = 349) and without M184V (n = 87)[c]	0	2 confirmed VL > 50 c/ml or single VL ≥ 200 c/ml

Table 2 continued

Cohort or study	Study type	Study population	PWH on DTG + 3TC, *N*	M184V					Definition of VF
				PWH with M184V/I, *n*	M184V detection method	Time point	PWH maintaining/achieving virologic effectiveness, *n* or %[a]	PWH with VF, *n*	
Galizzi (2020) [48]	Single-center, retrospective	Virologically suppressed	307	60[f]	Historical RNA	1.74 years (median follow-up)	NR for M184V; 97% and 97% estimated probability of remaining free of VF in PWH with M184V and without M184V	2[g]	Confirmed VL > 50 c/ml or single VL > 1000 c/ml
Battagin (2020) [45]	Retrospective	Virologically suppressed	61	7	Genotypic resistance test	Week 24	NR for M184V, but no PWH with M184V had VF	0	From undetectable to HIV-1 RNA > 20 c/ml

Duplicate studies have been removed

BL baseline, *bPI* boosted protease inhibitor, *c/ml* copies/ml, *DTG* dolutegravir, *INSTI* integrase strand transfer inhibitor, *NGS* next-generation sequencing, *NR* not reported, *PWH* people with HIV, *PYFU* person-years of follow-up, *RPV* rilpivirine, *3TC* lamivudine, *VF* virologic failure, *VL* viral load

[a] Defined as VL < 50 c/ml

[b] Studies included in the total number of PWH treated with DTG + 3TC in studies reporting M184V data

[c] Of 90 tested

[d] Only one publication from the ODOACRE cohort is presented to minimize the potential duplication of headcount from this cohort; this is not the publication used to establish the ODOACRE headcount of PWH receiving DTG + 3TC in the total number of PWH treated with DTG + 3TC in studies

[e] For the overall study population in which PWH were treated with 3TC + bPI or 3TC + INSTI

[f] Of 220 tested from the population receiving DTG + 3TC or DTG + RPV

[g] Three additional PWH had VF while receiving DTG + 3TC but did not have baseline resistance data available

Table 3 Reported lipid and renal outcomes in PWH receiving DTG + 3TC

Study	PWH on DTG + 3TC, *N*	Time point (week)[a]	Lipid outcomes with DTG + 3TC vs. BL		Renal outcomes with DTG + 3TC vs. BL
Maggiolo (2017) [69]	94	24	Significant decrease in TC (− 7 mg/dl; $P = 0.047$) and TG (− 31 mg/dl; $P = 0.012$) Significant increase in HDL (+ 4 mg/dl; $P = 0.036$) No significant change in LDL (− 7 mg/dl; $P = 0.355$)	Improved	Significant increase in mean creatinine level was observed in the first 8 weeks (0.06 mg/dl; $P < 0.0001$) and leveled out at 24 week
Hidalgo-Tenorio (2019) [52]	177	48	Significant decrease in TC (− 8 mg/dl; $P = 0.002$), TG (− 48 mg/dl; $P = 0.0001$), and HDL (− 25 mg/dl; $P = 0.002$) Significant increase in LDL (+ 14 mg/dl; $P = 0.003$) and TC:HDL ratio ($P = 0.0018$)	Improved	Significant increase in mean creatinine level from baseline (1.04 mg/dl) to Week 48 (1.15 mg/dl; $P = 0.001$) but changes were not considered clinically relevant
Reynes (2016) [70]	27	48	NR	–	Median decrease from baseline of − 2.5 and − 9 ml/min/1.73 m^2 for PWH switching from a previous regimen with or without TDF, respectively
Yagci-Caglayik (2017) [34]	32	30	No statistically significant change in lipids	Unchanged	eGFR increased to > 60 ml/min/m^2 in 3 of 13 PWH with BL eGFR < 60 ml/min/m^2 Creatinine increased in 1 individual
Baldin (2019) [30]	556	144	Significant decrease in TC (− 9.1 mg/dl; $P = 0.007$) and TG (− 2.7 mg/dl; $P = 0.009$) Significant increase in HDL (+ 5.4 mg/dl; $P = 0.036$)	Improved	NR
Tan (2019) [36]	56	112	No significant change in unfasted TC levels	Unchanged	Small decrease in median eGFR from baseline (− 1 ml/min/1.73 m^2)

Table 3 continued

Study	PWH on DTG + 3TC, *N*	Time point (week)[a]	Lipid outcomes with DTG + 3TC vs. BL		Renal outcomes with DTG + 3TC vs. BL
Hiryak (2020) [42]	49	16	NR	–	No change in median serum creatinine (− 0.06 mg/dl (IQR, − 0.15, 0.06)

Duplicate studies have been removed

BL baseline, *DTG* dolutegravir, *eGFR* estimated glomerular filtration rate, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *NR* not reported, *PWH* people with HIV, *TC* total cholesterol, *TG* triglycerides, *3TC* lamivudine

[a] Value in this column refers to the time point at which the outcome was reported or median follow-up/length of treatment if no specific time point was provided by the authors

for future virologic failure [74]. Because different methods were used to assess effectiveness outcomes across individual studies in this analysis, the ability to assess outcomes with dolutegravir plus lamivudine across real-world cohorts was limited. However, when only studies with the effectiveness outcome at Week 48 of HIV-1 RNA < 50 copies/ml were considered, virologic effectiveness ranged from 97% to 100% at Week 48 and 92% to 100% at Week 96; one study reported 97% at Week 144. In studies that reported effectiveness in PWH with M184V at baseline (n = 154), five PWH (3%) experienced virologic failure on treatment with dolutegravir plus lamivudine, and none of the five had detected treatment-emergent INSTI mutations. Thus, these findings provide evidence for very high effectiveness of dolutegravir plus lamivudine in clinical practice and are consistent with results seen in the phase III TANGO study in which < 1% of PWH had HIV-1 RNA ≥ 50 copies/ml (per FDA algorithm) and 86% maintained virologic suppression (defined as HIV-1 RNA < 50 copies/ml) at Week 144 after switching to dolutegravir/lamivudine from a tenofovir alafenamide–based three- or four-drug regimen [20]. The high effectiveness observed in real-world clinical practice provides reassurance in broad patient types beyond those included in phase III clinical trials.

Among those for whom genotypic resistance testing was performed at follow-up, two PWH across real-world studies of dolutegravir plus lamivudine were reported to have treatment-emergent resistance substitutions identified at time of virologic failure, one of which was an integrase substitution. Even among PWH on dolutegravir plus lamivudine who experienced virologic failure and underwent genotypic resistance testing, the incidence of treatment-emergent resistance was very low. The rare observation of treatment-emergent resistance in real-world cohorts is consistent with the high barrier to resistance of dolutegravir plus lamivudine observed in phase III randomized controlled trials. In GEMINI-1 and -2, there was only one case of emergent resistance in > 700 treatment-naive participants treated with dolutegravir plus lamivudine (administered as separate tablets) over 3 years, and in TANGO (where participants received fixed-dose dolutegravir/lamivudine), there were no cases of virologic failure or resistance reported in > 300 virologically suppressed participants through 144 weeks on dolutegravir/lamivudine [17, 20]. In these studies, there were no obvious trends of an impact of M184V substitution at time of switch and virologic effectiveness of dolutegravir plus lamivudine, particularly in PWH with long durations of virologic suppression [30, 66]. One potential explanation for the limited impact of M184V on efficacy of the lamivudine-containing regimen is its association with decreased viral fitness and lower replication capacity, which could reduce the likelihood of viral rebound over time [75, 76].

Overall, dolutegravir plus lamivudine was generally well tolerated, and rates of discontinuation due to AEs, toxicities, and intolerance were < 8%, with follow-up times ranging from approximately 0.5–3 years. In the studies included in this analysis, rate of discontinuation due to neuropsychiatric events was low (< 4%) and consistent with the safety profile of dolutegravir plus lamivudine in clinical studies [19, 27].

Several switch studies of dolutegravir plus lamivudine included in this analysis reported increases in creatinine levels [52, 69] and decreases in calculated creatinine clearance [36, 60, 70, 77], consistent with the known, non-pathological inhibitory effect of dolutegravir on creatinine secretion [78]. This analysis showed that switching to dolutegravir plus lamivudine was generally associated with minimal impact or improvements in total cholesterol and triglycerides, consistent with outcomes reported in the phase III TANGO study [27, 79]. Although real-world studies reporting on BMD outcomes with dolutegravir plus lamivudine are limited, two studies reported improvements in BMD after switching to dolutegravir plus lamivudine [71, 72], including in PWH previously on tenofovir disoproxil fumarate-containing regimens, which have been shown to negatively affect BMD [80]. This is consistent with the pooled analysis of the phase III GEMINI-1 and -2 trials in treatment-naive PWH in which changes from baseline in bone biomarkers at Week 144 favored dolutegravir plus lamivudine compared with dolutegravir plus tenofovir disoproxil fumarate/emtricitabine [17]. It should be noted that, unlike tenofovir disoproxil fumarate, the long-term effects of tenofovir alafenamide on bone and renal biomarkers and BMD is inconclusive. Taken together, a treatment regimen containing dolutegravir, which does not contain tenofovir and has a low risk of drug-drug interactions [81], may be an alternative treatment option for PWH with or at risk of renal, cardiovascular, or bone comorbidities, which is especially important as more PWH are aging and becoming increasingly at risk of these comorbidities.

Our systematic literature review has several limitations. Selection of studies was limited to those for which the authors chose to publish the research or present it at various HIV conferences. None of the studies that were retrospective analyses described how missing data were handled or reported data on adherence to medication, which could impact the observed treatment effect, for example, by underestimating tolerability issues not leading to treatment discontinuation. Although reporting of baseline regimens before switch was incomplete in the studies included in this analysis, based on the publication dates of some studies, it can be assumed that many individuals were switched from older regimens, which should be considered when assessing the overall efficacy and safety of dolutegravir plus lamivudine. Genotypic resistance testing was not performed in every individual with virologic failure, preventing a complete characterization of all virologic failures. In addition, although studies of duplicate populations were removed when identified, potential overlap between cohorts cannot be ruled out. Although the GEMINI-1 and -2 studies demonstrated efficacy and safety of dolutegravir plus lamivudine in ART-naive participants [19], only 1% (73/5017) of PWH receiving dolutegravir plus lamivudine in real-world cohorts were ART naive at baseline, highlighting the need for additional data from this population. However, the effectiveness data observed for first-line use of dolutegravir plus lamivudine in ART-naive PWH (n = 69) resemble the results observed in clinical trials. Moreover, study populations were predominantly White (29–100%) and male (60–97%), and only one study reported effectiveness by baseline CD4 + cell count, highlighting the need for additional real-world effectiveness and safety data for dolutegravir plus lamivudine in other populations [31]. Dolutegravir plus lamivudine has the potential to be beneficial in an aging population with other comorbidities and polypharmacy, although more real-world data will be needed to understand the extent of the benefit associated with this 2DR in older populations.

CONCLUSION

Dolutegravir plus lamivudine is a complete 2DR for the treatment of HIV-1 infection and reduces the number of antiretroviral drugs taken by individuals without compromising virologic control. On the basis of data reported from clinical practice, virologic suppression was achieved and maintained with dolutegravir plus lamivudine in a wide variety of PWH, including those simplifying their treatment from a 3DR to a 2DR. The regimen is generally well tolerated, with little impact on existing comorbidities and a low rate of discontinuations due to AEs. Overall, results from this systematic literature review demonstrate that real-world effectiveness and safety of dolutegravir plus lamivudine in clinical practice support data from randomized controlled trials with regard to high rates of virologic response, low rates of discontinuation due to AEs, and a high barrier to resistance.

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