Lipid Changes in Real-world Studies With the 2-Drug Regimen Dolutegravir and Lamivudine (DTG + 3TC) in People With HIV-1: A Systematic Literature Review

P165

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Key Takeaways

- **A systematic literature review of real-world studies was performed to assess the effect of dolutegravir and lamivudine (DTG + 3TC) on lipid parameters in antiretroviral therapy (ART)-naive and virologically suppressed switch populations**
- **Overall, outcomes from real-world observational studies from a variety of geographic regions and various pre-switch ART regimens generally showed improvements or no changes in lipid parameters after initiating or switching to DTG + 3TC, reflecting findings from clinical trials**
- **Few studies reporting lipid outcomes, small numbers of ART-naive participants assessed, and lack of data on lipid-modifying agents and lifestyle factors that could affect lipids indicate current data gaps in real-world studies**

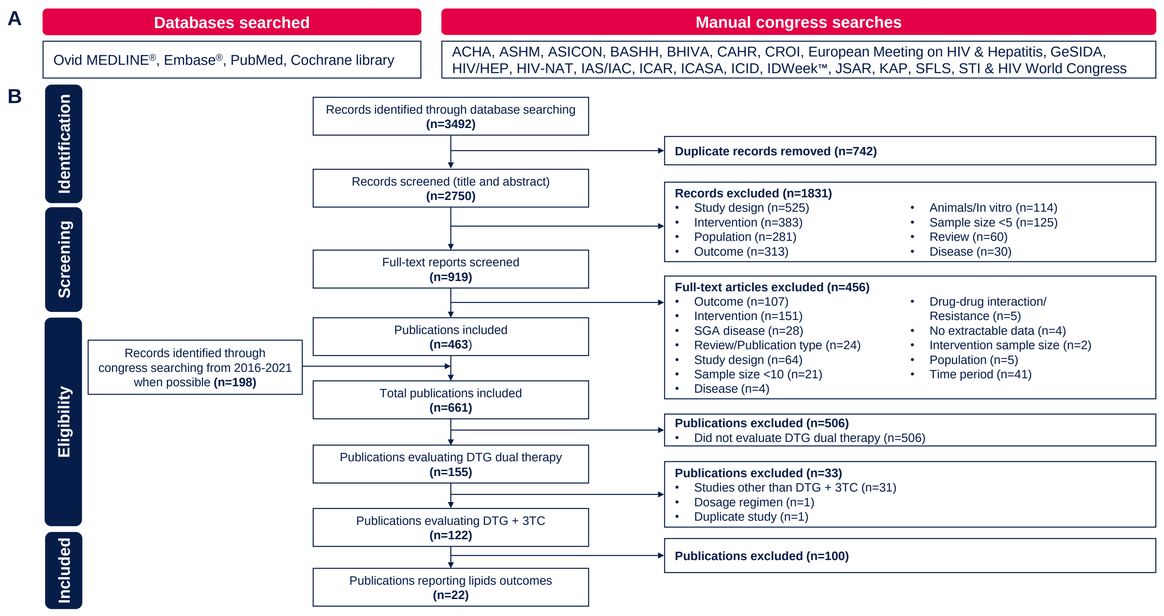
Introduction

- Virologically suppressed people with HIV-1 (PWH) experienced generally favorable changes in lipid parameters when switching to DTG/3TC from boosted TAF-based regimens through 144 weeks in the TANGO study[1] and minimal changes in lipids when switching from various ART regimens through 48 weeks in the SALSA study[2]
- In ART-naive PWH, favorable decreases in total cholesterol/HDL-C ratio were observed in both those initiating DTG + 3TC or a regimen containing lipid-modifying TDF (DTG + TDF/FTC) through Week 144 in the GEMINI-1/-2 studies[3]
- Randomized controlled trials (RCTs) are conducted under controlled settings in selected populations that may not always be representative of the population of interest, and RCTs may not report non-effectiveness outcomes that are important for overall health when living with HIV-1, such as treatment effect on lipid profiles over longer time periods
- Real-world evidence (RWE) can complement RCT results by reporting outcomes for individuals who would normally be excluded from RCTs[4] as well as fill data gaps related to other endpoints meaningful to PWH
- Here, we summarize RWE on the effect of DTG + 3TC on lipid parameters in ART-naive or suppressed switch settings

Methods

- We conducted a systematic literature review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement
- RWE studies reporting on DTG + 3TC use in PWH were retrieved from Ovid MEDLINE®, Embase®, PubMed, Cochrane library, and relevant international conference proceedings from January 2013 to February 2022 (Figure 1)
- Publications providing data on lipid parameters associated with DTG + 3TC use were included
- Lipid outcome analyses were based on the "main study" representing its cohort, defined as the study with the highest reported N values; if 2 or more studies reported the same N values in a cohort, the most recent study was chosen

Figure 1. (A) Databases and Congress Searches Included and (B) PRISMA Flow Diagram



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; 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; SGA, small for gestational age; SFLS, Société Française De Lutte Contre Le Sida; STI, sexually transmitted infection.

Results

Cohorts and Studies

- This systematic literature review includes 122 publications from 103 RWE studies of 44 unique cohorts (N=8034) reporting on DTG + 3TC use
- Of these 44 cohorts, 8 reported data on lipid outcomes in 22 studies (N=1141 PWH), including 20 studies of virologically suppressed PWH (n=1094)[5-24] and 2 of ART-naive PWH (n=47)[25,26] initiating DTG + 3TC (Table 1)

Participant Demographics and Characteristics

- Among suppressed cohorts reporting lipid outcomes, mean/median age ranged from 47.1 to 60.5 years, 74% of PWH were male, and various ART regimens were used before switch (median ART duration, 8.4-13 years; Table 2)
  - Duration of follow-up ranged from 30 weeks to 5 years
  - In these studies, DTG + 3TC was associated with generally improved lipid profiles, with reductions or no changes in most lipid parameters reported (Figure 2)
- Among ART-naive cohorts reporting lipid outcomes, median age ranged from 31 to 34.5 years and 89% of PWH were male (Table 2)
  - Duration of follow-up was 15.4 person-years in one cohort and 48 weeks in the other
  - Lipid outcomes for these studies are summarized in Figure 2

Table 1. Summary of Studies Reporting From Real-world Cohorts

Cohort	Studies included
Virologically suppressed PWH who switched to DTG + 3TC	
ODOACRE	Baldin 2016,[5] **Baldin 2019a,[6]** Baldin 2019b,[8] Baldin 2020,[7] Borghetti 2016,[9] Borghetti 2018,[11] Borghetti 2019,[12] Borghetti 2017a,[10] Borghetti 2017b,[13] Ciccullo 2019,[16] Lombardi 2018,[18] Lombardi 2019[24]
Calza	Calza 2020a,[14] **Calza 2020b[15]**
DOLAMA	**Hidalgo-Tenorio 2019[17]**
Maggiolo	Maggiolo 2017,[19] **Maggiolo 2021[20]**
Tan	**Tan 2019,[21]** Tan 2018[22]
HIVTR	**Yagci-Caglayik 2017[23]**
ART-naive PWH who initiated DTG + 3TC	
Deng	**Deng 2022[25]**
ODOACRE	**Ciccullo 2021[26]**

Bolded text indicates the main study for each cohort that was used for lipid analyses.

Table 2. Selected Demographics and Baseline Characteristics by Treatment Experience and Study

Virologically suppressed PWH who switched to DTG + 3TC

Main study (N)	Country	Age, median (IQR), y[a]	Sex, n (%)	Prior duration of ART, median (IQR), y[a]	Prior ART regimen: NRTIs	Prior ART regimen: Core agents	CD4+ cell count at switch, cells/mm³, median (IQR)[a]
Baldin 2019 (N=556)[6]	Italy	51.7 (45.3-57.4)	Male, 391 (70.3)	11.5 (6.1-18.3)	Dual therapy: 40.7%, triple therapy: 55.2%; TDF/FTC: 41.9%	NNRTI: 25.6%, PI or bPI: 14.0%, INI: 16.2%	668 (495-890)
Calza 2020 (N=59)[15]	Italy	47.1 (18.5)[b]	Male, 43 (72.9)	8.4 (2.6)[b]	ABC/3TC: 49.1%, TDF/FTC: 45.8%, TAF/FTC: 10.2%	DTG: 59.3%, bDRV: 18.6%, EVG/c: 13.6%	598 (217)[b]
Hidalgo-Tenorio 2019 (N=177)[17]	Spain	48.5 (14.2)[b]	Male, 137 (77.4)	13 (4-18)	bPI monotherapy (LPV- or DRV-based): 16.4%; dual therapy (various ART regimens): 18.1%; triple therapy: 65.5%		697.7 (337.2)[b]
Maggiolo 2021 (N=218)[20]	Multinational (Italy, 94%)	52 (12)	Male, 164 (75.2)	10.2 (13)	NRTI: 93.6%; TDF: 59.2%, ABC: 27.5%	NNRTI: 49.5%, EFV: 18.8%; PI: 32.6%, DRV: 14.7%; INI: 22.5%, RAL: 11.0%	669 (446)
Tan 2019 (N=52)[21]	UK	60.5	Male, 44 (84.6)	9.4	TDF: 64.3%, ABC: 62.5%	EFV: 48.2%, DRV/r: 44.6%	94% with >350 cells/mm³
Yagci-Caglayik 2017 (N=32)[23]	Turkey	54 (41-64)[c]	Male, 27 (84.4)	Not reported	TDF/FTC: 66%, 3TC: 25%	PI: 50%, LPV/r: 41%; NNRTI: 13%, EFV: 13%; INSTI: 53%, RAL: 22%, DTG: 22%	272 (131-471)

ART-naive PWH who initiated DTG + 3TC

Study (N)	Country	Age, median (IQR), y[a]	Sex, n (%)	HIV-1 RNA, median (IQR), c/mL[a]	CD4+ cell count, cells/mm³, median (IQR)[a]
Deng 2022 (N=27)[25]	China	31 (24-38)[c]	Male, 27 (100)	61,100 (33,500-229,000)[c]	222.07 (176.67)[b]
Ciccullo 2021 (N=20)[26]	Italy	34.5 (25.2-53.5)	Male, 15 (75.0)	4.78 $\log_{10}$ (4.01-5.00)	342 (239-472)

[a]Unless otherwise indicated. [b]Mean (SD). [c]Median (range).

Figure 2. Summary of Lipid Parameter Outcomes From RWE Cohorts Switching to or Initiating DTG + 3TC[a]

Main study (cohort)	N	Time of lipid assessment	Total cholesterol, mg/dL	Change from BL	LDL-C, mg/dL	Change from BL	HDL-C, mg/dL	Change from BL	Total cholesterol/ HDL-C ratio	Change from BL	Triglycerides, mg/dL	Change from BL
Virologically suppressed PWH who switched to DTG + 3TC												
Baldin 2019 (ODOACRE)[6]	556	144 wk	Median change from BL, −9.1	+ *P*=0.007	NR		Median change from BL, 5.4	+ *P*=0.036	NR		Median change from BL, −2.7	+ *P*=0.009
Calza 2020[15]	59	12 mo	Mean (SD) change from BL, 10.4 (5.9)	= *P*=0.338	Mean (SD) change from BL, 5.5 (2.8)	= *P*=0.511	Mean (SD) change from BL, 0.7 (0.2)	= *P*=0.768	NR		Mean (SD) change from BL, −11.9 (7.9)	= *P*=0.671
Hidalgo-Tenorio 2019 (DOLAMA)[17]	177	48 wk	Mean (SD): BL, 195.3 (52) Wk 48, 187.7 (57.17)	+ *P*=0.002	Mean (SD): BL, 93.08 (43.19) Wk 48, 107.81 (37.6)	− *P*=0.003	Mean (SD): BL, 74.02 (46.51) Wk 48, 49.1 (15.24)	− *P*=0.002	Mean (SD): BL, 3.49 (1.84) Wk 48, 4.13 (1.51)	− *P*=0.018	Mean (SD): BL, 212.3 (244.9) Wk 48, 164.6 (213.27)	+ *P*=0.0001
Maggiolo 2021[20]	218	5 y	NR	+ *P*=0.001[b]	NR		NR	= NS[c]	NR		NR	= NS[c]
Tan 2019[21]	52	>1 y	Mean unfasted cholesterol: BL, 5.65; >1 y, 5.16	= NS	NR		NR		NR		NR	
Yagci-Caglayik 2017 (HIVTR)[23]	32	Median 30 wk	NR	= NS[c]	NR	= NS[c]	NR	= NS[c]	NR		NR	= NS[c]
ART-naive PWH who initiated DTG + 3TC												
Deng 2022[25]	27	48 wk	Elevated levels; hypercholesterolemia after ART (n=1; 3.7%)	**NA[d]**	Elevated levels after ART (n=1; 3.7%)	**NA[d]**	Elevated levels after ART (n=2; 7.4%)	**NA[d]**	NR		Elevated levels; hypertriglyceridemia after ART (n=3; 11.1%)	**NA[d]**
Ciccullo 2021 (ODOACRE)[26]	20	15.4 PYFU	NR	= NS[c]	NR	= NS[c]	NR	= NS[c]	NR		NR	

BL, baseline; NA, not available; NR, not reported; NS, not statistically significant; PYFU, person-years of follow-up. [a]Point estimates for lipid changes were not available for any cohort. [b]*P* value was the only value reported in the publication. [c]Results were described as not significant and no other values were reported in the publication. [d]No statistical data were provided for change from baseline. Data shown are n (%) of PWH with elevated lipid parameters after ART initiation. [e]Improved was defined as an increase from baseline in HDL-C and as a decrease from baseline in total cholesterol, LDL-C, total cholesterol/HDL-C ratio, and triglycerides.

\+ Improved[e] − Worsened = Did not change

Conclusions

- Consistent with clinical trial experience, RWE data from >1000 PWH suggest that switching to DTG/3TC from various ART regimens or initiating DTG + 3TC has positive or minimal effects on lipid profiles
  - Virologically suppressed PWH generally experienced improvements or no changes in lipid profiles after switching to DTG + 3TC in most cohorts; 1 cohort observed unfavorable changes in LDL-C, HDL-C, and total cholesterol/HDL-C ratio
  - ART-naive PWH initiating DTG + 3TC experienced minimal impact on lipid profiles
- A data gap exists among RWE regarding the effect of DTG + 3TC on lipid profiles due to the lack of studies reporting lipid outcomes
  - A neutral effect on lipids is an important factor in overall health when living with HIV-1; additional RWE studies are needed to learn more about these outcomes and other HIV-1 treatment endpoints relevant to PWH

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