Systematic Literature Review of Real-world Experience With the 2-Drug Regimen Dolutegravir and Lamivudine in People With HIV Who Would Not Have Met Inclusion Criteria for the Phase 3 Clinical Program

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Key Takeaways

- **A systematic literature review was performed to summarize effectiveness outcomes reported from real-world evidence (RWE) studies in which people with HIV (PWH) with baseline characteristics that were not consistent with inclusion criteria for the dolutegravir and lamivudine (DTG + 3TC) phase 3 clinical development program randomized controlled trials (RCTs) either initiated or switched to DTG + 3TC**
- **RWE from PWH with various baseline characteristics, including clinical development program RCT exclusion criteria (eg, prior virologic failure [VF] or evidence of baseline drug resistance), support the durable efficacy and high barrier to resistance of DTG + 3TC**

Introduction

- In phase 3 clinical development program RCTs, DTG + 3TC demonstrated durable efficacy in both treatment-naive (GEMINI-1/-2)[1] and virologically suppressed switch (TANGO, SALSA)[2,3] participants
- Eligibility criteria for these RCTs included
  - No history of VF or any major nucleoside reverse transcriptase inhibitor or integrase inhibitor–associated mutations
  - No baseline hepatitis B virus (HBV) co-infection or need for hepatitis C virus (HCV) therapy
  - Viral load (VL) ≤500,000 c/mL at screening (GEMINI)[1] or <50 c/mL for >6 months (TANGO, SALSA)[2,3]
    - In the GEMINI studies, although participants had VL ≤500,000 c/mL at screening, 28 had VL ≥500,000 c/mL at treatment initiation[1]
- RCTs are conducted under controlled settings with a selected population that is not always representative of the population of interest; real-world studies can be used to better understand how DTG + 3TC performs in populations that include PWH whose characteristics would have prevented them from participating in RCTs
- This work is a follow-up to a previous systematic literature review of real-world data that supported the overall high effectiveness, safety, and durability of DTG + 3TC observed in clinical trials[4]
- We summarized studies of RWE for DTG + 3TC use in PWH with baseline characteristics not consistent with clinical development program RCT inclusion criteria

Methods

- We conducted a systematic literature review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement
- RWE studies that reported 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)
  - Studies with <10 PWH with baseline characteristics that would exclude them from phase 3 clinical development program RCTs, case reports, reviews, editorials, and preclinical studies were excluded

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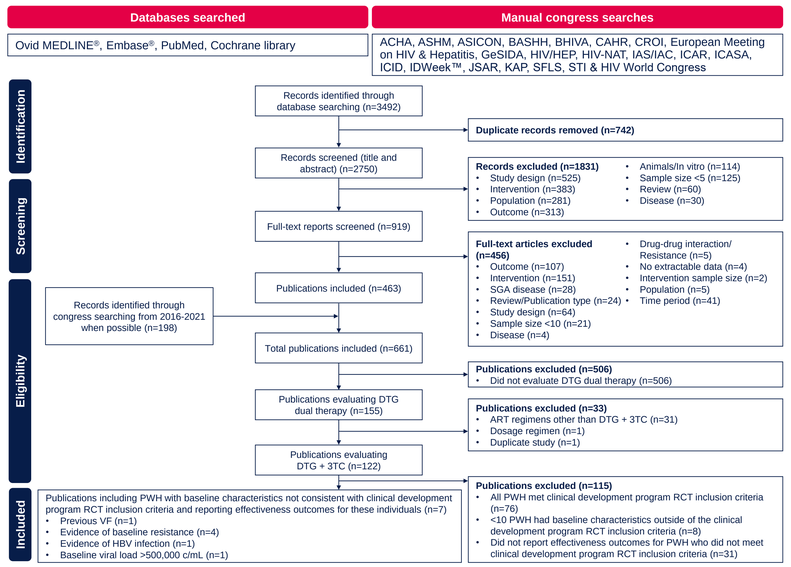
Figure 1. (A) Databases and Congress Searches Included and (B) PRISMA Flow Diagram



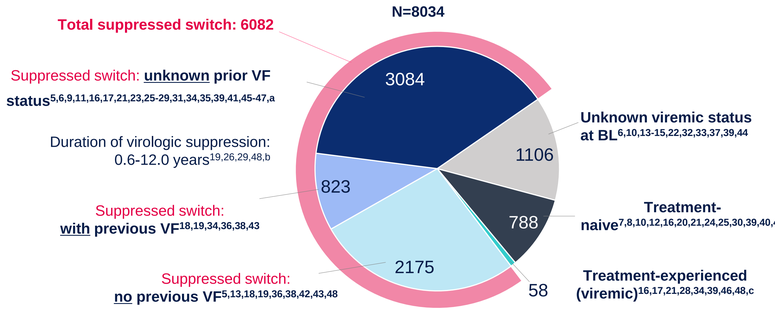
ACHA, Asian Conference on Hepatitis and AIDS; ASHM, Australasian HIV & AIDS Conference; ASICON, National Conference of AIDS Society of India; BASHH, British Association for Sexual Health and HIV; BHIVA, British HIV Association; CAHR, Canadian Conference on HIV/AIDS Research; CROI, Conference on Retroviruses 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 Participants

- This review includes 122 publications from 103 RWE studies of 44 unique cohorts (Figure 2)[5-48]

Figure 2. DTG + 3TC Real-world Cohorts According to Prior Treatment Experience and Viremic Status



BL, baseline; VF, virologic failure. Potential overlap between patient cohorts cannot be ruled out. [a]1 study used the term "therapeutic failures," the definition of which is unclear[47]; 74 PWH without previous therapeutic failure are included in the "no previous VF" population and 3 with therapeutic failure are included in the "unknown prior VF status" population. [b]Includes all studies reporting ranges for duration of virologic suppression; values reported here are IQRs only. [c]1 study defined viremic as ≥ or <20 c/mL and target detected.[23]

- Of the 8034 PWH receiving DTG + 3TC, 61% were based in Southern Europe (Italy, Spain, Portugal; n=4934),[5-9,11,14-20,23,24,27-30,32,34,36,37,40,42,44,47] 14% in Western Europe (France and Germany; n=1130),[26,33,39] 5% each in Northern Europe (UK; n=439)[13,21,22,43,46] and Canada (n=391),[45] 2% each in the United States (n=181)[10,25] and Brazil (n=123),[35,41] 1% in China (n=96),[12] and <1% in Turkey (n=32)[48]; the remaining 9% were from mixed regions in Europe (n=708)[31,38]
- 18 (41%) of the 44 unique real-world cohorts, represented by 65 unique studies (77 unique publications), included ≥1 study that reported ≥10 PWH whose baseline characteristics were not consistent with clinical development program RCT inclusion criteria; the 26 unique studies (27 unique publications) reporting these PWH are summarized in Figure 3
  - 9 unique studies (11 publications) were not characterized by cohort (eg, observed multiple cohorts)
  - 26 (59%) of the 44 unique real-world cohorts were not included:
    - 25 (57%) cohorts represented by 28 unique studies (33 unique publications) did not report PWH with baseline characteristics that were outside of the clinical development program RCT inclusion criteria
    - 1 (2%) cohort (representing 1 unique study and 1 unique publication) reported <10 PWH (n=1 PWH) with baseline characteristics that were outside of the clinical development program RCT inclusion criteria[21]

Figure 3. Reported Efficacy of DTG + 3TC From Real-world Studies in PWH With Characteristics Inconsistent With RCT Inclusion Criteria

Characteristic	Publications identifying PWH with characteristic		Number of PWH with characteristic		Cohort(s)[a]	Effectiveness outcomes
Previous VF	7	Total	1134	Total	Palmier[34] CSLHIV[36] LAMRES[38] Stephenson[43] ODOACRE[49] Multiple[50,b] ICONA[19]	• Over ~1500 PYFU, probability of VF at 1 year was low (0.4% or 1.2%, depending on VF criteria)
	1	Reported outcomes	194	Reported outcomes		
Evidence of BL drug resistance	10	Total	253	Total	Bravo[6,51] REDOLA[7] DOLAM(A)[24] Palmier[34] ICONA[52] Dat'AIDS[20] LAMRES[38] ODOACRE[49] Multiple[53,b]	• VF was low (ranging from 0%-5.4% at ~1 year) • The difference in VF between those with or without M184V/I was not significant in 3 of 4 cohorts • A treatment-emergent resistance mutation (M41L, not selected by DTG or 3TC) was observed in 1 PWH with evidence of BL resistance
	4	Reported outcomes	211	Reported outcomes		
Evidence of HBV	6	Total	166	Total	REDOLA[7] ICONA[19] Malagnino[23] Palmier[34] HIVTR[48] ODOACRE[54]	• No PWH with HBV experienced VF
	1	Reported outcomes	35	Reported outcomes		
Evidence of HCV	13	Total	431	Total	REDOLA[7] Calza[8,42] SCOLTA[14] Mendoza[16] ODOACRE[18] ICONA[19] DOLAM(A)[24] Maggiolo[29] CSLHIV[36] Rodríguez Alonso[37] HIVTR[48] Multiple[55,b]	• No studies reported effectiveness outcomes in this subgroup of PWH[c]
	0	Reported outcomes	0	Reported outcomes		
Treatment-naive PWH with BL VL >500,000 c/mL	1	Total	18	Total	Dou[12]	• 89% (16/18) of PWH with BL VL >500,000 c/mL achieved virologic suppression (VL <50 c/mL or 50-200 c/mL with subsequent VL <50 c/mL) at Week 24
	1	Reported outcomes	18	Reported outcomes		
Treatment-experienced PWH with VL <50 c/mL for <6 months before switch	1	Total	13	Total	ODOACRE[56]	• No studies reported effectiveness outcomes in this subgroup of PWH
	0	Reported outcomes	0	Reported outcomes		
Total	**27**	Unique publications[d]	**2015**	PWH	**18**	Unique cohorts[d]

[a]Studies for which cohort(s) may have partially overlapped with other named cohorts, or for which cohort name was not recorded, have been indicated by first author name for the lead study. [b]Data from multiple centers from the Antiviral Response Cohort Analysis (ARCA) database were aggregated and analyzed collectively; these studies are excluded from the 44 unique real-world cohort total as overlap with unique cohorts cannot be determined. [c]1 PWH reported for VF outcome had chronic HCV.[38] [d]A single publication can be reported more than once under different characteristics.

Conclusions

- In real-world cohorts reflective of routine clinical practice, DTG + 3TC has been used by PWH with broad baseline characteristics
- Outcomes from these RWE subgroups reinforce the clinical effectiveness of DTG + 3TC and further inform its application in routine clinical practice