Systematic Literature Review of Real-world Experience With the 2-Drug Regimen Dolutegravir + Lamivudine (DTG + 3TC) in People With HIV-1 Aged ≥50 Years

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Key Takeaways

- **A systematic literature review (SLR) of dolutegravir + lamivudine (DTG + 3TC) use in real-world settings was performed to address treatment outcome knowledge gaps for people with HIV-1 aged ≥50 years**
- **Initial results reported for 1799 people with HIV-1 aged ≥50 years show high effectiveness and safety and tolerability profiles consistent with outcomes in individuals aged ≥50 and <50 years reported from randomized controlled trials**
- **Outcomes data emerging in this population, including 905 individuals aged ≥50 years from clinical practice, reinforce that DTG + 3TC is an effective and well-tolerated option for people with HIV-1 seeking simplified treatment as they age**

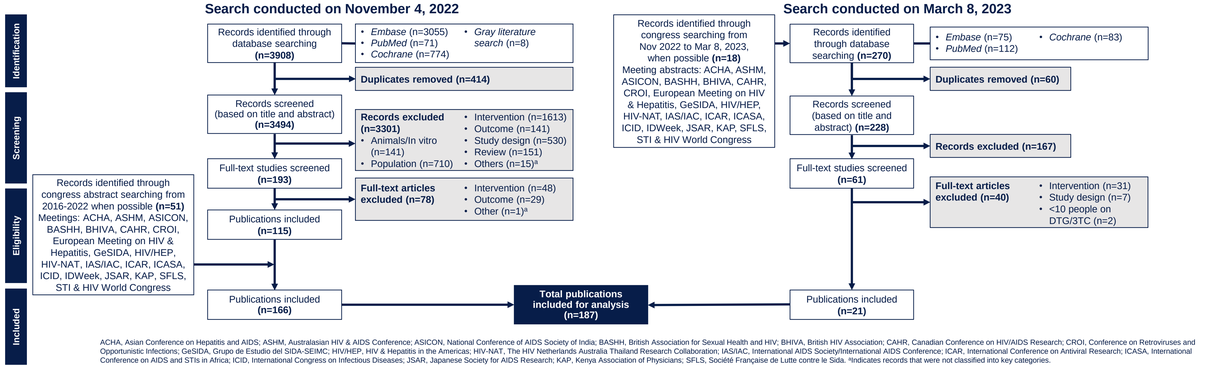
Introduction

- The number of people with HIV aged ≥50 years is increasing and is expected to continue to grow, yet this group is underrepresented in clinical studies of HIV[1,2]
- As a population with a high prevalence of comorbidities and polypharmacy,[3] people with HIV aged ≥50 years could potentially benefit from 2-drug regimens (2DRs) as a simplified treatment switch option to minimize drug-drug interactions and pill burden
- DTG + 3TC demonstrated high efficacy and a good safety profile in phase 3 randomized controlled trials, with comparable outcomes in participants aged ≥50 vs <50 years among treatment-naive (GEMINI-1/-2 at Week 144)[4] and suppressed-switch populations (pooled TANGO/SALSA at Week 48)[5]
  - The EYEWITNESS trial (NCT05911360) will assess efficacy and safety of DTG/3TC as maintenance therapy in a suppressed-switch population of individuals aged ≥50 years
- Real-world evidence (RWE) data from people with HIV aged ≥50 years can bridge knowledge gaps about DTG + 3TC outcomes in this understudied population until more robust clinical trial data are available

Methods

- The SLR was conducted following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines
- Publications from January 2013 to March 2023 reporting DTG + 3TC use in people with HIV-1 aged ≥50 years from clinical practice were obtained from Embase®, Ovid MEDLINE®, PubMed, and Cochrane databases and relevant international conference proceedings (Figure 1)
  - The original SLR searched from January 2013 to November 4, 2022; to supplement the original SLR, an updated SLR was conducted with identical search criteria and included publications up to March 8, 2023
  - An additional relevant reference was included from an observed publication alert in July 2023 (Calza et al. *AIDS Res Hum Retroviruses*. 2023)

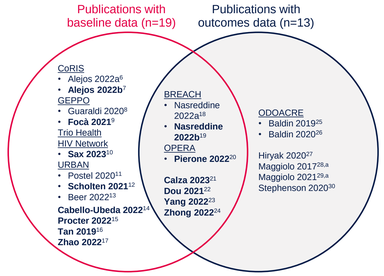
Figure 1. Systematic Literature Review PRISMA Flowchart



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; SFLS, Société Française de Lutte contre le Sida. [a]Indicates records that were not classified into key categories.

- Participants from a single cohort overlapping across publications were not double-counted; however, all potential overlap cannot be ruled out
- Publications reporting baseline data were classified as lead publications (Figure 2)

Figure 2. Publications Included in the Analysis by Cohort and Availability of Reported Baseline Data



Cohort names are underlined. Lead study for each cohort with reported baseline data indicated in **bold text**. If one cohort was represented by multiple relevant publications, then the publication with the highest N was chosen to represent the lead study for that cohort. [a]Publications under the same unnamed cohort.

Results

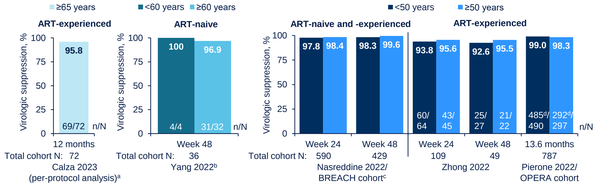
Cohorts and Participants

- The SLR and post hoc publication addition collectively identified 188 publications representing 147 studies, 67 cohorts, and 36,343 people with HIV-1 using DTG + 3TC
  - 14 lead publications representing 14 unique cohorts reported baseline data and DTG + 3TC use in 1799 people with HIV-1 aged ≥50 years
- 6 lead publications (N=905) reported outcomes for treatment-naive (n=68),[22,23] treatment-experienced (n=458),[20,21,23,24] and mixed naive/experienced populations (n=379)[19]
- Overall, 9 studies reported DTG + 3TC effectiveness outcomes, 3 reported safety, and 4 reported tolerability

Effectiveness Outcomes in Real-world Settings

- High virologic suppression rates were reported in individuals aged ≥50 years across both ART-naive and ART-experienced populations, from 88.9% (defined as HIV-1 RNA <20 c/mL) to 99.6% (defined as HIV-1 RNA <50 c/mL; Figure 3)
- Few virologic failures were observed across studies, and no treatment-emergent resistance mutations were reported at failure (Table 1)
- Additional outcomes reported in non-lead studies were supportive of the robust effectiveness and low virologic failure rates in individuals aged ≥50 years from lead studies (Table 2)

Figure 3. DTG + 3TC Effectiveness Outcomes Reported in People With HIV-1 Aged <50 and ≥50 Years From Lead RWE Publications With Reported Baseline Data



[a]Intention-to-treat analysis: 64/72 (88.9%). [b]Virologic suppression in the ART-experienced population was reported as a proportion of the entire cohort, 84/86 (97.7%). [c]n/N not reported. [d]Assumption based on the maximum possible value of ≤5 individuals reported to have met virologic failure criteria.

Table 1. Virologic Failure Outcomes Reported in People With HIV-1 Aged ≥50 Years From Lead RWE Publications

Name of study author/cohort	Country	Cohort size, N	Individuals aged ≥50 y, n	Virologic failure, n/N (%)	Definition of virologic failure
Calza 2023 (ART-experienced)	Italy	72	72 (≥65 y)	3/72 (4.2) aged ≥65 y	Confirmed HIV-1 RNA ≥20 c/mL
Nasreddine 2022b/ BREACH cohort (ART-naive and ART-experienced)	Belgium	734	379	1/734 (<1) aged <50 y	2 consecutive HIV-1 RNA >200 c/mL after previous suppression
Pierone 2022/ OPERA cohort (ART-experienced)	USA	787	297	≤5/490 aged <50 y[a] ≤5/297 aged ≥50 y[a]	2 HIV-1 RNA ≥200 c/mL or discontinuation after 1 HIV-1 RNA ≥200 c/mL
Yang 2022 (ART-naive)	China	36	32 (≥60 y)	1/36 (2.8) aged ≥60 y	HIV-1 RNA ≥50 c/mL
Yang 2022 (ART-experienced)	China	86	42 (≥60 y)	2/86 (2.3; at least 1 person aged ≥60 y)[b]	HIV-1 RNA ≥50 c/mL
Zhong 2022 (ART-experienced)	China	112	47	0/112	2 consecutive HIV-1 RNA ≥200 c/mL or 1 HIV-1 RNA ≥1000 c/mL

[a]Cells with 1 to 5 individuals were required to be masked by US federal law per the Health Insurance Portability and Accountability Act (HIPAA). [b]Age was only reported for 1 of the 2 treatment-experienced individuals meeting virologic failure criteria.

Table 2. Other RWE Publication Effectiveness Outcomes Reported in People With HIV-1 Aged ≥50 Years

Name of study author/cohort	Country	Cohort size, N	Individuals aged ≥50 y, n	Effectiveness outcomes
Baldin 2019/ ODOACRE cohort (ART-experienced)	Italy	556	NR; median (IQR) age, 51.7 (45.3-57.4)	5/12 individuals with virologic failure were aged ≥50 y[a]
Dou 2021 (ART-naive)	China	96	36	Logistic regression analysis found no association between virologic suppression and age ≥50 y (OR, 0.229; 95% CI, −1.729 to 2.449; *P*=0.823)
Hiryak 2020 (ART-experienced)	USA	49	NR; median (IQR) age, 55 (46-60)	Virologic suppression was maintained in n=21 individuals with post-switch data[b]
Stephenson 2020 (ART-naive and ART-experienced)	UK	4 ART-naive; 96 ART-experienced	NR; mean (range) age, 50 (45-60) ART-naive; 52.1 (21-74) ART-experienced	2/2 ART-experienced individuals with virologic failure were aged ≥50 y[c]

NR, not reported. [a]Defined as single HIV-1 RNA ≥1000 c/mL or 2 consecutive HIV-1 RNA ≥50 c/mL. [b]Reported as HIV-1 RNA <20 or <40 c/mL. [c]Undefined and assumed to be any detectable viral load; viral load at failure reported as 119 and 124 c/mL in 1 individual and >2000 c/mL in the other.

Safety Outcomes in Real-world Settings

- Lead studies reported good safety and tolerability profiles with DTG + 3TC and few treatment-associated discontinuations (Table 3)

Table 3. DTG + 3TC Safety Outcomes Reported in People With HIV-1 Aged ≥50 Years From Lead RWE Publications

Name of study author/cohort	Country	Cohort size, N	Individuals aged ≥50 y, n	AEs, n/N (%)	SAEs, n/N (%)	Discontinuations, n/N (%)
Calza 2023	Italy	72	72 (≥65 y)	Overall: 17/72 (23.6); Neuropsychiatric: 12/72 (16.7)	0/72	• 3/72 (4.2) due to virologic failure • 3/72 (4.2) due to AEs[a] • 2/72 (2.8) due to missing data
Nasreddine 2022/ BREACH cohort (ART-naive and ART-experienced)	Belgium	734	379	Median (IQR) change from baseline in weight at Week 48: ≥50 y, 1 (−1, 3) kg vs <50 y, 2 (−1, 4) kg; 4.1% aged ≥50 y had >10% increase in weight from baseline vs 6.5% aged <50 y[b]	NR	• 27/734 (3.7) • 10/734 (1.4) due to AEs • Regression analysis showed no significant association between baseline age and discontinuation • Median time to discontinuation, 17.1 weeks
Pierone 2022/ OPERA cohort (ART-experienced)	USA	787	297	NR	NR	Age <50 y: 104/490 (21) Age ≥50 y: 66/297 (22)
Yang 2022 (ART-naive)	China	36	32 (≥60 y)	Overall: 7/36 (19.4) Drug-related: 6/36 (16.7)	2/36 (5.6)[c]	0/36 due to AEs[d]
Yang 2022 (ART-experienced)	China	86	42 (≥60 y)	Overall: 5/86 (5.8) Drug-related: 4/86 (4.7)	0/86	0/86 due to AEs[d]
Zhong 2022 (ART-experienced)	China	112	47	5/112 (4.5) 3 neuropsychiatric	NR	• 4/112 (3.6) • 0 due to neuropsychiatric symptoms

AE, adverse event; NR, not reported; SAE, serious AE. [a]n=2 (2.8%) insomnia with sleep disturbances and n=1 (1.4%) headache. [b]Other AEs for DTG + 3TC and DTG + RPV were reported collectively. [c]Both SAEs (renal impairment) were reported in individuals aged ≥50 years. [d]Only discontinuations due to AEs were reported.

- Other safety and tolerability outcomes reported in non-lead studies were generally supportive of DTG + 3TC being well tolerated (Table 4)
  - Improved lipid parameters were observed in 2 cohorts[21,26]
  - In 1 cohort, individuals aged ≥50 years represented 91% (10/11) of discontinuations due to death (cancer, n=5; cirrhosis, variceal hemorrhage, sepsis, myocardial infarction, and unknown, n=1 each)[29]

Table 4. Other RWE Publication Safety and Tolerability Outcomes Reported in People With HIV-1 Aged ≥50 Years

Name of study author/cohort	Country	Cohort size, N	Individuals aged ≥50 y, n	Other safety and tolerability outcomes
Baldin 2020/ ODOACRE cohort (ART-experienced)	Italy	354	NR; median (IQR) age, 52.4 (43.4-58.5)	Significant reduction from baseline in TC in individuals aged >60 y (−17 mg/dL; *P*=0.005)
Calza 2023 (ART-experienced)	Italy	72	72 (≥65 y)	Significant reduction from baseline in median TC (−35.5 mg/dL), LDL-C (−19.1 mg/dL), and TG (−72.6 mg/dL); no significant change from baseline in median weight, BMI, HDL-C, or creatinine
Maggiolo 2017 (ART-experienced)	Italy	203	NR; median (IQR) age, 52 (47-58)	8/12 individuals who discontinued DTG + 3TC were aged ≥50 y (5/12 aged ≥60 y)
Maggiolo 2021 (ART-experienced)	Italy	218	NR; median (IQR) age, 52 (12)	10/11 individuals who discontinued DTG + 3TC due to death were aged ≥50 y (7/11 aged ≥60 y)
Stephenson 2020 (ART-naive and ART-experienced)	UK	4 ART-naive; 96 ART-experienced	NR; mean (range) age, 50 (45-60) ART-naive; 52.1 (21-74) ART-experienced	2/4 individuals who discontinued DTG + 3TC for tolerability reasons were aged ≥50 y

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NR, not reported; TC, total cholesterol; TG, triglycerides.

Conclusions

- High effectiveness and good safety and tolerability in people with HIV-1 aged ≥50 years receiving DTG + 3TC in clinical practice reinforce outcomes reported in randomized controlled trials
  - Virologic suppression rates were high (95.5%-99.6%) and virologic failure rates were low (0%-4.2%), with no treatment-emergent resistance and few treatment-associated discontinuations reported
- These emerging data support that DTG + 3TC is a suitable treatment option for people with HIV-1 as they age

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