A Systematic Literature Review to Identify the Clinical Efficacy and Safety Associated With Treatments for Virologically Suppressed People With HIV

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Conclusions

- Most randomized controlled trials (RCTs) had non-inferiority designs and evaluated daily oral regimens in virologically suppressed people with HIV, with comparatively few assessing long-acting injectables (LAIs).
- Trials consistently demonstrated durable viral suppression, and generally acceptable safety profiles, although reported treatment-related adverse events (TRAEs) varied across studies. The high proportion of non-inferiority design reflects the high efficacy of currently-available treatments for this population.
- However, heterogeneity in populations, analysis sets, timepoints, and outcome definitions/reporting limits cross-study comparability, underscoring the need for more standardised endpoints that better capture experiences of people with HIV (PWH).
- As most currently-available treatments generally have good efficacy and safety profiles, future research should focus on improving quality of life and reducing treatment burden for PWH.

Plain Language Summary

- This review looked at HIV treatments across 54 studies.
- The goal was to see how well these treatments were able to keep the virus under control (so it cannot be found in the blood). This is called virological suppression (VS). The review also checked how safe these treatments are for people that have HIV already under control.
- The studies compared different types of treatment. Some compared daily single tablet regimens (STRs) with other daily STRs. Others compared daily STRs to daily multiple tablet regimens (MTRs). Only four studies looked at a long-acting injectable given every two months.
- About three out of four studies were designed to show that a new treatment works just as well as the usual treatment, rather than better.
- Overall, most studies showed that the treatments worked well and were safe. In about 7 out of 10 treatment groups, more than 9 out of 10 people were able to keep their HIV under control.

Introduction

- Since the era of early antiretroviral therapy (ART), HIV therapy has advanced from high pill burdens, inconvenient dosing, treatment-limiting toxicities and incomplete VS, to current once daily, highly effective and better-tolerated oral regimens and long-acting formulations.[1]
- Current guidelines prioritize durable viral suppression alongside individualized treatment choices and shared decision-making for PWH.[2–5]
- These advancements may enhance patient experience and quality of life, support adherence and persistence, improve treatment outcomes and create the opportunity to expand access to care in resource-limited settings.[1]

Objectives

- This systematic literature review (SLR) aimed to identify efficacy and safety evidence for HIV-1 treatments in VS PWH.

Methods

- The SLR was conducted in accordance with Cochrane Collaboration guidance[6] and a pre-specified protocol.
- Searches (run in MEDLINE, Embase and the Cochrane Library) covered the period of January 2000* to September 2025. Supplementary hand-searches of key conferences, clinical trial registries and SLR reference lists were also conducted.
- Eligible studies were phase 3/4 RCTs evaluating oral antiretroviral regimens (single-tablet or multi-tablet, generally administered daily) and LAI therapies in VS PWH with no history of virologic failure.
- Two independent reviewers screened abstracts and full texts. Data extractions and quality assessments (using the tool developed by University of York's CRD)[7] were conducted by one reviewer, and verified by a second.

References: **1.** Łupina K, et al. Archives of Virology. 2025;170(9):195. **2.** WHO. 2021; https://www.who.int/publications/i/item/9789240031593. **3.** Horberg M, et al. Clinical Infectious Diseases. 2024;Oct 12:ciae479. **4.** EACS Guidelines version 13.0. 2025; https://www.eacsociety.org. **5.** DHHS Guidelines 2024; https://clinicalinfo.hiv.gov. **6.** Higgins J, et al. Cochrane. 2022; www.training.cochrane.org/handbook. **7.** Centre for Reviews and Dissemination. Systematic Reviews: CRD guidance. University of York; 2009.

Acknowledgments: This study was funded by Gilead Sciences Inc., Foster City, CA, USA and is part of a collaboration between Gilead Sciences Inc., Foster City, CA, USA and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Medical writing support was provided by Aaditya Rawal and Molly Murton (Costello Medical). Design support was provided by Jenny Chen (Costello Medical).

Disclosures: **AEU** has received consultancy and speaking fees from Gilead, Merck & Co., Inc., Rahway, New Jersey, USA, and ViiV Healthcare. **AS**, **JJ**, **KD** and **RW** are employees and shareholders of Gilead Sciences. **YW** and **LY** are employees and shareholders of Merck & Co., Inc., Rahway, New Jersey, USA. **HL** and **VY** are employees of Costello Medical. **SKG** has received consultancy fees from ViiV Healthcare and Gilead Sciences and an unrestricted research grant from ViiV Healthcare.

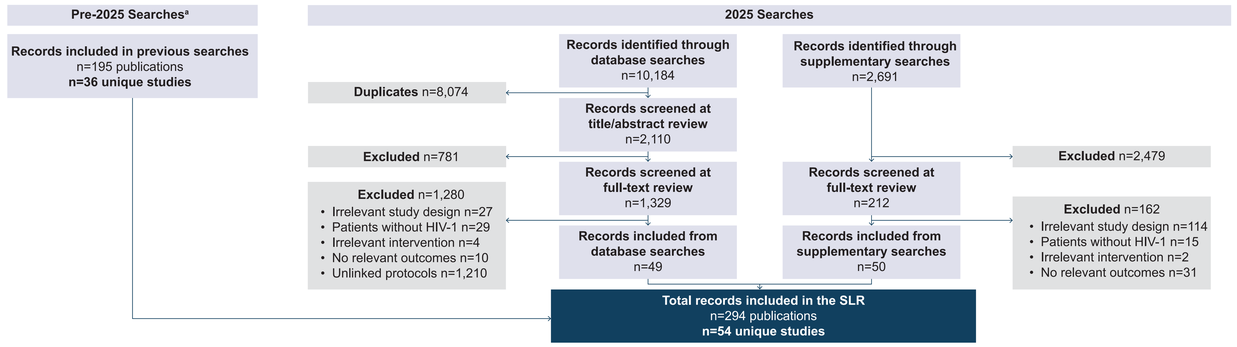
Abbreviations: **3TC:** lamivudine; **ABC:** abacavir; **AE:** adverse event; **ART:** antiretroviral therapy; **ANV:** ainuovirine; **ATV:** atazanavir; **bART:** baseline ART; **BIC:** bictegravir; **CAB:** cabotegravir; **CART:** combination ART; **COBIc:** cobicistat; **DOR:** doravirine; **DRV:** darunavir; **DTG:** dolutegravir; **EFV:** efavirenz; **EVG:** elvitegravir; **F:** emtricitabine; **INI:** integrase inhibitor; **ISL:** islatravir; **LAI:** long-acting injectable; **LPV-RTV:** lopinavir/ritonavir; **MTR:** multi-tablet regimen; **NNRTI:** non-nucleoside reverse transcriptase inhibitor; **NRTI:** nucleoside reverse transcriptase inhibitor; **PI:** protease inhibitor; **PRISMA:** Preferred Reporting Items for Systematic reviews and Meta-Analyses; **PWH:** people with HIV; **Q4W:** every 4 weeks; **Q8W:** every 8 weeks; **RCT:** randomized controlled trial; **RLP/RPV:** rilpivirine; **RoB:** Risk of Bias; **RTV:** ritonavir; **SLR:** systematic literature review; **STR:** single-tablet regimen; **TAF:** tenofovir alafenamide; **TDF:** tenofovir disoproxil fumarate; **TVD:** tenofovir/emtricitabine; **TRAE:** treatment-related AE; **VS:** virological suppression

Results

Overview

- In total, 294 publications reporting on 54 unique RCTs were included (**Figure 1**), of which ~75% were non-inferiority trials. The remaining studies lacked a pre-specified non-inferiority margin and were exploratory, pilot, or superiority trials.
- Most RCTs (15/54) evaluated STRs vs STRs, followed by STRs vs MTRs (13/54) and MTRs vs MTRs (10/54). Four RCTs investigated LAIs, comparing cabotegravir and rilpivirine (CAB/RPV) with oral ART or alternative dosing schedules. The remaining 12 RCTs included at least one arm with mixed treatment classes.

Figure 1. Abbreviated PRISMA Flow Diagram

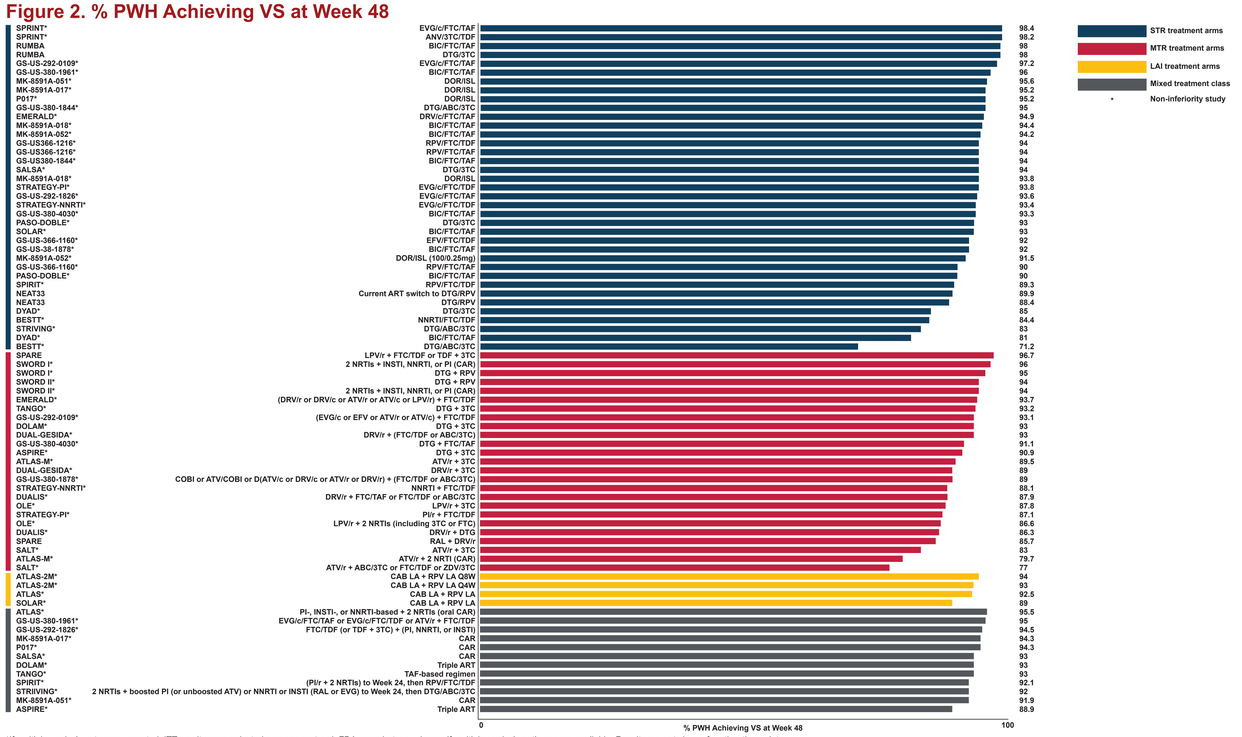


[a]Searches (run in MEDLINE, Embase and the Cochrane Library) covered the period of January 2000 to September 2025, with database searches run on separate occasions from 2017 to 2025.
Abbreviations: PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses.

Efficacy

- Maintenance of VS with RNA <50 copies/mL was reported by 44/54 studies. At Week 48, VS rates ranged from 92.5–94% across four LAI treatment arms (reported by only four trials). VS rates were high across both STR and MTR regimen arms. In STR arms, VS ranged from 71.2–98.4% (>90% in 27/37 arms), and 77–96.7% in MTR arms (>90% in 12/25 arms). Ranges reflect results across different studies and are not intended for direct comparison (**Figure 2; Table 1**).
- In nine non-inferiority trials directly comparing STR vs MTR, VS rates were generally comparable.
- At Week 48, virologic failure/rebound ranged from 0–12.5% of patients and mean change from baseline in CD4+ T cell count ranged from -67–79.9 cells/μL (Table 1).

Figure 2. % PWH Achieving VS at Week 48



*If multiple analysis sets were reported, ITT results were selected over per-protocol; FDA snapshot was chosen if multiple analysis options were available. Results are not shown for other timepoints.
Abbreviations: /c: cobicistat (booster); /r: ritonavir (booster); 3TC: lamivudine; ABC: abacavir; ANV: ainuovirine (NNRTI); ART: antiretroviral therapy; ATV: atazanavir; BIC: bictegravir; CAB: cabotegravir; CAR: current antiretroviral regimen; DOR: doravirine; DRV: darunavir; DTG: dolutegravir; EFV: efavirenz; EVG: elvitegravir; FDC: fixed-dose combination; FTC: emtricitabine; INSTI: integrase strand transfer inhibitor; ISL: islatravir; LA: long-acting; LPV: lopinavir; MTR: multi-tablet regimen; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside/nucleotide reverse transcriptase inhibitor; PI: protease inhibitor; PI/r: ritonavir-boosted protease inhibitor; PWH: people with HIV; Q4W: every 4 weeks; Q8W: every 8 weeks; RAL: raltegravir; RPV: rilpivirine; STR: single-tablet regimen; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate; Triple ART: 3-drug antiretroviral regimen; VS: virological suppression; ZDV: zidovudine.

Table 1. Efficacy Results at Week 48 by Treatment Class

	Maintenance of viral suppression (RNA <50 copies/mL), %	Virologic failure/rebound, %	Mean CfB in CD4+ T cell count, cells/μL*
LAI treatment arms (n=10 arms)	92.5–94 (4 treatment arms)	0.38–2 (8 treatment arms)	-8–9.9 (3 treatment arms)
STR treatment arms (n=56 arms)	71.2–98.4 (37 treatment arms)	0–9.4 (66 treatment arms)	-67–56 (36 treatment arms)
MTR treatment arms (n=25 arms)	77–96.7 (25 treatment arms)	0–12.50 (29 treatment arms)	-11–79.9 (26 treatment arms)

The % ranges presented for viral suppression and virologic failure do not sum to 100% across treatment classes as they are derived from all reported values across included studies (including different subgroups within studies). As such, values may pertain to different populations, and may use different denominators. Italicised values are calculated.*8 studies only reported a median CFB in CD4 cell count ranging from 2.0–760 cells/μL. Two studies either did not report CFB for individual arms (only difference across the arms reported) or only reported data graphically. Results for other timepoints are not shown.
Abbreviations: CfB: change from baseline; LAI: long-acting injectable; MTR: multi-tablet regimen; STR: single-tablet regimen.

Safety

- Discontinuation due to adverse events (AEs) ranged from 0–13% across 44/54 studies.
- ~80% of treatment arms reported low rates (<25%) for TRAEs; while the full range was 0–93% across 34/54 studies.
- At Week 48, one study (ATLAS) reported TRAEs for a LAI: CAB LA + RBP LA, at 83%. Twenty-three reported TRAEs for STRs, ranging from 0–25% in 21/23 studies (66–87% in the other two studies). Eleven studies reported TRAEs for MTRs, ranging from 0–19% in 10/11 studies (71–76% in the other study) (TRAE data at other timepoints are summarized in **Table 2**).

Study Risk of Bias

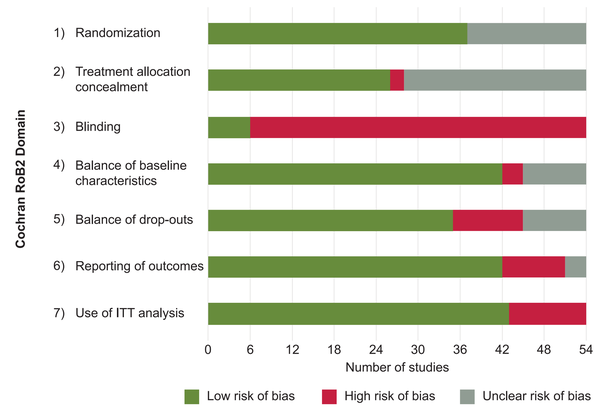
- RCTs were generally at moderate-to-low risk of bias across all domains of the checklist, except for blinding. All but six studies were unblinded, introducing potential bias in outcome assessment and reporting (**Figure 3**).

Table 2. Overall TRAEs by Treatment Class

	Overall TRAEs, % patients			
	Week 48	Week 52*	Week 96	>Week 100
Number of studies:	*LAI: 1; STR: 23; MTR: 10*	*LAI: 1; STR: 1; MTR: 0*	*LAI: 2; STR: 5; MTR: 3*	*LAI: 1; STR: 0; MTR: 1*
LAI treatment arms (n=10 arms)	83	20–93	0–80	82 (Week 152)
STR treatment arms (n=46 arms)	0–87	0–17	0–28	NR
MTR treatment arms (n=17 arms)	0–76	NR	0–19	6 (Week 148)

TRAE data for any other timepoints reported are not shown. Ranges are derived from all reported values across included studies (including different subgroups within studies) at timepoints shown. As such, values may pertain to different sub-populations, and may use different denominators. Wider ranges reflect heterogeneous outcome definitions and reporting; LAI rates are often elevated by injection-site reactions, and low values may reflect reporting from subgroups with small samples. The values are therefore not directly comparable across studies.*Includes data from one study which reported cumulative outcomes through the Month 11–12 analysis window; this includes events occurring during any oral lead-in period (~4 weeks).
Abbreviations: LAI: long-acting injectable; MTR: multi-tablet regimen; STR: single-tablet regimen; TRAE: treatment-related adverse event.

Figure 3. Summary of Study Risk of Bias



Abbreviations: ITT: intention-to-treat; RoB2: Risk of Bias 2