Systematic Literature Review and Meta-Analysis (SLR/MA) of Integrase Strand Transfer Inhibitor (INSTI)-based Single-Tablet Regimens (STRs) versus Multiple-Tablet Regimens (MTRs) for the Treatment of HIV

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Conclusions

- Integrase strand transfer inhibitor (INSTI)-based single-tablet regimens (STRs) were consistently associated with improved adherence and persistence, and lower discontinuation rate compared to INSTI-based multiple-tablet regimens (MTRs) in observational, real-world studies
- No differences between antiretroviral regimen types were seen in adherence or discontinuation in randomized controlled trials (RCTs)
- STRs are a potential tool for supporting adherence and persistence in real-world settings
- Further research should assess how real-world adherence to STRs may impact clinical outcomes

Plain Language Summary

This study looked at the differences in adherence (taking medicine as directed) and persistence (staying on medicine) in people with HIV (PWH) taking medicines called INSTIs as part of a single tablet regimen or as part of multi (many) tablet regimen. Data was taken from both clinical studies and real-world studies (information outside a clinical study and after the medicine is approved). The real-world studies showed that people had better adherence and persistence on STRs vs. MTRs. These studies also found that fewer people taking STRs stopped using the medication compared to those on MTRs. However, in the clinical trials, there was no difference in people taking STRs or MTRs as directed or stopping the medicine.

Introduction

- Systematic literature reviews (SLRs) and meta-analyses (MAs) [1-4] have shown that antiretroviral STRs have several advantages over MTRs for the treatment of HIV. The reduction in pill burden with the use of STRs has historically been associated with increased adherence and improved treatment satisfaction for PWH [1, 5]
- Antiretroviral regimens that include INSTIs in combination with a nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) backbone are recommended first-line treatments for most PWH [6-8]
- Despite being the preferred antiretroviral therapy (ART) class for treatment of HIV, no SLRs have focused on INSTI-based regimens
- The aim of this analysis was to systematically review and compare STRs and MTRs in adult PWH receiving INSTI-based regimens

Objectives

- The aim of this analysis was to systematically review and compare STRs and MTRs in adult PWH receiving INSTI-based regimens

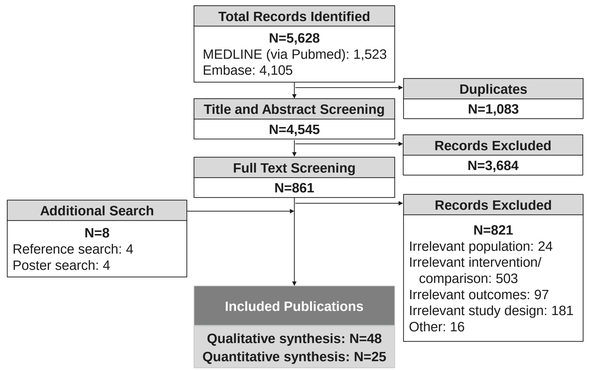
Methods

- Medline and Embase databases were searched on November 28, 2023 to identify clinical trials and real-world studies that evaluated INSTI-based STRs compared with ≥1 INSTI-based MTR in adult PWH
- A supplementary review of references of identified secondary research articles and abstracts from key congresses was also conducted
- Search terms included keywords related to PWH, STRs, and outcomes of interest (including adherence, persistence, and treatment discontinuation)
- Search was restricted to English-language full-text articles published between 2013 and 2023 and conference abstracts and posters published between 2020 and 2023
- Title, abstract, and full-text screening were conducted independently by two reviewers. Data extraction was performed independently by a single reviewer and verified by a second reviewer
- The Guidance for Undertaking Reviews in Health Care from the University of York Centre for Reviews and Dissemination (CRD) [9] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10] were followed in this analysis
- Frequentist pairwise meta-analyses were conducted to provide pooled relative estimates for key outcomes and to quantify heterogeneity
- The definitions of outcomes were author-defined and included: i) proportion of adherent PWH (defined as a ≤5-day gap between successive claims and an adherence threshold of the proportion of days covered ≥95%); ii) persistence as the proportion of PWH or number of PWH persisting on the index ART regimen; iii) discontinuations as the time to interruption or stopping the regimen due to any cause, typically defined as a gap of more than 90 days
- Additional subgroup analyses were performed and included the use of Bictegravir/Emtricitabine/Tenofovir (B/F/TAF), and history of ART use, i.e. treatment-experienced (TE) vs. treatment-naïve (TN)
- The SLR protocol was prospectively registered in the PROSPERO public registry under the identifier CRD42024525515

Results

- In total, 48 publications were considered eligible and included in the narrative synthesis and 25 were selected for the quantitative synthesis after a feasibility assessment (**Figure 1**)

Figure 1. PRISMA flow diagram



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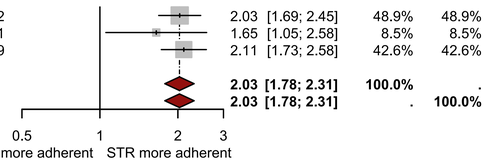
- In 3 retrospective studies, PWH had 2.03 times the odds of being adherent with STRs than MTRs (odds ratio [OR]=2.03; 95% confidence interval [CI] 1.78–2.31) (**Figure 2**), irrespective of adherence definition (not shown). The benefit of STRs was consistent across primary studies, with the pooled estimate not driven by any single study. In one non-inferiority RCT no difference in adherence was seen (OR=0.99; 95% CI 0.14–7.16)

Figure 2. Adherence from 3 retrospective studies

Author	Year	FU (months)	Region	Publication	Previous ART	N STR / N B/F/TAF	N MTR	OR	95%-CI	Weight (common)	Weight (random)
Hines	2019	12	USA	Full-text article	Treatment naïve	7102 / 0	932	2.03	[1.69; 2.45]	48.9%	48.9%
Cohen	2020	6	USA	Full-text article	Treatment naïve	900 / 0	151	1.65	[1.05; 2.58]	8.5%	8.5%
Sax	2020	6	USA	Poster	Experienced suppressed	1650 / 1130	579	2.11	[1.73; 2.58]	42.6%	42.6%
Common effect model								**2.03**	**[1.78; 2.31]**	**100.0%**	.
Random effects model								**2.03**	**[1.78; 2.31]**	.	**100.0%**

Heterogeneity: I^2 = 0.0%, τ^2 = 0, p = 0.6196

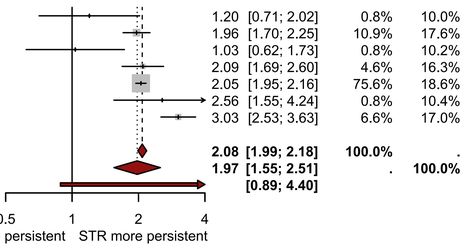


- In 7 retrospective studies, PWH treated with STRs had 1.97 times the odds of remaining persistent compared to those receiving MTRs (OR=1.97; 95% CI 1.55–2.51) (**Figure 3**). Results indicating the benefit of STRs were observed in the majority of primary studies. In a subgroup of 3 studies that evaluated the B/F/TAF regimen vs. MTRs, the positive effect on persistence was even stronger (OR=3.44; 95% CI 2.25–5.25; I^2=95%). No RCTs reporting persistence were identified

Figure 3. Persistence from 7 retrospective studies

Author	Year	FU (months)	Region	Publication	Previous ART	N STR / N B/F/TAF	N MTR	OR	95%-CI	Weight (common)	Weight (random)
Baldin	2019	12	Italy	Full-text article	Previous regimen	380 / 0	236	1.20	[0.71; 2.02]	0.8%	10.0%
Hines	2019	12	USA	Full-text article	Treatment naïve	7102 / 0	932	1.96	[1.70; 2.25]	10.9%	17.6%
Cohen	2020	12	USA	Full-text article	Treatment naïve	463 / 0	67	1.03	[0.62; 1.73]	0.8%	10.2%
Sutton	2020	12	USA	Abstract	Treatment naïve	1862 / 304	409	2.09	[1.69; 2.60]	4.6%	16.3%
Mezzio	2021	12	USA	Abstract	Treatment naïve	27505 / 9052	9963	2.05	[1.95; 2.16]	75.6%	18.6%
Wang	2022	12	Japan	Full-text article	Treatment naïve	153 / 0	192	2.56	[1.55; 4.24]	0.8%	10.4%
Colson	2024	26	USA	Full-text article	Previous regimen	3625 / 2727	626	3.03	[2.53; 3.63]	6.6%	17.0%
Common effect model								**2.08**	**[1.99; 2.18]**	**100.0%**	.
Random effects model								**1.97**	**[1.55; 2.51]**	.	**100.0%**
Prediction interval									**[0.89; 4.40]**		

Heterogeneity: I^2 = 79.7%, τ^2 = 0.0818, p < 0.0001

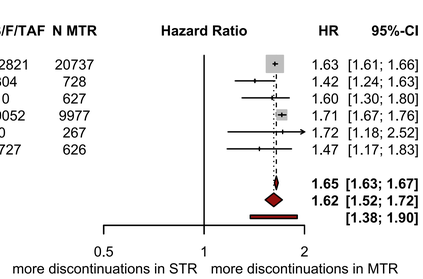


- In 6 retrospective studies, PWH treated with MTRs were 1.62 times more likely to discontinue therapy than those on STRs (hazard ratio [HR]=1.62; 95% CI 1.52–1.72) (**Figure 4**). The benefit of STRs was consistent across primary studies, with all 6 showing significantly lower discontinuation with STRs. A subgroup analysis of previous ART use showed a stronger discontinuation effect for MTRs vs. STRs in TN compared to TE PWH (p < 0.01). In a subgroup of 4 studies reporting results for B/F/TAF, PWH on MTRs were 3.59 times more likely to discontinue treatment than those on B/F/TAF (HR=3.59; 95% CI 2.27–5.69; I^2=98%)
- In 3 prospective cohort studies, PWH treated with MTRs had 8.11 times the odds of therapy discontinuation compared to those on STRs (OR=8.11; 95% CI 2.02–32.52; I^2=97%). A subgroup analysis showed a stronger effect of MTRs on discontinuation in TN compared to TE PWH (p < 0.01). In a subgroup analysis of the B/F/TAF regimen, one study found that PWH on MTRs had 18.25 times the odds of discontinuation than those on B/F/TAF (OR=18.25; 95% CI 8.07–41.29)
- In 4 non-inferiority RCTs, the odds of discontinuation were comparable between MTRs and STRs (0.82; 95% CI 0.54–1.26; I^2=0%), irrespective of previous treatment or regimen

Figure 4. Discontinuation from 6 retrospective studies

Author	Year	Region	Publication	Previous ART	N STR / N B/F/TAF	N MTR	HR	95%-CI	Weight (common)	Weight (random)
Cohen	2020	USA	Abstract	Treatment naïve	90949 / 12821	20737	1.63	[1.61; 1.66]	73.1%	35.6%
Sutton	2020	USA	Abstract	Treatment naïve	2591 / 304	728	1.42	[1.24; 1.63]	0.9%	12.4%
Cohen	2020(2)	USA	Full-text article	Treatment naïve	1782 / 0	627	1.60	[1.30; 1.80]	0.6%	9.7%
Mezzio	2021	USA	Abstract	Treatment naïve	34787 / 9052	9977	1.71	[1.67; 1.76]	24.8%	34.1%
Wang	2022	Japan	Full-text article	Treatment naïve	220 / 0	267	1.72	[1.18; 2.52]	0.1%	2.3%
Colson	2024	USA	Full-text article	Previous regimen	3625 / 2727	626	1.47	[1.17; 1.83]	0.3%	5.9%
Common effect model							**1.65**	**[1.63; 1.67]**	**100.0%**	.
Random effects model							**1.62**	**[1.52; 1.72]**	.	**100.0%**
Prediction interval								**[1.38; 1.90]**		

Heterogeneity: I^2 = 67.5%, τ^2 = 0.0025, p = 0.0088



Limitations

- Analyses were based on a small number of studies (including non-peer-reviewed abstracts and posters) with a limited total pooled sample size
- The RCTs included in the analyses were non-inferiority trials designed to prove no difference between specific STR and MTR regimens, with some using a matching placebo with the STR, which likely masked the potential benefits of the reduced-tablet regimen. This could lead to conflicting conclusions when compared to observational studies

References: **1**. Nachega JB, et al. Clin Infect Dis. 2014;58(9);1297-307. **2**. Altice F, et al. Patient Prefer Adherence. 2019;13;475-90. **3**. Sweet D, et al. Abstract MOPE054. 20th International AIDS Conference. 2014; Melbourne, Australia. **4**. Clay PG, et al. AIDS Res Ther. 2018;15(1);17. **5**. Hodder SL, et al. AIDS Patient Care STDS. 2010;24(2):87-96. **6**. Department of Health and Human Services. Panel on Antiretroviral Guidelines for Adults and Adolescents, Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents With HIV. 2024. **7**. European AIDS Clinical Society, Guidelines, version 12.0. 2023. **8**. World Health Organization, Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. 2021. **9**. Centre for Reviews and Dissemination, University of York, Systematic reviews. CRD's guidance for undertaking reviews in health care. 2009. **10**. Page MJ, et al. Syst Rev. 2021;10(1);89.

Abbreviations: ART, antiretroviral therapy; B/F/TAF, Bictegravir/Emtricitabine/Tenofovir; CI, confidence interval; CRD, The Centre for Reviews and Dissemination; HR, hazard ratio; INSTI, integrase strand transfer inhibitor; IRR, incidence rate ratio; MA, meta-analysis; MTR, multiple-tablet regimen; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; OR, odds ratio; PWH, people with HIV; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomized controlled trial; SLR, systematic literature review; STR, single-tablet regimen; TE, treatment-experienced; TN, treatment-naïve; USA, United States of America.

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Disclosures: **MJC**, **UM**, **WZ**, **JG**, **KH**, **SP**, **MC** are employees of Gilead Sciences, Inc. **JT**, **MD**, **KL** are employees of Maple Health Group, LLC.

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