Table S1: PRISMA checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	2
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	2
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	2
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	3
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	3
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	3
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	3
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	3
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	3
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	N/A
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	N/A
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	3
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	3

Section and Topic	Item #	Checklist item	Location where item is reported
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	3
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	3
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	3
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	3
Study characteristics	17	Cite each included study and present its characteristics.	3
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	3
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	3
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	3-4
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	3-4
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	3-4
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	3-4
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	3-4
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	3-4
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	5
	23b	Discuss any limitations of the evidence included in the review.	5
	23c	Discuss any limitations of the review processes used.	5
	23d	Discuss implications of the results for practice, policy, and future research.	5
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	(CRD42024592574)
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Not prepared
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A

Section and Topic	Item #	Checklist item	Location where item is reported
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	N/A
Competing interests	26	Declare any competing interests of review authors.	N/A
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	N/A

Table S2 - Detailed Search Strategy

Database	Search string	Results
PubMed	("dolutegravir"[Supplementary Concept] OR "dolutegravir"[All Fields] OR "dolutegravir s"[All Fields] OR ("lamivudine"[MeSH Terms] OR "lamivudine"[All Fields] OR "lamivudin"[All Fields]) OR ("2-drug"[All Fields] AND ("clinical protocols"[MeSH Terms] OR ("clinical"[All Fields] AND "protocols"[All Fields]) OR "clinical protocols"[All Fields] OR "regimen"[All Fields] OR "regimens"[All Fields] OR "regimen s"[All Fields])) OR ("dual"[All Fields] AND ("therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "therapies"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "therapy s"[All Fields] OR "therapys"[All Fields]))) AND (("3-drug"[All Fields] AND ("clinical protocols"[MeSH Terms] OR ("clinical"[All Fields] AND "protocols"[All Fields]) OR "clinical protocols"[All Fields] OR "regimen"[All Fields] OR "regimens"[All Fields] OR "regimen s"[All Fields])) OR ("4-drug"[All Fields] AND ("clinical protocols"[MeSH Terms] OR ("clinical"[All Fields] AND "protocols"[All Fields]) OR "clinical protocols"[All Fields] OR "regimen"[All Fields] OR "regimens"[All Fields] OR "regimen s"[All Fields])) OR (("triple"[All Fields] OR "triples"[All Fields]) AND ("therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "therapies"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "therapy s"[All Fields] OR "therapys"[All Fields])) OR (("quadruple"[All Fields] OR "quadruples"[All Fields]) AND ("therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "therapies"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "therapy s"[All Fields] OR "therapys"[All Fields]))) AND ("hiv 1"[MeSH Terms] OR "hiv 1"[All Fields] OR "hiv 1"[All Fields] OR (("hiv"[MeSH Terms] OR "hiv"[All Fields]) AND "type"[All Fields] AND "1"[All Fields]) OR ("hiv 1"[MeSH Terms] OR "hiv 1"[All Fields] OR "human immunodeficiency virus 1"[All Fields]))	434
Cochrane CENTRAL	(Dolutegravir AND Lamivudine) AND ("3-drug regimen" OR "4-drug regimen" OR "triple therapy" OR "quadruple therapy") AND ("HIV-1" OR "HIV type 1" OR "Human Immunodeficiency Virus 1" OR AIDS OR ‘’Acquired Immunodeficiency Syndrome’’)	38
Science Direct	(Dolutegravir AND Lamivudine) AND (3-drug regimen OR 4-drug regimen) AND (HIV-1 OR Human Immunodeficiency Virus 1 OR AIDS OR Acquired Immunodeficiency Syndrome)	1,030

Google Scholar	(Dolutegravir or DTG) AND (Lamivudine OR L3C) AND (3-drug regimen OR 4-drug regimen OR triple therapy OR quadruple therapy) AND (HIV-1 OR HIV type 1 OR Human Immunodeficiency Virus 1 OR AIDS OR Acquired Immunodeficiency Syndrome)	339

Table S3. Risk Of Bias Table

	Bias	Risk of Bias	Author Judgement
Llibere et al 2023	Random sequence generation (selection bias)	Low Risk	Principles from the International Conference on Harmonization Good Clinical Practice (ICH-GCP) and the Declaration of Helsinki ensure that the trial's randomization was effectively designed and implemented, preventing any predictability or manipulation.
	Allocation concealment (selection bias)	Low Risk	The ICH-GCP guidelines suggest methods for allocation concealment to avoid selection bias in clinical trials. These methods include using centralized randomization systems that keep group assignments hidden until the participant is enrolled.
	Blinding of participants and personnel (performance bias)	High Risk	In this open-label study, both participants and researchers knew the intervention assignments, potentially introducing performance bias. This awareness might affect behavior and observations. However, the study should be evaluated based on how these biases were managed and their impact. Despite this risk, the findings should be considered within the broader context and any mitigating factors.
	Blinding of outcome assessment (detection bias)	Low Risk	Although the study lacks detailed information on blinding outcome assessors, there is no evidence suggesting they knew the participants' group assignments. If assessors were unaware of the interventions, the risk of detection bias would be low.
	Incomplete outcome data (attrition bias)	Low Risk	While details on participant attrition are limited, there's no significant evidence of issues with dropout rates or missing data.
	Selective reporting (Reporting bias)	Low Risk	The study includes all pre-specified outcomes and shows no signs of selective reporting.
	Other bias	Low Risk	There is no indication of other sources of bias affecting the study, and the design and conduct appear robust.

	Bias	Risk of Bias	Author Judgement

Cossarizza 2023	Random sequence generation (selection bias)	Low Risk	Participants were assigned to groups using simple randomization.
	Allocation concealment (selection bias)	Low Risk	Opaque envelopes were used to conceal allocation, ensuring that the random assignment remained hidden from recruiters until participants had completed all screening tests and were deemed eligible.
	Blinding of participants and personnel (performance bias)	High Risk	In this open-label study, both participants and researchers knew the intervention assignments, which increases the risk of performance bias. This knowledge could potentially influence behavior and outcomes. Despite this, the study's design and monitoring aimed to minimize these effects, though the risk remains higher due to the lack of blinding.
	Blinding of outcome assessment (detection bias)	Low Risk	The study featured rigorous outcome assessment protocols, with independent assessors applying standardized procedures, which helps reduce the chance of detection bias.
	Incomplete outcome data (attrition bias)	Low Risk	Attrition rates were low, and missing data were managed effectively, indicating a low risk of attrition bias.
	Selective reporting (Reporting bias)	Low Risk	All pre-specified outcomes were reported as intended, with no indications of selective reporting.
	Other bias	Low Risk	There is no indication of additional biases impacting the study. The design and execution of the study are sound, with no other factors undermining the validity of the results.

	Bias	Risk of Bias	Author Judgement
Taiwo et al 2017	Random sequence generation (selection bias)	Low Risk	Strict randomization methods were used, with no evidence of systematic group differences, minimizing selection bias.
	Allocation concealment (selection bias)	Low Risk	Allocation procedures were meticulously managed to ensure that participants were evenly distributed across groups, without any systematic differences. This thorough approach maintains comparability between the groups from the start.
	Blinding of participants and personnel	High Risk	Since both participants and researchers were aware of the intervention assignments, there is an increased risk of performance bias. However, the study's design included

	(performance bias)		measures to minimize the impact of this bias on the outcomes, and the overall results should be interpreted with this context in mind.
	Blinding of outcome assessment (detection bias)	Low Risk	The study implemented thorough outcome assessment protocols, with independent assessors using standardized methods.
	Incomplete outcome data (attrition bias)	Low Risk	With low attrition rates and effective management of missing data, the study demonstrates a low risk of attrition bias.
	Selective reporting (Reporting bias)	Low Risk	All pre-specified outcomes were reported as planned, with no evidence of selective outcome reporting.
	Other bias	Low Risk	There are no signs of other biases affecting the study. The study's design and execution are robust, with no additional factors compromising the validity of the results.

	Bias	Risk of Bias	Author Judgement
J. wan Wyk 2021	Random sequence generation (selection bias)	Low Risk	The study used a stratified randomization method based on baseline third agent class to ensure that the treatment groups were balanced concerning this important baseline characteristic. The randomization was carried out following a pre-established protocol, and the stratification was implemented successfully.
	Allocation concealment (selection bias)	Low Risk	Allocation concealed by stratifying participants, this method was designed to ensure that treatment assignments were made in a manner that preserved the integrity of allocation concealment. This approach to allocation concealment ensures that the assignment of participants to treatment groups was not influenced by knowledge of their baseline characteristics.
	Blinding of participants and personnel (performance bias)	High Risk	This open-label study faces a high risk of performance bias. Although the study employed various measures to mitigate bias, the open-label design inherently increases the risk of performance bias.
	Blinding of outcome assessment (detection bias)	Low Risk	The study utilized detailed outcome assessment procedures, with independent evaluators applying standardized methods.

	Incomplete outcome data (attrition bias)	Low Risk	The study demonstrates a minimal risk of attrition bias due to its low dropout rates and thorough management of missing data.
	Selective reporting (Reporting bias)	Low Risk	All planned outcomes were reported as specified, with no signs of selective reporting.
	Other bias	Low Risk	No other biases appear to affect the study. The design and execution are solid, and there are no additional elements compromising the credibility of the findings.

	Bias	Risk of Bias	Author Judgement
Jhon Rojas 2021	Random sequence generation (selection bias)	Low Risk	Participants were assigned to treatment groups using computer-generated randomization. This method ensures that group assignments were made randomly and reduces the risk of selection bias, as there is no indication of systematic influence over the allocation process.
	Allocation concealment (selection bias)	High Risk	Allocation was open-label, meaning that both investigators and participants were aware of the treatment assignments. This transparency could introduce selection bias if the knowledge of treatment assignments influenced participant management or investigator decisions.
	Blinding of participants and personnel (performance bias)	High Risk	The open-label design of the study, where both participants and investigators knew the treatment assignments, could influence how treatments were delivered and perceived.
	Blinding of outcome assessment (detection bias)	Low Risk	The study used comprehensive outcome assessment procedures, with independent evaluators adhering to standardized techniques.
	Incomplete outcome data (attrition bias)	Low Risk	The study exhibits a low risk of attrition bias, owing to its low dropout rates and comprehensive management of missing data.
	Selective reporting (Reporting bias)	Low Risk	All intended outcomes were reported as outlined, with no evidence of selective reporting.
	Other bias	Low Risk	No additional biases seem to affect the study. The design and implementation are strong, and there are no other factors compromising the integrity of the findings.

Figure S1: Risk of bias Summary

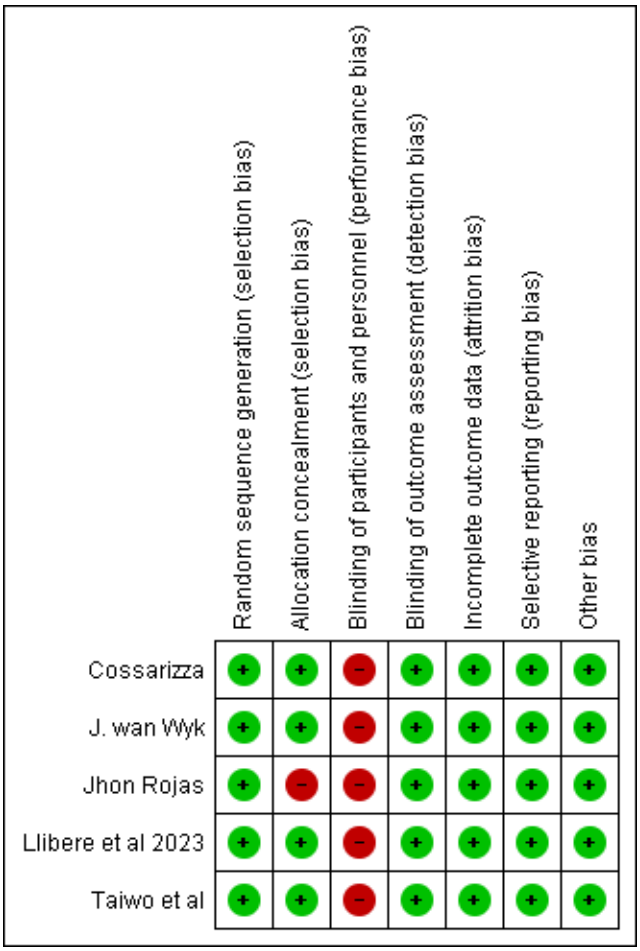

Figure S2: Risk Of Bias Graph