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Safety and Efficacy of Long-acting Intramuscular Cabotegravir and Rilpivirine in Adults with HIV-1 Infection: A Systematic Review and Meta-analysis Protocol

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Abstract

Introduction: Current antiretroviral regimens have, for the most part, achieved optimal antiretroviral efficacy and tolerability, transforming human immunodeficiency virus (HIV) infection from a deadly disease into a manageable chronic condition. Still, adherence to daily oral drug intake remains an issue, as it is the most important determinant for sustained viral suppression and prevention of the emergence of drug-resistant viral strains. The long-acting (LA) antiretroviral Cabotegravir (CAB) and Rilpivirine (RPV) combination, a novel drug delivery approach, is about to revolutionize the therapy of people living with HIV. We aim to generate a clinically useful summary of the interventions based on their efficacy.

Methods and analysis: We will search the literature in four electronic databases. Two methodological trained researchers will select the qualified studies for data extraction independently. Cochrane Risk of Bias tool will be used to assess the risk of bias of included studies. Statistical heterogeneity will be computed by Cochrane X^2 and I^2 tests. Sensitivity analysis will be conducted to evaluate the stability of the results. Publication biases will be evaluated by Begg's and Egger's tests. The quality of evidence will be assessed by the GRADE system. The RevMan 5.3 and stata 14.0 software will be applied for statistical analyses.

Ethics and Dissemination: Ethical approval will not be required for this systematic review because the data used are not linked to the individual patient. The results of this review will be disseminated by being published in a peer-reviewed journal.

PROSPERO Registration number: CRD42022310414

Keywords: HIV, Cabotegravir and Rilpivirine, Systematic Review, Protocol, Meta-analysis

Article summary

Strengths and limitations of this study

- To our knowledge, this is the first systematic review and meta-analysis that investigated the safety and efficacy of long-acting intramuscular (LAI) CAB and RPV in adults with HIV-1 infection.
- This systematic review aims to find the optimal dosing strategies by summarizing the available evidence.
- All the English publications until 30 March 2022 will be searched without any restriction of countries or article type. The exclusion of papers not published in English may mean those important additional findings are missed.
- This review only includes randomized controlled trials (RCTs) therefore may ignore some studies of other types.

1. Introduction

June 2021 marks the 40th anniversary of the first description of acquired immunodeficiency syndrome (AIDS).[1] Despite scientific and programmatic progress, the end of AIDS is not in sight[1]. Even before the coronavirus disease (COVID-19) pandemic, progress in the global AIDS response was not on track to reach the 2020 UNAIDS HIV targets.[2] The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that in 2019, 38 million persons worldwide were living with HIV, 1.7 million became newly infected, and 690,000 died with HIV disease.[3]

Antiretroviral therapy (ART) improvements have helped reduce HIV-related mortality substantially.[4,5] To sustain viral suppression, current guideline-recommended first-line treatments for HIV-1 mandate lifelong daily adherence to oral regimens.[6] The oral daily intake of antiretroviral drugs is a burden, which may present physical, emotional, and logistical challenges for people with HIV (PWH)[7-10] and lead to substantial patient non-adherence.[11] Non-adherence can predispose to the emergence of drug-resistant HIV strains, treatment failure, and disease progression.[12-14] Simplified regimens for the treatment of HIV-1 infection may increase patient satisfaction and facilitate adherence.

Being developed as potential alternatives to pill-based treatment regimens for HIV, long-acting (LA) ART provide the convenience of reduced dosing frequency and may be beneficial or improve the quality of life for individuals with pill fatigue or concerns about disclosure of HIV status or stigma associated with daily oral medication.[15]

CAB is a novel integrase strand transfer inhibitor (INSTI) and structural analog of Dolutegravir (DTG).[16,17] RPV is a non-nucleoside reverse transcriptase inhibitor (NNRTI) first approved in an oral tablet formulation in 2011.[18,19] In the past few years, the combination of CAB and RPA has made some breakthroughs in the treatment and prevention of HIV,[20-24] however, there are still challenges in applying them to the real world. Key outstanding questions include management of patient compliance, special populations, virological failure, and drug resistance. Therefore, this systematic review aims to summarize the available evidence on the safety and efficacy of LAI CAB and RPA in adults with HIV-1 infection, to find the optimal dosing strategies.

2. Objective: The objective is to estimate the safety and efficacy of LAI CAB and RPV in adults with HIV-1 infection.

3.Review question(s):

1. What is the efficacy of LAI CAB and RPV for maintaining HIV-1 suppression compared with standard oral antiretroviral drugs?

2. How is the security?

3. Can the patient tolerate it?

4. Which regimen is better to inject every four weeks(Q4W) or every eight weeks(Q8W)?

4. Methods and analysis

4.1 Protocol registration and reporting:

This is a protocol that was registered in the PROSPERO (registration number CRD42022310414). This systematic review and meta-analysis will be reported based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statements.[25] It will be performed following the recommendations of the Cochrane Handbook.

4.2 Search strategy:

We will search the literature in four electronic databases including PubMed, EMBASE, Cochrane Library, and Cochrane Controlled Register of Trials (CENTRAL) databases. All the English publications until 30 March 2022 will be searched without any restriction of countries or article types. Medical Subject Headings (MeSH) terms combined with free text words, including “HIV”, “AIDS”, “Cabotegravir”, “Rilpivirine”, “Cabotegravir and Rilpivirine” were searched. Additionally, Google Scholar databases will be screened for gray literature and manual searches will be performed by hand-searching reference lists of included studies and previous reviews. Searches will be conducted by two independent investigators (Yuanni Wu and Hai Yu) using keywords and any discrepancies will be resolved by a third investigator (Lianfeng Lu)–also in a blinded fashion. Reference lists of all selected articles will be screened independently to identify additional studies left out in the initial search. The search strategy that will be used for PubMed is reported in Table 1. We will modify our search strategy to suit each database. We will update the search six months ahead of publishing the systematic review paper. All results will be managed by EndNote software. Duplicate records will be recognized and removed.

4.3 Eligibility Criteria:

Inclusion criteria based on PICOs (Cochrane standard) are:

P (Participants or population): Adults with HIV-1 infection (as diagnosed by a clinician, or using any recognized diagnostic criteria) will be included.

I (Intervention): The main intervention is intramuscular injections of long-acting CAB and RPV.

C (comparison): The control groups receive oral antiretroviral therapy.

O (Outcome): Primary outcome is the percentage of participants with plasma human immunodeficiency virus-ribonucleic acid (HIV-RNA) < 50 copies per milliliter (C/mL) as per food and drug administration (FDA) Snapshot Algorithm. Secondary outcomes are the percentage of HIV-RNA > 50 C/mL and confirmed virologic failure (CVF), adverse events (AEs), mean plasma CAB and RPV concentrations, and treatment satisfaction.

S (Study design): Randomized controlled trials (RCTs) will be included.

4.4 Exclusion Criteria:

Studies without specific data, review articles, papers not published in English, and non-RCTs studies will be excluded.

4.5 Study screening and selection:

Two independent investigators (Yuanni Wu and Hai Yu) will evaluate studies according to title and abstract and the chosen full texts that comply with the inclusion criteria will be entered for full-text review. When there are conflicts, they will be resolved by the third author (Lianfeng Lu). We will note the reasons for all excluded studies. A PRISMA flow chart (Figure 1) will be drawn to present the whole process of study selection.[25]

4.6 Data extraction and quality assessment:

Data from the included studies will be extracted and summarized independently by two authors (Yuanni Wu and Hai Yu) using a pre-defined data extraction form to include the following information: first author's surname, publication year, trial name (NCT ID), phase, study characteristics, subject characteristics, interventions, follow-up period, clinical efficacy, CVF, AEs, mean plasma, and treatment satisfaction. Disagreements will be resolved by discussion or consensus with a third reviewer (Xiaodi Li).

Two reviewers (Xiaodi Li and Xiaosheng Liu) will independently assess the risk of bias based on

the following domains from recommendations from the Cochrane handbook: (1) Adequate sequence generation; (2) Allocation concealment; (3) Blinding of participants and personnel; (4) Blinding of outcome assessment; (5) Incomplete outcome data and how it was addressed; (6) Selective reporting of the outcome; (7) Any other biases.[26] Results of bias assessment will be presented in a figure and a graph indicating low, high, or unclear risk of bias for each of the 7 items in each trial. Sensitivity analysis will be conducted based on the bias assessment to assess the robustness of the results.

4.7 Statistical analysis:

After completing the data extraction phase, the results of the included papers will be categorized and summarized in Table 2. For the meta-analysis, we will calculate risk ratio (RR) for binary outcomes and weighted mean difference (WMD) for continuous outcomes, with a 95 % confidence interval (CI). All statistical analyses will be performed using RevMan 5.3 and Stata software (version 14.0).

Publication biases will be evaluated by Begg's and Egger's tests. Statistical heterogeneity will be computed by Cochrane X^2 and I^2 tests; an $I^2 < 50$ % suggests low heterogeneity, based on which the fixed effect model will be employed; an $I^2 > 50$ % indicates significant heterogeneity, based on which a random effect model will be used.[27,28] In the case of high heterogeneity, we will conduct subgroup analysis according to the region of the studies, age, stage of the subjects, types of treatments, and different outcomes. We will evaluate the credibility of the subgroup analysis in terms of the guidance. If there is enough research, meta-regression will be performed to clarify the source of heterogeneity. We will also use sensitivity analysis to explore the source of heterogeneity, when necessary; if heterogeneity still exists, the descriptive analysis will be used to explain the results.

Two subgroup analyses will also be performed:

The first is to assess if an injection of different doses and injection schedules (e.g. Q4W or Q8W injection) produces different therapeutic effects; the second is to investigate whether CAB and RAP injection are equally effective among different patient groups (ART-naive or 6 months of uninterrupted ART).

4.8 Confidence in cumulative evidence:

The most distinct feature of evidence-based medicine is to grade the quality of evidence to

quantify the reliability of research results. The quality of evidence from meta-analyses will be rated by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system,[29] which uses study design as the starting point and then addresses five reasons to possibly rate down the quality of evidence (expressed by reducing scores) and three reasons to possibly rate up the quality (expressed by adding points).

5. Patient and Public Involvement statement

As this is a protocol for a systematic review, patients were not directly involved in the design of this study.

6. Discussion

LA ART is an exciting area of investigation and may provide a welcome alternative for patients to both prevent and treat HIV infection. Here, this study will review and summarize the clinical trial evidence so far; evaluate the safety and effectiveness of LAI CAB and RPV; analyze the pharmacokinetic characteristics, any AEs, and treatment satisfaction; and discusses practicability of special populations. To our knowledge, this is the first systematic review and meta-analysis that investigated the safety and efficacy of LAI CAB and RPV in adults with HIV-1 infection.

To minimize potential bias, each process of initial screening, data extraction, and quality evaluation will be performed by two independent reviewers. The exclusion of papers not published in English and non-RCTs studies may mean those important additional findings are missed. If amendments are needed, we will update our protocol to include any changes in the whole process of research.

In summary, this review study will produce robust data on the safety and efficacy of LAI CAB and RPV in adults with HIV-1 infection. These findings may provide more guidance for clinicians in the treatment of HIV.

7. Ethics and Dissemination

There are no ethical issues related to this study. This article does not contain any studies with human participants or animals performed by any of the authors because this is a protocol for a systematic review relying on primary studies. The results of our research will be published in a peer-reviewed

journal.

8. Author Contributions

After conceptualizing and designing the study, Yuanni Wu registered the protocol on the PROSPERO database. Yuanni Wu and Hai Yu critically revised the protocol and contributed to the drafting of the final manuscript. Wei Cao and Taisheng Li tested the feasibility of the study and involved in the revision of the protocol. Yuanni Wu, Hai Yu, Lianfeng Lu, Xiaodi Li, and Xiaosheng Li will perform the data collection and analyses. All authors read and approved the final manuscript.

9. Funding statement

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10. Competing interests

All authors declared there are no conflicts of interest.

11. Acknowledgements

The authors would like to thank all those who have contributed to the preparation of this protocol.

12. Availability of data and materials

Data will be available upon request of the corresponding author via the following email address: litsh@263.net

13. Amendments

If amendments are needed, we will update our protocol to include any changes in the whole process of research.

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Table 1: Search strategy in PubMed

Search	Search terms
#1	("HIV"[Mesh]) OR ((((((((((((((((((((((((Human Immunodeficiency Virus[Title/Abstract]) OR (Immunodeficiency Virus, Human[Title/Abstract])) OR (Immunodeficiency Viruses, Human[Title/Abstract])) OR (Virus, Human Immunodeficiency[Title/Abstract])) OR (Viruses, Human Immunodeficiency[Title/Abstract])) OR (Human Immunodeficiency Viruses[Title/Abstract])) OR (Human T Cell Lymphotropic Virus Type III[Title/Abstract])) OR (Human T-Cell Lymphotropic Virus Type III[Title/Abstract])) OR (Human T-Cell Leukemia Virus Type III[Title/Abstract])) OR (Human T Cell Leukemia Virus Type III[Title/Abstract])) OR (LAV-HTLV-III[Title/Abstract])) OR (Lymphadenopathy-Associated Virus[Title/Abstract])) OR (Lymphadenopathy Associated Virus[Title/Abstract])) OR (Lymphadenopathy-Associated Viruses[Title/Abstract])) OR (Virus, Lymphadenopathy-Associated[Title/Abstract])) OR (Viruses, Lymphadenopathy-Associated[Title/Abstract])) OR (Human T Lymphotropic Virus Type III[Title/Abstract])) OR (Human T-Lymphotropic Virus Type III[Title/Abstract])) OR (AIDS Virus[Title/Abstract])) OR (AIDS Viruses[Title/Abstract])) OR (Virus, AIDS[Title/Abstract])) OR (Viruses, AIDS[Title/Abstract])) OR (Acquired Immune Deficiency Syndrome Virus[Title/Abstract])) OR (Acquired Immunodeficiency Syndrome Virus[Title/Abstract])) OR (HTLV-III[Title/Abstract]))
#2	("cabotegravir"[Supplementary Concept]) OR (((((((N-((2,4-difluorophenyl)methyl)-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro(1,3)oxazolo(3,2-a)pyrido(1,2-d)pyrazine-8-carboxamide[Title/Abstract]) OR (Cabotegravir*[Title/Abstract])) OR (GSK-1265744*[Title/Abstract])) OR (S-265744*[Title/Abstract])) OR (GSK1265744*[Title/Abstract])) OR (Vocabria [Title/Abstract])) OR (GSK744 [Title/Abstract]))
#3	("Rilpivirine" [Mesh]) OR (((((((((Rilpivirine Hydrochloride[Title/Abstract]) OR (Hydrochloride, Rilpivirine[Title/Abstract])) OR (Rilpivirine HCl[Title/Abstract])) OR (HCl, Rilpivirine[Title/Abstract])) OR (R278474[Title/Abstract])) OR (TMC 278[Title/Abstract])) OR (278, TMC[Title/Abstract])) OR (TMC278[Title/Abstract])) OR (TMC-278[Title/Abstract]))
#4	# 2 AND #3
#5	(cabotegravir, rilpivirine drug combination [Supplementary Concept]) OR (cabenuva)
#6	(cabotegravir/rilpivirine) OR (cabotegravir + rilpivirine) OR (CAB+RPV) OR (CAB/RPV)
#7	#4 OR #5 OR #6
#8	#1 AND #7

Table 2: Data extraction form of the included studies

First author/ Publication year	Trial name (NCT ID)	Intervention ((T /C))	Study characteristics			Number of cases (T /C)	Subject characteristics			Follow-up period (weeks)	HIV-1 subtype	Outcomes
			Phase	Masking	Location		Age (year)	Gender (M/F)	ART naïve (yes/no)			
XXX 2022	YYYY NCT0000	CAB+RPV(q4w) 3TC+TDF+EFV	III	Double-blind	Multicenter	500/500	40	T:250/250 C:250/250	yes	48	B/AE	①②③④⑤⑥

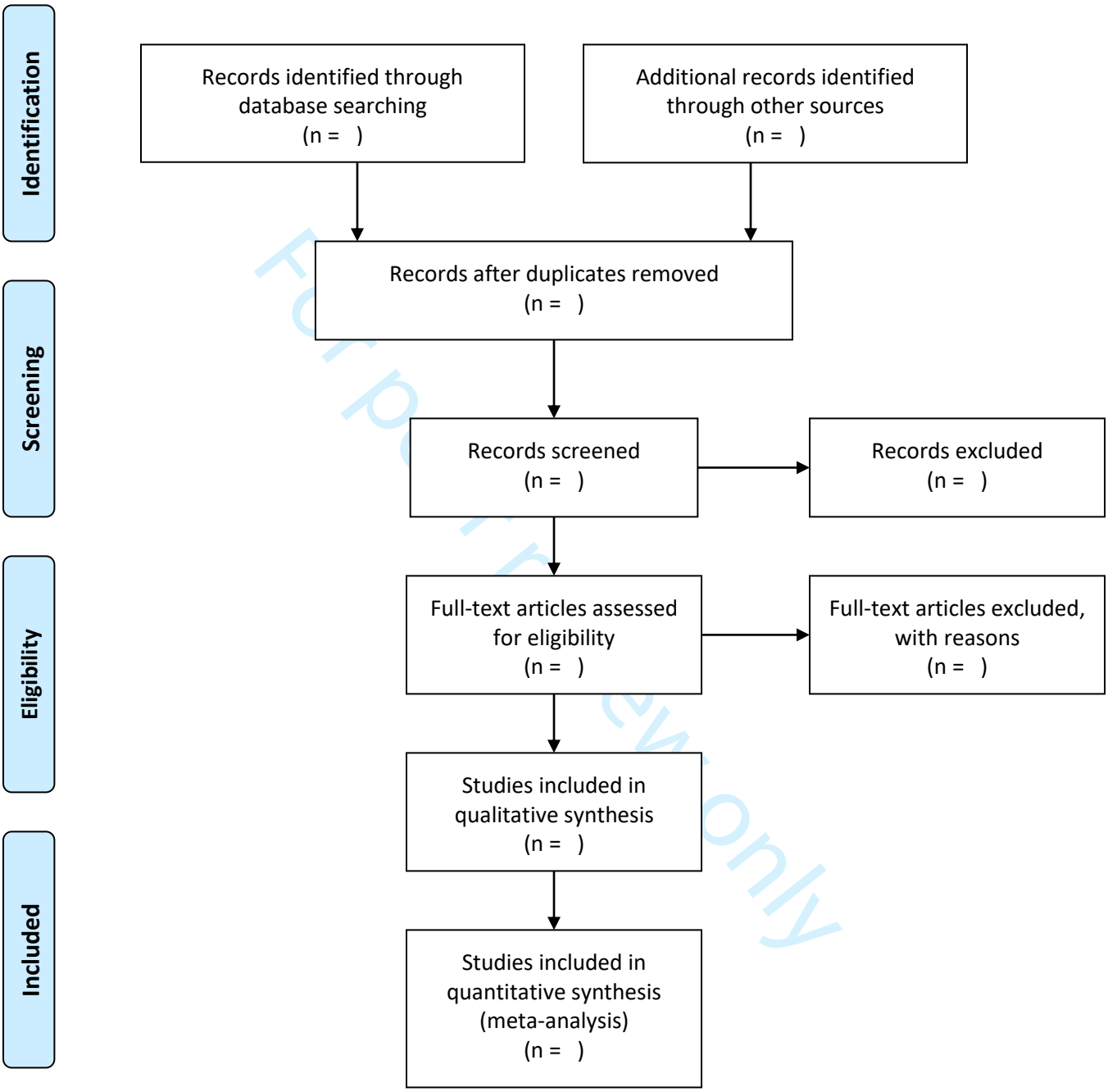
Notes:

XXX, first author example; YYYY, trial name example; T, treatment groups; C, control groups; M, male; F, female; CAB, Cabotegravir; RPV, Rilpivirine; 3TC, Lamivudine; TDF, Tenofovir; EFV, Efavirenz.

①HIV-RNA < 50 C/mL; ②HIV-RNA > 50 C/mL; ③Confirmed virologic failure (CVF); ④Adverse events (AEs); ⑤mean plasma CAB and RPV concentrations; ⑥ treatment satisfaction.

Figure legends (Figure 1 will be uploaded separately)

Figure 1 Flow chart of study selection.



Reporting checklist for protocol of a systematic review and meta analysis.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	Page 1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Page 2
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 8

Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support			
Sources	#5a	Indicate sources of financial or other support for the review	Page 8
Sponsor	#5b	Provide name for the review funder and / or sponsor	N/A
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	N/A
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	Page 3-4
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 5
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Page 4-5
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Page 5
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Page 4,12
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 5
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 5
Study records - data	#11c	Describe planned method of extracting data from reports (such as	Page 5

collection process		piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Page 5,13
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page 5,13
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page 5-6
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	Page 6
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	Page 6
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Page 6
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Page 6
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 6
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page 6-7

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Safety and Efficacy of Long-acting Intramuscular Cabotegravir and Rilpivirine in Adults with HIV-1 Infection: A Systematic Review and Meta-analysis Protocol

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Safety and Efficacy of Long-acting Intramuscular Cabotegravir and Rilpivirine in Adults with HIV-1 Infection: A Systematic Review and Meta-analysis Protocol

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Abstract

Background: Current antiretroviral regimens have, for the most part, achieved optimal antiretroviral efficacy and tolerability, transforming human immunodeficiency virus (HIV) infection from a deadly disease into a manageable chronic condition. Still, adherence to daily oral drug intake remains an issue, as it is the most important determinant for sustained viral suppression and prevention of the emergence of drug-resistant viral strains. The long-acting injection (LAI) antiretroviral Cabotegravir (CAB) and Rilpivirine (RPV) combination, a novel drug delivery approach, is about to revolutionize the therapy for people living with HIV. We aim to generate a clinically useful summary of the interventions based on their efficacy.

Methods and analysis: We searched the literature for eligible studies published from inception up to 16 August 2022 through PubMed, Embase, Cochrane Library, SCOPUS, and Clinicaltrials.gov. Two methodological trained researchers will select the qualified studies for data extraction independently. Cochrane Risk of Bias tool will be used to assess the risk of bias in included studies. Statistical heterogeneity will be computed by Cochrane X^2 and I^2 tests. Sensitivity analysis will be conducted to evaluate the stability of the results. Publication biases will be evaluated by Begg's and Egger's tests. The quality of evidence will be assessed by the GRADE system. The RevMan 5.3 and stata 14.0 software will be applied for statistical analyses.

Ethics and Dissemination: Ethical approval will not be required for this systematic review because the data used are not linked to the individual patient. The results of this review will be disseminated by being published in a peer-reviewed journal.

PROSPERO Registration number: CRD42022310414

Keywords: HIV, Cabotegravir and Rilpivirine, Systematic Review, Protocol, Meta-analysis

Article summary

Strengths and limitations of this study

- The protocol was crafted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols guidelines.
- Search and screening will cover an extensive range of publications.
- Each process of initial screening, data extraction, and quality evaluation will be performed by two independent reviewers to minimize potential bias.
- The exclusion of papers not published in English may mean those important additional findings are missed.
- This review only includes randomized controlled trials (RCTs) therefore may ignore some studies of other types.

1. Introduction

June 2021 marked the 40th anniversary of the first description of acquired immunodeficiency syndrome (AIDS).[1] Despite scientific and programmatic progress, the end of AIDS is not in sight[1]. Even before the coronavirus disease (COVID-19) pandemic, progress in the global AIDS response

was not on track to reach the 2020 UNAIDS HIV targets.[2] The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that in 2019, 38 million persons worldwide were living with HIV, 1.7 million became newly infected, and 690,000 died with HIV disease.[3]

Antiretroviral therapy (ART) improvements have helped reduce HIV-related mortality substantially.[4,5] To sustain viral suppression, current guideline-recommended first-line treatments for HIV-1 mandate lifelong daily adherence to oral regimens.[6] The oral daily intake of antiretroviral drugs is a burden, which may present physical, emotional, and logistical challenges for people with HIV (PWH)[7-10] and lead to substantial patient non-adherence.[11] Non-adherence can predispose to the emergence of drug-resistant HIV strains, treatment failure, and disease progression.[12-14] Simplified regimens for the treatment of HIV-1 infection may increase patient satisfaction and facilitate adherence.

Being developed as potential alternatives to pill-based treatment regimens for HIV, long-acting (LA) ART provide the convenience of reduced dosing frequency and may be beneficial or improve the quality of life for individuals with pill fatigue or concerns about disclosure of HIV status or stigma associated with daily oral medication.[15]

CAB is a novel integrase strand transfer inhibitor (INSTI) and structural analog of Dolutegravir (DTG).[16,17] RPV is a non-nucleoside reverse transcriptase inhibitor (NNRTI) first approved in an oral tablet formulation in 2011.[18,19] In January 2021, LAI formulations of the INSTI CAB and the NNRTI RPV were approved by the Food and Drug Administration (FDA). This combination can be used to replace an existing oral ARV regimen in people with HIV with sustained viral suppression for 3 to 6 months (optimal duration is not defined), who have good adherence and engagement in care, no baseline resistance to either medication, no prior virologic failures; who do not have active or occult HBV infection (unless the patient also is receiving an HBV active regimen); who are not pregnant or planning on becoming pregnant; and who are not receiving medications with significant drug interactions with oral (during lead-in or bridging therapy) or injectable CAB or RPV.

In the past few years, the combination of CAB and RPA has made some breakthroughs in the treatment and prevention of HIV,[20-24] however, there are still challenges in applying them to the real world. Key outstanding questions include management of patient compliance, special

populations, virological failure, and drug resistance. Therefore, this systematic review aims to summarize the available evidence on the safety and efficacy of LAI CAB and RPA in adults with HIV-1 infection, to give reference for clinical work.

2. Objective: The objective is to estimate the safety and efficacy of LAI CAB and RPV in adults with HIV-1 infection.

3.Review question(s):

1. What is the efficacy of LAI CAB and RPV for maintaining HIV-1 suppression compared with standard oral antiretroviral drugs?

2. How is the security?

3. Can the patient tolerate it?

4. Which regimen is better to inject every four weeks(Q4W) or every eight weeks(Q8W)?

4. Methods and analysis

4.1 Protocol registration and reporting:

This is a protocol that was registered in the PROSPERO (registration number CRD42022310414). This systematic review and meta-analysis will be reported based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statements.[25] It will be performed following the recommendations of the Cochrane Handbook.

4.2 Search strategy:

We will search the literature through PubMed, EMBASE, Cochrane Library, SCOPUS, and Clinicaltrials.gov. Detailed information is provided in Table S1 of the Supplementary Material. All the English publications until 17 August 2022 will be searched without any restriction of countries or article types. Medical Subject Headings (MeSH) terms combined with free text words, including “HIV”, “AIDS”, “Cabotegravir”, “Rilpivirine”, “Cabotegravir and Rilpivirine” were searched. Additionally, Google Scholar databases will be screened for gray literature and manual searches will be performed by hand-searching reference lists of included studies and previous reviews. Searches will be conducted by two independent investigators (Yuanni Wu and Hai Yu) using keywords and any discrepancies will be resolved by a third investigator (Lianfeng Lu)–also in a blinded fashion. Reference lists of all selected articles will be screened independently to identify additional studies left out in the initial search. The search strategy that will be used for PubMed is

reported in Table 1. We will modify our search strategy to suit each database. We will update the search six months ahead of publishing the systematic review paper. All results will be managed by EndNote software. Duplicate records will be recognized and removed.

4.3 Eligibility Criteria:

Inclusion criteria based on PICOs (Cochrane standard) are:

P (Participants or population): Adults with HIV-1 infection (as diagnosed by a clinician, or using any recognized diagnostic criteria) will be included.

I (Intervention): The main intervention was the intramuscular injection of long-acting CAB and RPV, regardless of the frequency of injection and duration of treatment. Studies comparing LAI CAB and RPV formulations with any pair of the conventional oral ART regimens will be included.

C (comparison): The control groups receive oral antiretroviral therapy.

O (Outcome):

The outcome measures of interest were the efficacy and safety of the combination regimen (as defined in the Supplementary material). Primary efficacy outcomes are the percentage of participants with virologic success (plasma human immunodeficiency virus-ribonucleic acid [HIV-RNA] < 50 copies per milliliter [C/mL]), virologic failure (HIV RNA ≥ 50 copies/mL) and confirmed virologic failure (CVF, HIV-1-RNA levels ≥200 copies/mL) at week 48 or 96 as per FDA Snapshot Algorithm. Primary safety outcomes include frequencies of any adverse events (AEs), serious AEs, and AEs-related withdrawal. Secondary outcomes include incidence and severity of laboratory abnormalities, ithe ncidence of treatment-emergent genotypic and phenotypic resistance, mean plasma CAB and RPV concentrations, treatment satisfaction, and change in CD4+ T cell counts from baseline.

S (Study Design): Randomized controlled trials (RCTs) will be included.

4.4 Exclusion Criteria:

Studies that meet the following criteria will be excluded:

- Irretrievable full-text articles or studies not in English;
- Studies without specific data;
- Review articles;
- non-RCTs studies;

- Studies for HIV pre-exposure prophylaxis rather than treatment.

4.5 Study screening and selection:

Two independent investigators (Yuanni Wu and Hai Yu) will evaluate studies according to title and abstract and the chosen full texts that comply with the inclusion criteria will be entered for full-text review. When there are conflicts, they will be resolved by the third author (Lianfeng Lu). We will note the reasons for all excluded studies. A PRISMA flow chart (Figure 1) will be drawn to present the whole process of study selection.[25]

4.6 Data extraction and quality assessment:

Data from the included studies will be extracted independently by two authors (Yuanni Wu and Hai Yu) using a pre-defined data extraction form constructed and standardized before being applied (Table S2). Disagreements will be resolved by discussion or consensus with a third reviewer (Xiaodi Li). After completing the data extraction phase, the results of the included papers will be categorized and summarized in Table S3.

Two reviewers (Xiaodi Li and Xiaosheng Liu) will independently assess the risk of bias based on the following domains from recommendations from the Cochrane handbook: (1) Adequate sequence generation; (2) Allocation concealment; (3) Blinding of participants and personnel; (4) Blinding of outcome assessment; (5) Incomplete outcome data and how it was addressed; (6) Selective reporting of the outcome; (7) Any other biases.[26] Results of the bias assessment will be presented in a figure and a graph indicating low, high, or unclear risk of bias for each of the 7 items in each trial. Sensitivity analysis will be conducted based on the bias assessment to assess the robustness of the results.

4.7 Statistical analysis:

After completing the data extraction phase, the results of the included papers will be categorized and summarized in Table S3. For the meta-analysis, we will calculate the risk ratio (RR) for binary outcomes and weighted mean difference (WMD) for continuous outcomes, with a 95 % confidence interval (CI). All statistical analyses will be performed using RevMan 5.3 and Stata software (version 14.0).

Publication biases will be evaluated by Begg's and Egger's tests. Statistical heterogeneity will be computed by Cochrane X^2 and I^2 tests; an $I^2 < 50$ % suggests low heterogeneity, based on which

the fixed effect model will be employed; an $I^2 > 50$ % indicates significant heterogeneity, based on which a random effect model will be used.[27,28] In the case of high heterogeneity, we will conduct subgroup analysis according to the region of the studies, age, stage of the subjects, types of treatments, and different outcomes. We will evaluate the credibility of the subgroup analysis in terms of the guidance. If there is enough research, meta-regression will be performed to clarify the source of heterogeneity. We will also use sensitivity analysis to explore the source of heterogeneity, when necessary; if heterogeneity still exists, the descriptive analysis will be used to explain the results.

Two subgroup analyses will also be performed:

The first is to assess if an injection of different doses and injection schedules (e.g. Q4W or Q8W injection) produces different therapeutic effects; the second is to investigate whether CAB and RAP injections are equally effective among different patient groups (ART-naive or 6 months of uninterrupted ART).

4.8 Confidence in cumulative evidence:

The most distinct feature of evidence-based medicine is to grade the quality of evidence to quantify the reliability of research results. The quality of evidence from meta-analyses will be rated by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system,[29] which uses study design as the starting point and then addresses five reasons to possibly rate down the quality of evidence (expressed by reducing scores) and three reasons to possibly rate up the quality (expressed by adding points).

5. Patient and Public Involvement statement

As this is a protocol for a systematic review, patients were not directly involved in the design of this study.

6. Discussion

This study will review and summarize the clinical trial evidence so far; evaluate the safety and effectiveness of LAI CAB and RPV; analyze the pharmacokinetic characteristics, any AEs, and treatment satisfaction; and discusses the practicability of special populations.

To minimize potential bias, each process of initial screening, data extraction, and quality evaluation will be performed by two independent reviewers. When the initial screening, data

extraction, and quality evaluation opinions are inconsistent, the third party can discuss and solve. Before the meta-analysis, strict and unified inclusion criteria and data extraction criteria were formulated to reduce the heterogeneity among studies, but the existence of heterogeneity should be acknowledged even so. If there was significant heterogeneity among studies, subgroup analysis and meta-regressionn (included age, sex at birth, body-mass index category, years since HIV infection, years since ART, the baseline of CD4+T counts and HIV RNA levels, duration the of previous cabotegravir plus rilpivirine long-acting exposure, and injected doses) were used to explore the source of heterogeneity. Finally, the exclusion of papers not published in English and non-RCTs studies may mean those important additional findings are missed. If amendments are needed, we will update our protocol to include any changes in the whole process of research.

In summary, this review study will produce robust data on the safety and efficacy of LAI CAB and RPV in adults with HIV-1 infection. These findings may provide more guidance for clinicians in the treatment of HIV.

7. Ethics and Dissemination

There are no ethical issues related to this study. This article does not contain any studies with human participants or animals performed by any of the authors because this is a protocol for a systematic review relying on primary studies. The results of our research will be published in a peer-reviewed journal.

8. Author Contributions

After conceptualizing and designing the study, Yuanni Wu registered the protocol on the PROSPERO database. Yuanni Wu and Hai Yu critically revised the protocol and contributed to the drafting of the final manuscript. Wei Cao and Taisheng Li tested the feasibility of the study and were involved in the revision of the protocol. Yuanni Wu, Hai Yu, Lianfeng Lu, Xiaodi Li, and Xiaosheng Li will perform the data collection and analyses. All authors read and approved the final manuscript.

9. Funding statement

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10. Competing interests

All authors declared there are no conflicts of interest.

11. Acknowledgements

The authors would like to thank all those who have contributed to the preparation of this protocol.

12. Availability of data and materials

Data will be available upon request of the corresponding author via the following email address: litsh@263.net

13. Amendments

If amendments are needed, we will update our protocol to include any changes in the whole process of research.

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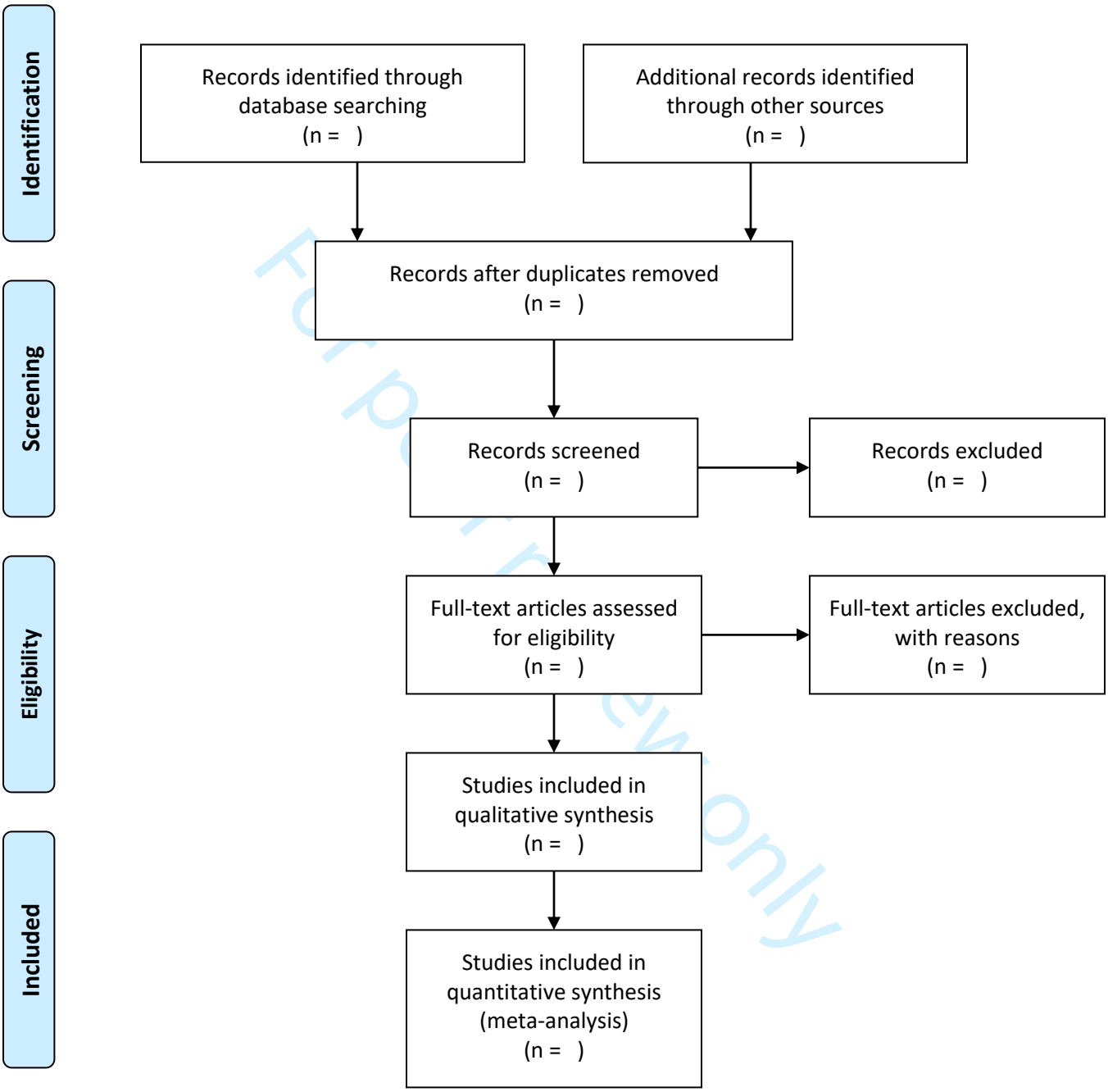
Table 1: Search strategy in PubMed

Database	Search	Search terms
PubMed (12)	#1	("HIV"[Mesh]) OR ((((((((((((((((((((((((Human Immunodeficiency Virus[Title/Abstract]) OR (Immunodeficiency Virus, Human[Title/Abstract])) OR (Immunodeficiency Viruses, Human[Title/Abstract])) OR (Virus, Human Immunodeficiency[Title/Abstract])) OR (Viruses, Human Immunodeficiency[Title/Abstract])) OR (Human Immunodeficiency Viruses[Title/Abstract])) OR (Human T Cell Lymphotropic Virus Type III[Title/Abstract])) OR (Human T-Cell Lymphotropic Virus Type III[Title/Abstract])) OR (Human T-Cell Leukemia Virus Type III[Title/Abstract])) OR (Human T Cell Leukemia Virus Type III[Title/Abstract])) OR (LAV-HTLV-III[Title/Abstract])) OR (Lymphadenopathy-Associated Virus[Title/Abstract])) OR (Lymphadenopathy Associated Virus[Title/Abstract])) OR (Lymphadenopathy-Associated Viruses[Title/Abstract])) OR (Virus, Lymphadenopathy-Associated[Title/Abstract])) OR (Viruses, Lymphadenopathy-Associated[Title/Abstract])) OR (Human T Lymphotropic Virus Type III[Title/Abstract])) OR (Human T-Lymphotropic Virus Type III[Title/Abstract])) OR (AIDS Virus[Title/Abstract])) OR (AIDS Viruses[Title/Abstract])) OR (Virus, AIDS[Title/Abstract])) OR (Viruses, AIDS[Title/Abstract])) OR (Acquired Immune Deficiency Syndrome Virus[Title/Abstract])) OR (Acquired Immunodeficiency Syndrome Virus[Title/Abstract])) OR (HTLV-III[Title/Abstract]))
	#2	("cabotegravir"[Supplementary Concept]) OR (((((((N-((2,4-difluorophenyl)methyl)-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro(1,3)oxazolo(3,2-a)pyrido(1,2-d)pyrazine-8-carboxamide[Title/Abstract]) OR (Cabotegravir*[Title/Abstract])) OR (GSK-1265744*[Title/Abstract])) OR (S-265744*[Title/Abstract])) OR (GSK1265744*[Title/Abstract])) OR (Vocabria [Title/Abstract])) OR (GSK744 [Title/Abstract]))
	#3	("Rilpivirine" [Mesh]) OR (((((((((Rilpivirine Hydrochloride[Title/Abstract]) OR (Hydrochloride, Rilpivirine[Title/Abstract])) OR (Rilpivirine HCl[Title/Abstract])) OR (HCl, Rilpivirine[Title/Abstract])) OR (R278474[Title/Abstract])) OR (TMC 278[Title/Abstract])) OR (278, TMC[Title/Abstract])) OR (TMC278[Title/Abstract])) OR (TMC-278[Title/Abstract]))
	#4	# 2 AND #3
	#5	(cabotegravir, rilpivirine drug combination [Supplementary Concept]) OR (cabenuva)
	#6	(cabotegravir/rilpivirine) OR (cabotegravir + rilpivirine) OR (CAB+RPV) OR (CAB/RPV) OR (cabotegravir plus rilpivirine)
	#7	#4 OR #5 OR #6
	#8	(((((((((randomized controlled trial[Title/Abstract]) OR RCT[Title/Abstract]) OR random[Title/Abstract]) OR randomly[Title/Abstract]) OR random allocation[Title/Abstract]) OR allocation[Title/Abstract]) OR randomized control trial[Title/Abstract]) OR controlled

		clinical trial[Title/Abstract]) OR clinical trial[Title/Abstract]) OR clinical study[Title/Abstract]
	#9	#1 AND #7 AND #8

Figure legends (Figure 1 will be uploaded separately)

Figure 1 Flow chart of study selection.



Supplementary Material

Safety and Efficacy of Long-acting Intramuscular Cabotegravir and Rilpivirine in Adults with HIV-1 Infection: A Systematic Review and Meta-analysis Protocol

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Supplementary tables

Table S1. Search strategy

Database	Search	Search terms
PubMed (12)	#1	("HIV"[Mesh]) OR ((((((((((((((((((((((((Human Immunodeficiency Virus[Title/Abstract]) OR (Immunodeficiency Virus, Human[Title/Abstract])) OR (Immunodeficiency Viruses, Human[Title/Abstract])) OR (Virus, Human Immunodeficiency[Title/Abstract])) OR (Viruses, Human Immunodeficiency[Title/Abstract])) OR (Human Immunodeficiency Viruses[Title/Abstract])) OR (Human T Cell Lymphotropic Virus Type III[Title/Abstract])) OR (Human T-Cell Lymphotropic Virus Type III[Title/Abstract])) OR (Human T-Cell Leukemia Virus Type III[Title/Abstract])) OR (Human T Cell Leukemia Virus Type III[Title/Abstract])) OR (LAV-HTLV-III[Title/Abstract])) OR (Lymphadenopathy-Associated Virus[Title/Abstract])) OR (Lymphadenopathy Associated Virus[Title/Abstract])) OR (Lymphadenopathy-Associated Viruses[Title/Abstract])) OR (Virus, Lymphadenopathy-Associated[Title/Abstract])) OR (Viruses, Lymphadenopathy-Associated[Title/Abstract])) OR (Human T Lymphotropic Virus Type III[Title/Abstract])) OR (Human T-Lymphotropic Virus Type III[Title/Abstract])) OR (AIDS Virus[Title/Abstract])) OR (AIDS Viruses[Title/Abstract])) OR (Virus, AIDS[Title/Abstract])) OR (Viruses, AIDS[Title/Abstract])) OR (Acquired Immune Deficiency Syndrome Virus[Title/Abstract])) OR (Acquired Immunodeficiency Syndrome Virus[Title/Abstract])) OR (HTLV-III[Title/Abstract]))
	#2	("cabotegravir"[Supplementary Concept]) OR (((((((N-((2,4-difluorophenyl)methyl)-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro(1,3)oxazolo(3,2-a)pyrido(1,2-d)pyrazine-8-carboxamide[Title/Abstract]) OR (Cabotegravir*[Title/Abstract])) OR

		(GSK-1265744*[Title/Abstract])) OR (S-265744*[Title/Abstract])) OR (GSK1265744*[Title/Abstract])) OR (Vocabria [Title/Abstract])) OR (GSK744 [Title/Abstract]))
	#3	("Rilpivirine" [Mesh]) OR (((((((((Rilpivirine Hydrochloride[Title/Abstract]) OR (Hydrochloride, Rilpivirine[Title/Abstract])) OR (Rilpivirine HCl[Title/Abstract])) OR (HCl, Rilpivirine[Title/Abstract])) OR (R278474[Title/Abstract])) OR (TMC 278[Title/Abstract])) OR (278, TMC[Title/Abstract])) OR (TMC278[Title/Abstract])) OR (TMC-278[Title/Abstract]))
	#4	# 2 AND #3
	#5	(cabotegravir, rilpivirine drug combination [Supplementary Concept]) OR (cabenuva)
	#6	(cabotegravir/rilpivirine) OR (cabotegravir + rilpivirine) OR (CAB+RPV) OR (CAB/RPV) OR (cabotegravir plus rilpivirine)
	#7	#4 OR #5 OR #6
	#8	(((((((((randomized controlled trial[Title/Abstract]) OR RCT[Title/Abstract]) OR random[Title/Abstract]) OR randomly[Title/Abstract]) OR random allocation[Title/Abstract]) OR allocation[Title/Abstract]) OR randomized control trial[Title/Abstract]) OR controlled clinical trial[Title/Abstract]) OR clinical trial[Title/Abstract]) OR clinical study[Title/Abstract]
	#9	#1 AND #7 AND #8
Embase (28)	#1	'hiv'/exp OR hiv OR 'human immunodeficiency virus':ti,ab,kw OR 'immunodeficiency virus, human':ti,ab,kw OR 'human t cell lymphotropic virus type iii':ti,ab,kw OR 'human t-cell leukemia virus type iii':ti,ab,kw OR 'lav htlv iii':ti,ab,kw OR 'lymphadenopathy-associated virus':ti,ab,kw OR 'aids virus':ti,ab,kw OR 'acquired immune deficiency syndrome virus':ti,ab,kw OR 'htlv iii':ti,ab,kw
	#2	'human immunodeficiency virus'/exp
	#3	#1 OR #2
	#4	cabotegravir:ti,ab,kw OR (n-:ti,ab,kw AND '2,4 difluorophenyl':ti,ab,kw AND methyl:ti,ab,kw AND '6 hydroxy 3 methyl 5,7 dioxo 2,3,5,7,11,11a hexahydro':ti,ab,kw AND 1,3:ti,ab,kw AND oxazolo:ti,ab,kw AND '3,2 a':ti,ab,kw AND pyrido:ti,ab,kw AND '1,2 d':ti,ab,kw AND 'pyrazine 8 carboxamide':ti,ab,kw) OR 'gsk 1265744':ti,ab,kw OR 'gsk 1265744a':ti,ab,kw OR 'gsk 1265744b':ti,ab,kw OR 's 265744':ti,ab,kw OR 's 265744b':ti,ab,kw OR gsk1265744:ti,ab,kw OR vocabria:ti,ab,kw OR gsk744:ti,ab,kw
	#5	'cabotegravir'/exp
	#6	#4 OR #5
	#7	rilpivirine:ti,ab,kw OR 'rilpivirine hydrochloride':ti,ab,kw OR 'hydrochloride, rilpivirine':ti,ab,kw OR 'rilpivirine hcl':ti,ab,kw OR 'hcl, rilpivirine':ti,ab,kw OR r278474:ti,ab,kw OR '278, tmc':ti,ab,kw OR tmc278:ti,ab,kw OR 'tmc 278':ti,ab,kw
	#8	'rilpivirine'/exp
	#9	#7 OR #8
	#10	#6 AND #9
	#11	'cabotegravir, rilpivirine drug combination':ti,ab,kw OR cabenuva:ti,ab,kw OR cabotegravir+rilpivirine:ti,ab,kw OR 'cabotegravir plus rilpivirine':ti,ab,kw OR 'cabotegravir/rilpivirine':ti,ab,kw

	#12	#10 OR #11
	#13	'randomized controlled trial':ti,ab,kw OR rct:ti,ab,kw OR random:ti,ab,kw OR randomly:ti,ab,kw OR 'random allocation':ti,ab,kw OR allocation:ti,ab,kw OR 'randomized control trial':ti,ab,kw OR 'controlled clinical trial':ti,ab,kw OR 'clinical trial':ti,ab,kw OR 'clinical study':ti,ab,kw
	#14	#3 AND #12 AND #13
Cochrane Library (61)	#1	(HIV):ti,ab,kw OR (Human Immunodeficiency Virus):ti,ab,kw OR (Immunodeficiency Viruses, Human):ti,ab,kw OR (Virus, Human Immunodeficiency):ti,ab,kw OR (Human T Cell Lymphotropic Virus Type III):ti,ab,kw OR (Human T Cell Leukemia Virus Type III):ti,ab,kw OR (LAV-HTLV-III):ti,ab,kw OR (Lymphadenopathy-Associated Virus):ti,ab,kw OR (AIDS Virus):ti,ab,kw OR (Acquired Immune Deficiency Syndrome Virus):ti,ab,kw OR (HTLV-III):ti,ab,kw
	#2	MeSH descriptor: [HIV] explode all trees
	#3	#1 OR #2
	#4	(cabotegravir):ti,ab,kw OR (GSK-1265744):ti,ab,kw OR (S-26574):ti,ab,kw OR (GSK1265744):ti,ab,kw OR (Vocabria):ti,ab,kw OR (GSK744):ti,ab,kw
	#5	MeSH descriptor: [Rilpivirine] explode all trees
	#6	(Rilpivirine):ti,ab,kw OR (Rilpivirine Hydrochloride):ti,ab,kw OR (Hydrochloride, Rilpivirine):ti,ab,kw OR (Rilpivirine HCl):ti,ab,kw OR (HCl, Rilpivirine):ti,ab,kw OR (R278474):ti,ab,kw OR (TMC 278):ti,ab,kw OR (278, TMC):ti,ab,kw OR (TMC278):ti,ab,kw OR (TMC-278):ti,ab,kw
	#7	#5 OR #6
	#8	#4 AND #7
	#9	(cabotegravir, rilpivirine drug combination):ti,ab,kw OR (cabenuva):ti,ab,kw OR (cabotegravir plus rilpivirine):ti,ab,kw
	#10	#8 OR #9
	#11	(randomized controlled trial):ti,ab,kw OR (RCT):ti,ab,kw OR (random):ti,ab,kw OR (randomly):ti,ab,kw OR (random allocation):ti,ab,kw OR (allocation):ti,ab,kw OR (randomized control trial):ti,ab,kw OR (controlled clinical trial):ti,ab,kw OR (clinical trial):ti,ab,kw OR (clinical study):ti,ab,kw
	#12	#1 AND #10 AND #11
SCOPUS (149)	#1	(TITLE-ABS-KEY (“HIV”) OR TITLE-ABS-KEY (“human immunodeficiency virus”) OR TITLE-ABS-KEY (“Human T Cell Lymphotropic Virus Type III”) OR TITLE-ABS-KEY (“Human T Cell Leukemia Virus Type III”) OR TITLE-ABS-KEY (“LAV-HTLV-III”) OR TITLE-ABS-KEY (“Lymphadenopathy-Associated Virus”) OR TITLE-ABS-KEY (“aids virus”) OR TITLE-ABS-KEY (“acquired immune deficiency syndrome virus”) OR TITLE-ABS-KEY (“AIDS”))
	#2	((TITLE-ABS-KEY (“cabotegravir”) OR TITLE-ABS-KEY (“gsk-1265744”) OR TITLE-ABS-KEY (“s-26574”) OR TITLE-ABS-KEY (“gsk1265744”) OR TITLE-ABS-KEY (“vocabria”) OR TITLE-ABS-KEY (“gsk744”)) AND ((TITLE-ABS-KEY (“rilpivirine”) OR TITLE-ABS-KEY (“rilpivirine hydrochloride”) OR TITLE-ABS-KEY (“hydrochloride, rilpivirine”) OR TITLE-ABS-KEY (“rilpivirine hcl”) OR TITLE-ABS-KEY (“hcl, rilpivirine”) OR TITLE-ABS-KEY (“r278474”) OR TITLE-ABS-KEY (“tmc 278”) OR TITLE-ABS-KEY (“278,

		tmc") OR TITLE-ABS-KEY ("tmc278") OR TITLE-ABS-KEY ("tmc-278")))) OR ((TITLE-ABS-KEY ("cabotegravir, rilpivirine drug combination") OR TITLE-ABS-KEY ("cabenuva") OR TITLE-ABS-KEY ("cabotegravir+rilpivirine") OR TITLE-ABS-KEY ("cabotegravir plus rilpivirine") OR TITLE-ABS-KEY ("cabotegravir/rilpivirine")))
	#3	(TITLE-ABS-KEY ("randomized controlled trial") OR TITLE-ABS-KEY ("rct") OR TITLE-ABS-KEY ("random") OR TITLE-ABS-KEY ("randomly") OR TITLE-ABS-KEY ("random allocation") OR TITLE-ABS-KEY ("allocation") OR TITLE-ABS-KEY ("randomized control trial") OR TITLE-ABS-KEY ("controlled clinical trial") OR TITLE-ABS-KEY ("clinical trial") OR TITLE-ABS-KEY ("clinical study"))
	#4	#1 AND #2 AND #3
Google Scholar (545)		((((("Cabotegravir" OR "GSK-1265744" OR "S-265744" OR "GSK1265744" OR "Vocabria" OR "GSK744") AND ("Rilpivirine" OR "TMC278" OR "r278474" OR "TMC-278" OR "TMC 278")) AND ("HIV" OR "AIDS" OR"human immunodeficiency virus")) AND ("randomized controlled trial" OR "RCT" OR "random" OR "randomly"))
Clinicaltrials. gov (47)		Condition or disease: HIV Other terms: (Rilpivirine OR Cabotegravir) AND (Injectable OR Injection)

Table S2 A data collection form for long-acting intramuscular injection of Cabotegravir and Rilpivirine in adults with HIV-1 infection

Basic Information							
Title							
Author							
Journal of the publication							
Fixed number of years of the publication							
Select Level	Full text □		Abstract □		Conference □		Other □
Main points of the study (PICOS)							
P	Sample size		Gender (M/F)		Mean age (years)		
	Study sites		Nationality		Treatment course		
I	Specific therapy		dosage		Treatment course		
C	Specific therapy		dosage		Treatment course		
O	Measurement index				Units		
S	Design	RCTs □	NON-RCT □	Before-after study □	HCT □		Cohort study □
	Method	Random □		Control □	Blinding □		Other □
Result							
Group		Treatment group			Control group		
Two-category data	Event count		Sample size		Event count		Sample size
Continuous data	Mean ± SD		Sample size		Mean ± SD		Sample size
Effect size	Index						
	95% CI						
	SE						

Non-randomized controlled trial, NON-RCT; Historial control trial, HCT; Male, M; female, F; Confidence intervals, CI; Standard Deviation, SD; Standard Error, SE.

Table S3: Study Characteristics of the included studies

First author/ Publication year	Trial name (NCT ID)	Intervention ((T /C))	Study characteristics			Number of cases (T /C)	Subject characteristics			Follow-up period (weeks)	HIV-1 subtype	Outcomes
			Phase	Masking	Location		Age (year)	Gender (M/F)	ART naïve (yes/no)			
r												

Notes:

T, treatment groups; C, control groups; M, male; F, female; CAB, Cabotegravir; RPV, Rilpivirine;

Definitions

Efficacy

In this study, efficacy outcomes were defined as the proportion of patients with virologic success (HIV-1 Ribonucleic Acid [RNA] < 50 Copies Per Milliliter [mL]) Using Snapshot Algorithm according to Human immunodeficiency virus-1 infection: Developing antiretroviral drugs for treatment (2015) [1]. In contrast, HIV RNA≥50 copies/mL was defined as virologic failure. The CVF was defined as a rebound as indicated by two consecutive plasma HIV-1-RNA levels ≥200 copies/mL after prior suppression to <200 copies/mL.

Safety

Whenever possible, safety outcomes were defined according to the corrected version 2.1 of Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events [2]. Adverse event (AE) was defined as any untoward event (i.e. sign, symptoms, disease) temporally associated with medical procedures or treatments, regardless of its causalities. According to the grading criteria, adverse events grade ≥2 encompass moderate-or-higher AE severity, including moderate (grade 2), severe (grade 3), life-threatening events (grade 4), and events resulting in death (grade 5). On the other hand, serious AE was defined as AE resulting in death, life-threatening situations, significant impairments, birth defects or requiring immediate intervention, inpatient care, or prolongation of hospitalization.

Reporting checklist for protocol of a systematic review and meta analysis.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	Page 1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Page 2
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 1
Contribution	#3b	Describe contributions of protocol authors and identify the	Page 8

		guarantor of the review	
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support			
Sources	#5a	Indicate sources of financial or other support for the review	Page 8
Sponsor	#5b	Provide name for the review funder and / or sponsor	N/A
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	N/A
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	Page 3-4
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 5
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Page 5
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Page 4
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Page 4,13
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 6
Study records -	#11b	State the process that will be used for selecting studies (such	Page 6

selection process		as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page 6
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Page 5,12
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page 5
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page 5-6
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	Page 6
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	Page 6
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Page 6
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Page 6
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 6
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page 6-7

BMJ Open

Safety and Efficacy of Long-acting Intramuscular Cabotegravir and Rilpivirine in Adults with HIV-1 Infection: A Systematic Review and Meta-analysis Protocol

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Safety and Efficacy of Long-acting Intramuscular Cabotegravir and Rilpivirine in Adults with HIV-1 Infection: A Systematic Review and Meta-analysis Protocol

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Abstract

Background: Current antiretroviral regimens have, for the most part, achieved optimal antiretroviral efficacy and tolerability, transforming human immunodeficiency virus (HIV) infection from a deadly disease into a manageable chronic condition. Still, adherence to daily oral drug intake remains an issue, as it is the most important determinant for sustained viral suppression and prevention of the emergence of drug-resistant viral strains. The long-acting injection (LAI) antiretroviral Cabotegravir (CAB) and Rilpivirine (RPV) combination, a novel drug delivery approach, is about to revolutionize the therapy for people living with HIV. We aim to generate a clinically useful summary of the interventions based on their efficacy.

Methods and analysis: We searched the literature for eligible studies published from inception up to 16 August 2022 through PubMed, Embase, Cochrane Library, SCOPUS, and Clinicaltrials.gov. Two methodological trained researchers will select the qualified studies for data extraction independently. Cochrane Risk of Bias tool will be used to assess the risk of bias in included studies. Statistical heterogeneity will be computed by Cochrane X^2 and I^2 tests. Sensitivity analysis will be conducted to evaluate the stability of the results. Publication biases will be evaluated by Begg's and Egger's tests. The quality of evidence will be assessed by the GRADE system. The RevMan 5.3 and stata 14.0 software will be applied for statistical analyses.

Ethics and Dissemination: Ethical approval will not be required for this systematic review because the data used are not linked to the individual patient. The results of this review will be disseminated by being published in a peer-reviewed journal.

PROSPERO Registration number: CRD42022310414

Keywords: HIV, Cabotegravir and Rilpivirine, Systematic Review, Protocol, Meta-analysis

Article summary

Strengths and limitations of this study

- This protocol followed the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P).
- Search and screening will cover an extensive range of publications.
- Each process of initial screening, data extraction, and quality evaluation will be performed by two independent reviewers to minimize potential bias.
- The exclusion of papers not published in English may mean those important additional findings are missed.
- This review only includes randomized controlled trials (RCTs) therefore may ignore some studies of other types.

1. Introduction

June 2021 marked the 40th anniversary of the first description of acquired immunodeficiency syndrome (AIDS).[1] Despite scientific and programmatic progress, the end of AIDS is not in sight[1]. Even before the coronavirus disease (COVID-19) pandemic, progress in the global AIDS response

was not on track to reach the 2020 UNAIDS HIV targets.[2] The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that in 2019, 38 million persons worldwide were living with HIV, 1.7 million became newly infected, and 690,000 died with HIV disease.[3]

Antiretroviral therapy (ART) improvements have helped reduce HIV-related mortality substantially.[4,5] To sustain viral suppression, current guideline-recommended first-line treatments for HIV-1 mandate lifelong daily adherence to oral regimens.[6] The oral daily intake of antiretroviral drugs is a burden, which may present physical, emotional, and logistical challenges for people with HIV (PWH)[7-10] and lead to substantial patient non-adherence.[11] Non-adherence can predispose to the emergence of drug-resistant HIV strains, treatment failure, and disease progression.[12-14] Simplified regimens for the treatment of HIV-1 infection may increase patient satisfaction and facilitate adherence.

Being developed as potential alternatives to pill-based treatment regimens for HIV, long-acting (LA) ART provide the convenience of reduced dosing frequency and may be beneficial or improve the quality of life for individuals with pill fatigue or concerns about disclosure of HIV status or stigma associated with daily oral medication.[15]

CAB is a novel integrase strand transfer inhibitor (INSTI) and structural analog of Dolutegravir (DTG).[16,17] RPV is a non-nucleoside reverse transcriptase inhibitor (NNRTI) first approved in an oral tablet formulation in 2011.[18,19] In January 2021, LAI formulations of the INSTI CAB and the NNRTI RPV were approved by the Food and Drug Administration (FDA). This combination can be used to replace an existing oral ARV regimen in people with HIV with sustained viral suppression for 3 to 6 months (optimal duration is not defined), who have good adherence and engagement in care, no baseline resistance to either medication, no prior virologic failures; who do not have active or occult HBV infection (unless the patient also is receiving an HBV active regimen); who are not pregnant or planning on becoming pregnant; and who are not receiving medications with significant drug interactions with oral (during lead-in or bridging therapy) or injectable CAB or RPV.

In the past few years, the combination of CAB and RPA has made some breakthroughs in the treatment and prevention of HIV,[20-24] however, there are still challenges in applying them to the real world. Key outstanding questions include management of patient compliance, special

populations, virological failure, and drug resistance. Therefore, this systematic review aims to summarize the available evidence on the safety and efficacy of LAI CAB and RPA in adults with HIV-1 infection, to give reference for clinical work.

2. Objective: The objective is to estimate the safety and efficacy of LAI CAB and RPV in adults with HIV-1 infection.

3.Review question(s):

1. What is the efficacy of LAI CAB and RPV for maintaining HIV-1 suppression compared with standard oral antiretroviral drugs?

2. How is the security?

3. Can the patient tolerate it?

4. Which regimen is better to inject every four weeks(Q4W) or every eight weeks(Q8W)?

4. Methods and analysis

4.1 Protocol registration and reporting:

This is a protocol that was registered in the PROSPERO (registration number CRD42022310414). This systematic review and meta-analysis will be reported based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statements.[25] It will be performed following the recommendations of the Cochrane Handbook.

4.2 Search strategy:

We will search the literature through PubMed, EMBASE, Cochrane Library, SCOPUS, and Clinicaltrials.gov. Detailed information is provided in Table S1 of the Supplementary Material. All the English publications until 17 August 2022 will be searched without any restriction of countries or article types. Medical Subject Headings (MeSH) terms combined with free text words, including “HIV”, “AIDS”, “Cabotegravir”, “Rilpivirine”, “Cabotegravir and Rilpivirine” were searched. Additionally, Google Scholar databases will be screened for gray literature and manual searches will be performed by hand-searching reference lists of included studies and previous reviews. Searches will be conducted by two independent investigators (Yuanni Wu and Hai Yu) using keywords and any discrepancies will be resolved by a third investigator (Lianfeng Lu)–also in a blinded fashion. Reference lists of all selected articles will be screened independently to identify additional studies left out in the initial search. The search strategy that will be used for PubMed is

reported in Table 1. We will modify our search strategy to suit each database. We will update the search six months ahead of publishing the systematic review paper. All results will be managed by EndNote software. Duplicate records will be recognized and removed.

4.3 Eligibility Criteria:

Inclusion criteria based on PICOs (Cochrane standard) are:

P (Participants or population): Adults with HIV-1 infection (as diagnosed by a clinician, or using any recognized diagnostic criteria) will be included.

I (Intervention): The main intervention was the intramuscular injection of long-acting CAB and RPV, regardless of the frequency of injection and duration of treatment. Studies comparing LAI CAB and RPV formulations with any pair of the conventional oral ART regimens will be included.

C (comparison): The control groups receive oral antiretroviral therapy.

O (Outcome):

The outcome measures of interest were the efficacy and safety of the combination regimen (as defined in the Supplementary material). Primary efficacy outcomes are the percentage of participants with virologic success (plasma human immunodeficiency virus-ribonucleic acid [HIV-RNA] < 50 copies per milliliter [C/mL]), virologic failure (HIV RNA ≥ 50 copies/mL) and confirmed virologic failure (CVF, HIV-1-RNA levels ≥200 copies/mL) at week 48 or 96 as per FDA Snapshot Algorithm. Primary safety outcomes include frequencies of any adverse events (AEs), serious AEs, and AEs-related withdrawal. Secondary outcomes include incidence and severity of laboratory abnormalities, ithe ncidence of treatment-emergent genotypic and phenotypic resistance, mean plasma CAB and RPV concentrations, treatment satisfaction, and change in CD4+ T cell counts from baseline.

S (Study Design): Randomized controlled trials (RCTs) will be included.

4.4 Exclusion Criteria:

Studies that meet the following criteria will be excluded:

- Irretrievable full-text articles or studies not in English;
- Studies without specific data;
- Review articles;
- non-RCTs studies;

- Studies for HIV pre-exposure prophylaxis rather than treatment.

4.5 Study screening and selection:

Two independent investigators (Yuanni Wu and Hai Yu) will evaluate studies according to title and abstract and the chosen full texts that comply with the inclusion criteria will be entered for full-text review. When there are conflicts, they will be resolved by the third author (Lianfeng Lu). We will note the reasons for all excluded studies. A PRISMA flow chart (Figure 1) will be drawn to present the whole process of study selection.[25]

4.6 Data extraction and quality assessment:

Data from the included studies will be extracted independently by two authors (Yuanni Wu and Hai Yu) using a pre-defined data extraction form constructed and standardized before being applied (Table S2). Disagreements will be resolved by discussion or consensus with a third reviewer (Xiaodi Li). After completing the data extraction phase, the results of the included papers will be categorized and summarized in Table S3.

Two reviewers (Xiaodi Li and Xiaosheng Liu) will independently assess the risk of bias based on the following domains from recommendations from the Cochrane handbook: (1) Adequate sequence generation; (2) Allocation concealment; (3) Blinding of participants and personnel; (4) Blinding of outcome assessment; (5) Incomplete outcome data and how it was addressed; (6) Selective reporting of the outcome; (7) Any other biases.[26] Results of the bias assessment will be presented in a figure and a graph indicating low, high, or unclear risk of bias for each of the 7 items in each trial. Sensitivity analysis will be conducted based on the bias assessment to assess the robustness of the results.

4.7 Statistical analysis:

After completing the data extraction phase, the results of the included papers will be categorized and summarized in Table S3. For the meta-analysis, we will calculate the risk ratio (RR) for binary outcomes and weighted mean difference (WMD) for continuous outcomes, with a 95 % confidence interval (CI). All statistical analyses will be performed using RevMan 5.3 and Stata software (version 14.0).

Publication biases will be evaluated by Begg's and Egger's tests. Statistical heterogeneity will be computed by Cochrane X^2 and I^2 tests; an $I^2 < 50$ % suggests low heterogeneity, based on which

the fixed effect model will be employed; an $I^2 > 50$ % indicates significant heterogeneity, based on which a random effect model will be used.[27,28] In the case of high heterogeneity, we will conduct subgroup analysis according to the region of the studies, age, stage of the subjects, types of treatments, and different outcomes. We will evaluate the credibility of the subgroup analysis in terms of the guidance. If there is enough research, meta-regression will be performed to clarify the source of heterogeneity. We will also use sensitivity analysis to explore the source of heterogeneity, when necessary; if heterogeneity still exists, the descriptive analysis will be used to explain the results.

Two subgroup analyses will also be performed:

The first is to assess if an injection of different doses and injection schedules (e.g. Q4W or Q8W injection) produces different therapeutic effects; the second is to investigate whether CAB and RAP injections are equally effective among different patient groups (ART-naive or 6 months of uninterrupted ART).

4.8 Confidence in cumulative evidence:

The most distinct feature of evidence-based medicine is to grade the quality of evidence to quantify the reliability of research results. The quality of evidence from meta-analyses will be rated by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system,[29] which uses study design as the starting point and then addresses five reasons to possibly rate down the quality of evidence (expressed by reducing scores) and three reasons to possibly rate up the quality (expressed by adding points).

5. Patient and Public Involvement statement

As this is a protocol for a systematic review, patients were not directly involved in the design of this study.

6. Discussion

This study will review and summarize the clinical trial evidence so far; evaluate the safety and effectiveness of LAI CAB and RPV; analyze the pharmacokinetic characteristics, any AEs, and treatment satisfaction; and discusses the practicability of special populations.

To minimize potential bias, each process of initial screening, data extraction, and quality evaluation will be performed by two independent reviewers. When the initial screening, data

extraction, and quality evaluation opinions are inconsistent, the third party can discuss and solve. Before the meta-analysis, strict and unified inclusion criteria and data extraction criteria were formulated to reduce the heterogeneity among studies, but the existence of heterogeneity should be acknowledged even so. If there was significant heterogeneity among studies, subgroup analysis and meta-regressionn (included age, sex at birth, body-mass index category, years since HIV infection, years since ART, the baseline of CD4+T counts and HIV RNA levels, duration the of previous cabotegravir plus rilpivirine long-acting exposure, and injected doses) were used to explore the source of heterogeneity. Finally, the exclusion of papers not published in English and non-RCTs studies may mean those important additional findings are missed. If amendments are needed, we will update our protocol to include any changes in the whole process of research.

In summary, this review study will produce robust data on the safety and efficacy of LAI CAB and RPV in adults with HIV-1 infection. These findings may provide more guidance for clinicians in the treatment of HIV.

7. Ethics and Dissemination

There are no ethical issues related to this study. This article does not contain any studies with human participants or animals performed by any of the authors because this is a protocol for a systematic review relying on primary studies. The results of our research will be published in a peer-reviewed journal.

8. Author Contributions

After conceptualizing and designing the study, Yuanni Wu registered the protocol on the PROSPERO database. Yuanni Wu and Hai Yu critically revised the protocol and contributed to the drafting of the final manuscript. Wei Cao and Taisheng Li tested the feasibility of the study and were involved in the revision of the protocol. Yuanni Wu, Hai Yu, Lianfeng Lu, Xiaodi Li, and Xiaosheng Li will perform the data collection and analyses. All authors read and approved the final manuscript.

9. Funding statement

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10. Competing interests

All authors declared there are no conflicts of interest.

11. Acknowledgements

The authors would like to thank all those who have contributed to the preparation of this protocol.

12. Availability of data and materials

Data will be available upon request of the corresponding author via the following email address: litsh@263.net

13. Amendments

If amendments are needed, we will update our protocol to include any changes in the whole process of research.

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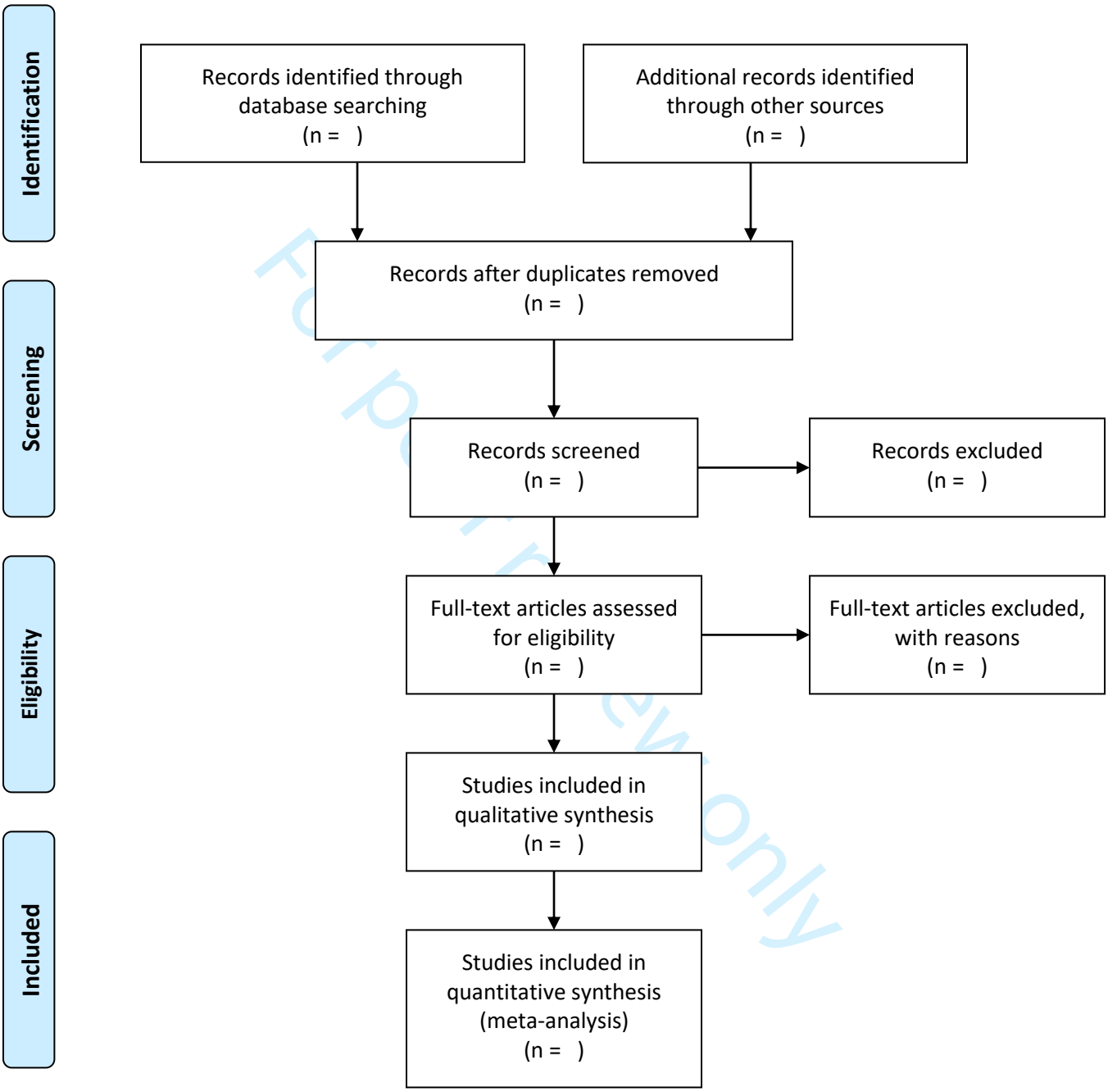
Table 1: Search strategy in PubMed

Database	Search	Search terms
PubMed (12)	#1	("HIV"[Mesh]) OR ((((((((((((((((((((((((Human Immunodeficiency Virus[Title/Abstract]) OR (Immunodeficiency Virus, Human[Title/Abstract])) OR (Immunodeficiency Viruses, Human[Title/Abstract])) OR (Virus, Human Immunodeficiency[Title/Abstract])) OR (Viruses, Human Immunodeficiency[Title/Abstract])) OR (Human Immunodeficiency Viruses[Title/Abstract])) OR (Human T Cell Lymphotropic Virus Type III[Title/Abstract])) OR (Human T-Cell Lymphotropic Virus Type III[Title/Abstract])) OR (Human T-Cell Leukemia Virus Type III[Title/Abstract])) OR (Human T Cell Leukemia Virus Type III[Title/Abstract])) OR (LAV-HTLV-III[Title/Abstract])) OR (Lymphadenopathy-Associated Virus[Title/Abstract])) OR (Lymphadenopathy Associated Virus[Title/Abstract])) OR (Lymphadenopathy-Associated Viruses[Title/Abstract])) OR (Virus, Lymphadenopathy-Associated[Title/Abstract])) OR (Viruses, Lymphadenopathy-Associated[Title/Abstract])) OR (Human T Lymphotropic Virus Type III[Title/Abstract])) OR (Human T-Lymphotropic Virus Type III[Title/Abstract])) OR (AIDS Virus[Title/Abstract])) OR (AIDS Viruses[Title/Abstract])) OR (Virus, AIDS[Title/Abstract])) OR (Viruses, AIDS[Title/Abstract])) OR (Acquired Immune Deficiency Syndrome Virus[Title/Abstract])) OR (Acquired Immunodeficiency Syndrome Virus[Title/Abstract])) OR (HTLV-III[Title/Abstract]))
	#2	("cabotegravir"[Supplementary Concept]) OR (((((((N-((2,4-difluorophenyl)methyl)-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro(1,3)oxazolo(3,2-a)pyrido(1,2-d)pyrazine-8-carboxamide[Title/Abstract]) OR (Cabotegravir*[Title/Abstract])) OR (GSK-1265744*[Title/Abstract])) OR (S-265744*[Title/Abstract])) OR (GSK1265744*[Title/Abstract])) OR (Vocabria [Title/Abstract])) OR (GSK744 [Title/Abstract]))
	#3	("Rilpivirine" [Mesh]) OR (((((((((Rilpivirine Hydrochloride[Title/Abstract]) OR (Hydrochloride, Rilpivirine[Title/Abstract])) OR (Rilpivirine HCl[Title/Abstract])) OR (HCl, Rilpivirine[Title/Abstract])) OR (R278474[Title/Abstract])) OR (TMC 278[Title/Abstract])) OR (278, TMC[Title/Abstract])) OR (TMC278[Title/Abstract])) OR (TMC-278[Title/Abstract]))
	#4	# 2 AND #3
	#5	(cabotegravir, rilpivirine drug combination [Supplementary Concept]) OR (cabenuva)
	#6	(cabotegravir/rilpivirine) OR (cabotegravir + rilpivirine) OR (CAB+RPV) OR (CAB/RPV) OR (cabotegravir plus rilpivirine)
	#7	#4 OR #5 OR #6
	#8	(((((((((randomized controlled trial[Title/Abstract]) OR RCT[Title/Abstract]) OR random[Title/Abstract]) OR randomly[Title/Abstract]) OR random allocation[Title/Abstract]) OR allocation[Title/Abstract]) OR randomized control trial[Title/Abstract]) OR controlled

		clinical trial[Title/Abstract]) OR clinical trial[Title/Abstract]) OR clinical study[Title/Abstract]
	#9	#1 AND #7 AND #8

Figure legends (Figure 1 will be uploaded separately)

Figure 1 Flow chart of study selection.



Supplementary Material

Safety and Efficacy of Long-acting Intramuscular Cabotegravir and Rilpivirine in Adults with HIV-1 Infection: A Systematic Review and Meta-analysis Protocol

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Supplementary tables

Table S1. Search strategy

Database	Search	Search terms
PubMed (12)	#1	("HIV"[Mesh]) OR ((((((((((((((((((((((((Human Immunodeficiency Virus[Title/Abstract]) OR (Immunodeficiency Virus, Human[Title/Abstract])) OR (Immunodeficiency Viruses, Human[Title/Abstract])) OR (Virus, Human Immunodeficiency[Title/Abstract])) OR (Viruses, Human Immunodeficiency[Title/Abstract])) OR (Human Immunodeficiency Viruses[Title/Abstract])) OR (Human T Cell Lymphotropic Virus Type III[Title/Abstract])) OR (Human T-Cell Lymphotropic Virus Type III[Title/Abstract])) OR (Human T-Cell Leukemia Virus Type III[Title/Abstract])) OR (Human T Cell Leukemia Virus Type III[Title/Abstract])) OR (LAV-HTLV-III[Title/Abstract])) OR (Lymphadenopathy-Associated Virus[Title/Abstract])) OR (Lymphadenopathy Associated Virus[Title/Abstract])) OR (Lymphadenopathy-Associated Viruses[Title/Abstract])) OR (Virus, Lymphadenopathy-Associated[Title/Abstract])) OR (Viruses, Lymphadenopathy-Associated[Title/Abstract])) OR (Human T Lymphotropic Virus Type III[Title/Abstract])) OR (Human T-Lymphotropic Virus Type III[Title/Abstract])) OR (AIDS Virus[Title/Abstract])) OR (AIDS Viruses[Title/Abstract])) OR (Virus, AIDS[Title/Abstract])) OR (Viruses, AIDS[Title/Abstract])) OR (Acquired Immune Deficiency Syndrome Virus[Title/Abstract])) OR (Acquired Immunodeficiency Syndrome Virus[Title/Abstract])) OR (HTLV-III[Title/Abstract]))
	#2	("cabotegravir"[Supplementary Concept]) OR (((((((N-((2,4-difluorophenyl)methyl)-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro(1,3)oxazolo(3,2-a)pyrido(1,2-d)pyrazine-8-carboxamide[Title/Abstract]) OR (Cabotegravir*[Title/Abstract])) OR

		(GSK-1265744*[Title/Abstract])) OR (S-265744*[Title/Abstract])) OR (GSK1265744*[Title/Abstract])) OR (Vocabria [Title/Abstract])) OR (GSK744 [Title/Abstract]))
	#3	("Rilpivirine" [Mesh]) OR (((((((((Rilpivirine Hydrochloride[Title/Abstract]) OR (Hydrochloride, Rilpivirine[Title/Abstract])) OR (Rilpivirine HCl[Title/Abstract])) OR (HCl, Rilpivirine[Title/Abstract])) OR (R278474[Title/Abstract])) OR (TMC 278[Title/Abstract])) OR (278, TMC[Title/Abstract])) OR (TMC278[Title/Abstract])) OR (TMC-278[Title/Abstract]))
	#4	# 2 AND #3
	#5	(cabotegravir, rilpivirine drug combination [Supplementary Concept]) OR (cabenuva)
	#6	(cabotegravir/rilpivirine) OR (cabotegravir + rilpivirine) OR (CAB+RPV) OR (CAB/RPV) OR (cabotegravir plus rilpivirine)
	#7	#4 OR #5 OR #6
	#8	(((((((((randomized controlled trial[Title/Abstract]) OR RCT[Title/Abstract]) OR random[Title/Abstract]) OR randomly[Title/Abstract]) OR random allocation[Title/Abstract]) OR allocation[Title/Abstract]) OR randomized control trial[Title/Abstract]) OR controlled clinical trial[Title/Abstract]) OR clinical trial[Title/Abstract]) OR clinical study[Title/Abstract]
	#9	#1 AND #7 AND #8
Embase (28)	#1	'hiv'/exp OR hiv OR 'human immunodeficiency virus':ti,ab,kw OR 'immunodeficiency virus, human':ti,ab,kw OR 'human t cell lymphotropic virus type iii':ti,ab,kw OR 'human t-cell leukemia virus type iii':ti,ab,kw OR 'lav htlv iii':ti,ab,kw OR 'lymphadenopathy-associated virus':ti,ab,kw OR 'aids virus':ti,ab,kw OR 'acquired immune deficiency syndrome virus':ti,ab,kw OR 'htlv iii':ti,ab,kw
	#2	'human immunodeficiency virus'/exp
	#3	#1 OR #2
	#4	cabotegravir:ti,ab,kw OR (n-:ti,ab,kw AND '2,4 difluorophenyl':ti,ab,kw AND methyl:ti,ab,kw AND '6 hydroxy 3 methyl 5,7 dioxo 2,3,5,7,11,11a hexahydro':ti,ab,kw AND 1,3:ti,ab,kw AND oxazolo:ti,ab,kw AND '3,2 a':ti,ab,kw AND pyrido:ti,ab,kw AND '1,2 d':ti,ab,kw AND 'pyrazine 8 carboxamide':ti,ab,kw) OR 'gsk 1265744':ti,ab,kw OR 'gsk 1265744a':ti,ab,kw OR 'gsk 1265744b':ti,ab,kw OR 's 265744':ti,ab,kw OR 's 265744b':ti,ab,kw OR gsk1265744:ti,ab,kw OR vocabria:ti,ab,kw OR gsk744:ti,ab,kw
	#5	'cabotegravir'/exp
	#6	#4 OR #5
	#7	rilpivirine:ti,ab,kw OR 'rilpivirine hydrochloride':ti,ab,kw OR 'hydrochloride, rilpivirine':ti,ab,kw OR 'rilpivirine hcl':ti,ab,kw OR 'hcl, rilpivirine':ti,ab,kw OR r278474:ti,ab,kw OR '278, tmc':ti,ab,kw OR tmc278:ti,ab,kw OR 'tmc 278':ti,ab,kw
	#8	'rilpivirine'/exp
	#9	#7 OR #8
	#10	#6 AND #9
	#11	'cabotegravir, rilpivirine drug combination':ti,ab,kw OR cabenuva:ti,ab,kw OR cabotegravir+rilpivirine:ti,ab,kw OR 'cabotegravir plus rilpivirine':ti,ab,kw OR 'cabotegravir/rilpivirine':ti,ab,kw

	#12	#10 OR #11
	#13	'randomized controlled trial':ti,ab,kw OR rct:ti,ab,kw OR random:ti,ab,kw OR randomly:ti,ab,kw OR 'random allocation':ti,ab,kw OR allocation:ti,ab,kw OR 'randomized control trial':ti,ab,kw OR 'controlled clinical trial':ti,ab,kw OR 'clinical trial':ti,ab,kw OR 'clinical study':ti,ab,kw
	#14	#3 AND #12 AND #13
Cochrane Library (61)	#1	(HIV):ti,ab,kw OR (Human Immunodeficiency Virus):ti,ab,kw OR (Immunodeficiency Viruses, Human):ti,ab,kw OR (Virus, Human Immunodeficiency):ti,ab,kw OR (Human T Cell Lymphotropic Virus Type III):ti,ab,kw OR (Human T Cell Leukemia Virus Type III):ti,ab,kw OR (LAV-HTLV-III):ti,ab,kw OR (Lymphadenopathy-Associated Virus):ti,ab,kw OR (AIDS Virus):ti,ab,kw OR (Acquired Immune Deficiency Syndrome Virus):ti,ab,kw OR (HTLV-III):ti,ab,kw
	#2	MeSH descriptor: [HIV] explode all trees
	#3	#1 OR #2
	#4	(cabotegravir):ti,ab,kw OR (GSK-1265744):ti,ab,kw OR (S-26574):ti,ab,kw OR (GSK1265744):ti,ab,kw OR (Vocabria):ti,ab,kw OR (GSK744):ti,ab,kw
	#5	MeSH descriptor: [Rilpivirine] explode all trees
	#6	(Rilpivirine):ti,ab,kw OR (Rilpivirine Hydrochloride):ti,ab,kw OR (Hydrochloride, Rilpivirine):ti,ab,kw OR (Rilpivirine HCl):ti,ab,kw OR (HCl, Rilpivirine):ti,ab,kw OR (R278474):ti,ab,kw OR (TMC 278):ti,ab,kw OR (278, TMC):ti,ab,kw OR (TMC278):ti,ab,kw OR (TMC-278):ti,ab,kw
	#7	#5 OR #6
	#8	#4 AND #7
	#9	(cabotegravir, rilpivirine drug combination):ti,ab,kw OR (cabenuva):ti,ab,kw OR (cabotegravir plus rilpivirine):ti,ab,kw
	#10	#8 OR #9
	#11	(randomized controlled trial):ti,ab,kw OR (RCT):ti,ab,kw OR (random):ti,ab,kw OR (randomly):ti,ab,kw OR (random allocation):ti,ab,kw OR (allocation):ti,ab,kw OR (randomized control trial):ti,ab,kw OR (controlled clinical trial):ti,ab,kw OR (clinical trial):ti,ab,kw OR (clinical study):ti,ab,kw
	#12	#1 AND #10 AND #11
SCOPUS (149)	#1	(TITLE-ABS-KEY (“HIV”) OR TITLE-ABS-KEY (“human immunodeficiency virus”) OR TITLE-ABS-KEY (“Human T Cell Lymphotropic Virus Type III”) OR TITLE-ABS-KEY (“Human T Cell Leukemia Virus Type III”) OR TITLE-ABS-KEY (“LAV-HTLV-III”) OR TITLE-ABS-KEY (“Lymphadenopathy-Associated Virus”) OR TITLE-ABS-KEY (“aids virus”) OR TITLE-ABS-KEY (“acquired immune deficiency syndrome virus”) OR TITLE-ABS-KEY (“AIDS”))
	#2	((TITLE-ABS-KEY (“cabotegravir”) OR TITLE-ABS-KEY (“gsk-1265744”) OR TITLE-ABS-KEY (“s-26574”) OR TITLE-ABS-KEY (“gsk1265744”) OR TITLE-ABS-KEY (“vocabria”) OR TITLE-ABS-KEY (“gsk744”)) AND ((TITLE-ABS-KEY (“rilpivirine”) OR TITLE-ABS-KEY (“rilpivirine hydrochloride”) OR TITLE-ABS-KEY (“hydrochloride, rilpivirine”) OR TITLE-ABS-KEY (“rilpivirine hcl”) OR TITLE-ABS-KEY (“hcl, rilpivirine”) OR TITLE-ABS-KEY (“r278474”) OR TITLE-ABS-KEY (“tmc 278”) OR TITLE-ABS-KEY (“278,

		tmc") OR TITLE-ABS-KEY ("tmc278") OR TITLE-ABS-KEY ("tmc-278")))) OR ((TITLE-ABS-KEY ("cabotegravir, rilpivirine drug combination") OR TITLE-ABS-KEY ("cabenuva") OR TITLE-ABS-KEY ("cabotegravir+rilpivirine") OR TITLE-ABS-KEY ("cabotegravir plus rilpivirine") OR TITLE-ABS-KEY ("cabotegravir/rilpivirine")))
	#3	(TITLE-ABS-KEY ("randomized controlled trial") OR TITLE-ABS-KEY ("rct") OR TITLE-ABS-KEY ("random") OR TITLE-ABS-KEY ("randomly") OR TITLE-ABS-KEY ("random allocation") OR TITLE-ABS-KEY ("allocation") OR TITLE-ABS-KEY ("randomized control trial") OR TITLE-ABS-KEY ("controlled clinical trial") OR TITLE-ABS-KEY ("clinical trial") OR TITLE-ABS-KEY ("clinical study"))
	#4	#1 AND #2 AND #3
Google Scholar (545)		((((("Cabotegravir" OR "GSK-1265744" OR "S-265744" OR "GSK1265744" OR "Vocabria" OR "GSK744") AND ("Rilpivirine" OR "TMC278" OR "r278474" OR "TMC-278" OR "TMC 278")) AND ("HIV" OR "AIDS" OR"human immunodeficiency virus")) AND ("randomized controlled trial" OR "RCT" OR "random" OR "randomly"))
Clinicaltrials. gov (47)		Condition or disease: HIV Other terms: (Rilpivirine OR Cabotegravir) AND (Injectable OR Injection)

Table S2 A data collection form for long-acting intramuscular injection of Cabotegravir and Rilpivirine in adults with HIV-1 infection

Basic Information							
Title							
Author							
Journal of the publication							
Fixed number of years of the publication							
Select Level	Full text □		Abstract □		Conference □		Other □
Main points of the study (PICOS)							
P	Sample size		Gender (M/F)		Mean age (years)		
	Study sites		Nationality		Treatment course		
I	Specific therapy		dosage		Treatment course		
C	Specific therapy		dosage		Treatment course		
O	Measurement index				Units		
S	Design	RCTs □	NON-RCT □	Before-after study □	HCT □		Cohort study □
	Method	Random □		Control □	Blinding □		Other □
Result							
Group		Treatment group			Control group		
Two-category data	Event count		Sample size		Event count		Sample size
Continuous data	Mean ± SD		Sample size		Mean ± SD		Sample size
Effect size	Index						
	95% CI						
	SE						

Non-randomized controlled trial, NON-RCT; Historial control trial, HCT; Male, M; female, F; Confidence intervals, CI; Standard Deviation, SD; Standard Error, SE.

Table S3: Study Characteristics of the included studies

First author/ Publication year	Trial name (NCT ID)	Intervention ((T /C))	Study characteristics			Number of cases (T /C)	Subject characteristics			Follow-up period (weeks)	HIV-1 subtype	Outcomes
			Phase	Masking	Location		Age (year)	Gender (M/F)	ART naïve (yes/no)			
r												

Notes:

T, treatment groups; C, control groups; M, male; F, female; CAB, Cabotegravir; RPV, Rilpivirine;

Definitions

Efficacy

In this study, efficacy outcomes were defined as the proportion of patients with virologic success (HIV-1 Ribonucleic Acid [RNA] < 50 Copies Per Milliliter [mL]) Using Snapshot Algorithm according to Human immunodeficiency virus-1 infection: Developing antiretroviral drugs for treatment (2015) [1]. In contrast, HIV RNA≥50 copies/mL was defined as virologic failure. The CVF was defined as a rebound as indicated by two consecutive plasma HIV-1-RNA levels ≥200 copies/mL after prior suppression to <200 copies/mL.

Safety

Whenever possible, safety outcomes were defined according to the corrected version 2.1 of Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events [2]. Adverse event (AE) was defined as any untoward event (i.e. sign, symptoms, disease) temporally associated with medical procedures or treatments, regardless of its causalities. According to the grading criteria, adverse events grade ≥2 encompass moderate-or-higher AE severity, including moderate (grade 2), severe (grade 3), life-threatening events (grade 4), and events resulting in death (grade 5). On the other hand, serious AE was defined as AE resulting in death, life-threatening situations, significant impairments, birth defects or requiring immediate intervention, inpatient care, or prolongation of hospitalization.

Reporting checklist for protocol of a systematic review and meta analysis.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	Page 1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Page 2
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 1
Contribution	#3b	Describe contributions of protocol authors and identify the	Page 8

		guarantor of the review	
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support			
Sources	#5a	Indicate sources of financial or other support for the review	Page 8
Sponsor	#5b	Provide name for the review funder and / or sponsor	N/A
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	N/A
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	Page 3-4
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 5
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Page 5
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Page 4
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Page 4,13
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 6
Study records -	#11b	State the process that will be used for selecting studies (such	Page 6

selection process		as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page 6
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Page 5,12
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page 5
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page 5-6
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	Page 6
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	Page 6
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Page 6
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Page 6
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 6
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page 6-7