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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 HIV infection from a deadly disease into a manageable chronic condition. However, 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 antiretroviral cabotegravir and rilpivirine combination, a novel drug delivery approach, is about to revolutionise the therapy for people living with HIV. In this protocol, 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 methodologically 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 Grading of Recommendations Assessment, Development and Evaluation system. The RevMan V.5.3 and Stata V.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

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This protocol followed the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols.
⇒ 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 minimise potential bias.
⇒ The exclusion of papers not published in English may mean those important additional findings are missed.
⇒ This review only includes randomised controlled trials therefore may ignore some studies of other types.

INTRODUCTION

June 2021 marked the 40th anniversary of the first description of 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.[4 12 13] 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,

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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.[14]

Cabotegravir (CAB) is a novel integrase strand transfer inhibitor (INSTI) and structural analogue of dolutegravir.[15 16] Rilpivirine (RPV) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) first approved in an oral tablet formulation in 2011.[17 18] In January 2021, long-acting injection (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 antiretroviral regimen in people with HIV with sustained viral suppression for 3–6 months (optimal duration is not defined), who have good adherence and engagement in care, no baseline resistance to either medication, no prior virological failures; who do not have active or occult hepatitis B virus (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,[19–23] 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 summarise 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.

Objective

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

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 4 weeks (Q4W) or every 8 weeks (Q8W)?

METHODS AND ANALYSIS

Protocol registration and reporting

This is a protocol that was registered in the PROSPERO. This systematic review and meta-analysis will be reported based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statements.[24] It will be performed following the recommendations of the Cochrane Handbook.

Search strategy

We will search the literature through PubMed, EMBASE, Cochrane Library, Scopus and ClinicalTrials.gov. Detailed information is provided in online supplemental table S1. All the English publications until 17 August 2022 will be searched without any restriction of countries or article types. Medical Subject Headings terms combined with free-text words, including 'HIV', 'AIDS', 'Cabotegravir', 'Rilpivirine', 'Cabotegravir and Rilpivirine' were searched. Additionally, Google Scholar databases will be screened for grey 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 (YW and HY) using keywords and any discrepancies will be resolved by a third investigator (LL)—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 6 months ahead of publishing the systematic review paper. All results will be managed by EndNote software. Duplicate records will be recognised and removed.

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 recognised diagnostic criteria) will be included.

I (intervention)

The main intervention was the intramuscular injection of LA 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 ART.

O (outcome)

The outcome measures of interest were the efficacy and safety of the combination regimen (as defined in the online supplemental material). Primary efficacy outcomes are the percentage of participants with virological success (plasma HIV-RNA<50 copies per millilitre (C/mL)), virological failure (HIV RNA≥50 C/mL) and confirmed virological failure (HIV-1-RNA levels≥200 C/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, incidence of treatment-emergent genotypic and phenotypic resistance, mean plasma CAB and

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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

MeSH, Medical Subject Headings.

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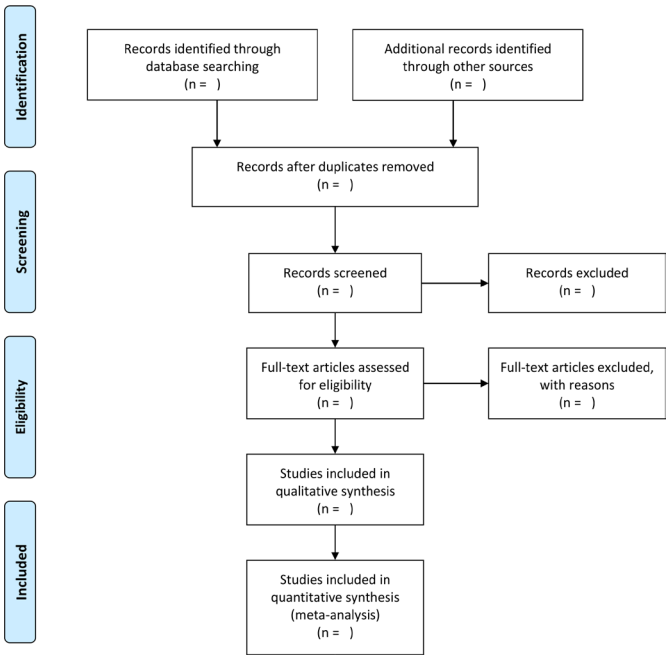

Figure 1 Flow chart of study selection.

RPV concentrations, treatment satisfaction and change in CD4+ T cell counts from baseline.

S (study design)

Randomised controlled trials (RCTs) will be included.

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.

Study screening and selection

Two independent investigators (YW and HY) 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 (LL). 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.[24]

Data extraction and quality assessment

Data from the included studies will be extracted independently by two authors (YW and HY) using a predefined data extraction form constructed and standardised before being applied (online supplemental table S2). Disagreements will be resolved by discussion or consensus with a third reviewer (XLi). After completing the data extraction phase, the results of the included papers will be categorised and summarised in online supplemental table S3.

Two reviewers (XLi and XLiu) 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.[25] 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 seven items in each trial. Sensitivity analysis will be conducted based on the bias assessment to assess the robustness of the results.

Statistical analysis

After completing the data extraction phase, the results of the included papers will be categorised and summarised in online supplemental table S3. For the meta-analysis, we will calculate the risk ratio for binary outcomes and weighted mean difference for continuous outcomes, with a 95% CI. All statistical analyses will be performed using RevMan V.5.3 and Stata software (V.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.[26 27] 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 (eg, 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).

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 system,[28] 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).

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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.

DISCUSSION

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

To minimise 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 CAB plus RPV LA 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.

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.

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

Contributors After conceptualising and designing the study, YW registered the protocol on the PROSPERO database. YW and HY critically revised the protocol and contributed to the drafting of the final manuscript. WC and TL tested the feasibility of the study and were involved in the revision of the protocol. YW, HY, LL, XLi and XLiu will perform the data collection and analyses. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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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.