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Efficacy, effectiveness, and safety of integrase inhibitors in the treatment of HIV/AIDS in patients with tuberculosis: systematic review and meta-analysis

Eficácia, efetividade e segurança dos inibidores da integrase no tratamento de HIV/AIDS em pacientes com tuberculose: revisão sistemática e metanálise

Eficacia, efectividad y seguridad de los inhibidores de la integrasa en el tratamiento del VIH/SIDA en pacientes con tuberculosis: revisión sistemática y metanálisis

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Abstract
Integrase Inhibitors are a promising new class of antiretroviral. However, studies of these drugs in tuberculosis (TB) and, HIV/aids coinfection are scarce. Therefore, the aim of this review was evaluate the efficacy, effectiveness, and safety of integrase inhibitors in the treatment of HIV/AIDS in patients coinfected with tuberculosis (TB). The searches were performed in the MEDLINE, EMBASE, LILACS, COCHRANE, Web of Science, Scopus, and CINAHL databases using the terms "HIV", "AIDS", "tuberculosis", "raltegravir potassium", "dolutegravir", "elvitegravir", "bictegravir", "integrase inhibitor", and their respective synonyms. Reports from three randomised clinical trials and a historical cohort were included. Patients coinfected with TB and HIV/AIDS showed a good response to TB treatment (cure or treatment completed), which was above 85% in all arms of the evaluated studies. As a primary outcome, the HIV viral load suppression rates at week 48 were greater than 60% in all arms. The therapies evaluated in patients coinfected with TB and HIV/AIDS were also within the limits of the included studies, there were no significant drug-related adverse events. However, there was no significant difference in the efficacy outcomes viral load suppression between the efavirenz and integrase inhibitor arms, and regarding safety outcomes, there were few events compared with the total. Integrase inhibitors in patients co-infected with TB and HIV/AIDS appear to be effective, well tolerated and constitute an alternative to efavirenz in clinical protocols. However, the use of this drug twice a day compromises adherence to treatment. The role of these drugs should be better determined by further good methodological quality studies to assess their long-term efficacy, effectiveness and safety.
Keywords: HIV; AIDS; Tuberculosis; Integrase inhibitor; Systematic review.

Resumo
Os inibidores da integrase são uma classe de antirretrovirais promissora. Entretanto, os estudos desses medicamentos na coinfecção tuberculose (TB) e HIV/aids são escassos. Portanto, o objetivo dessa revisão foi de avaliar a eficácia,

efetividade e segurança dos inibidores da integrase na coinfecção. As buscas foram realizadas nas bases de dados MEDLINE, EMBASE, LILACS, COCHRANE, Web of Science, Scopus e CINAHL, utilizando-se os termos HIV, AIDS, Tuberculosis, Raltegravir Potassium, dolutegravir, elvitegravir, bictegravir, Integrase Inhibitor e seus respectivos sinônimos. Foram incluídos os relatos referentes a três ensaios clínicos randomizados e a uma coorte histórica. Os pacientes coinfectados com TB e HIV/aids apresentaram respostas ao tratamento da TB superiores a 85% em todos os braços dos estudos avaliados. Como desfecho primário, as taxas de supressão da carga viral para o HIV na semana 48 foram superiores a 60% em todos os braços. As terapias avaliadas em pacientes coinfectados com TB e HIV/aids também demonstraram ser seguras. No entanto, não houve diferença significativa nos desfechos de eficácia entre os braços do efavirenz versus inibidores da integrase e para os desfechos de segurança observaram-se poucos eventos em relação ao total. Os inibidores da integrase em pacientes coinfectados com TB e HIV/aids parecem ser eficazes, bem tolerados e constituir uma alternativa ao efavirenz nos protocolos clínicos. Entretanto, a utilização desse medicamento duas vezes ao dia compromete a adesão ao tratamento. O papel desses medicamentos deve ser melhor determinado por mais estudos de boa qualidade metodológica para avaliar sua eficácia, efetividade e segurança a longo prazo.
Palavras-chave: HIV; AIDS; Tuberculose; Inibidores da integrase; Revisão sistemática.

Resumen
Los inhibidores de la integrasa son una clase prometedora de antirretrovirales. Sin embargo, los estudios de estos farmacos en la coinfección de tuberculosis (TB) y VIH/SIDA son escasos. Por lo tanto, el objetivo de esta revisión fue evaluar la eficacia, la efectividad y la seguridad de los inhibidores de la integrasa en la coinfección. Se realizaron búsquedas en las bases de datos MEDLINE, EMBASE, LILACS, COCHRANE, Web of Science, Scopus y CINAHL, utilizando los términos HIV, AIDS, Tuberculosis, Raltegravir Potassium, dolutegravir, elvitegravir, bictegravir, Integrase Inhibitor y sus respectivos sinónimos. Se incluyeron informes referentes a tres ensayos clínicos aleatorizados y una cohorte histórica. Los pacientes coinfectados con TB y VIH/SIDA mostraron una buena respuesta al tratamiento de la TB, superior al 85% en todos los brazos de los estudios evaluados. Como criterio principal de valoración, las tasas de supresión de la carga viral del VIH en la semana 48 fueron superiores al 60 % en todos los brazos. Las terapias evaluadas en pacientes coinfectados con TB y VIH/SIDA también han demostrado ser seguras. Sin embargo, no hubo diferencia significativa en los resultados de eficacia entre los brazos de efavirenz versus inhibidor de la integrasa y para los resultados de seguridad se observaron pocos eventos en relación con el total. Los inhibidores de la integrasa en pacientes coinfectados con TB y VIH/SIDA parecen ser efectivos, bien tolerados y constituir una alternativa a efavirenz en los protocolos clínicos. Sin embargo, el uso de este fármaco dos veces al día compromete la adherencia al tratamiento. El papel de estos fármacos debe determinarse mejor mediante estudios adicionales de buena calidad metodológica para evaluar su eficacia, efectividad y seguridad a largo plazo.
Palabras clave: VIH; SIDA; Tuberculosis; Inhibidores de la integrasa; Revisión sistemática.

1. Introduction

Tuberculosis (TB) is one of the top ten causes of death worldwide and the leading cause of death in people living with human immunodeficiency virus (PLHIV) (WHO, 2021). The risk of developing TB is 19-fold higher for PLHIV compared with the general population. In 2019, 1.2 million people without HIV and 208,000 PLHIV died from TB. TB is one of the leading causes of death from infectious diseases worldwide, mainly after the human immunodeficiency virus (HIV) epidemics. Patient with HIV-related illness are more likely to present with severe TB due to immunosuppression (Pecego, et al., 2016). Globally, the incidence of TB in PLHIV was 2.1 per 100 person-years (WHO, 2021).

Treatment of both diseases is recommended to reduce the risk of death and the onset of new infectious diseases (Manosuthi et al., 2016). However, concomitant therapy is a challenge considering the clinical condition of coinfected patients, the use of multiple drugs, drug interactions, overlapping toxicities, and immune reconstitution inflammatory syndrome (IRIS) (Manosuthi et al., 2016; McIlleron et al., 2007; Blanc et al. 2011).

Drug-sensitive tuberculosis treatment consists of the use of rifampicin (RMP), combined with isoniazid, pyrazinamide, and ethambutol (WHO, 2009). RMP is an enzymatic inducer of cytochrome P450 isoenzymes and also enzymes such as UDP-glucuronosyl-transferase. On the other hand, antiretroviral therapy (ART) options in TB and HIV/AIDS coinfection are limited. The protease inhibitors, reverse transcriptase nucleoside analogue inhibitors, and integrase inhibitors used for HIV treatment are substrates of enzymes that are induced by RMP. Therefore, the concomitant use of ART and RMP

can decrease antiretroviral (ARV) effectiveness (Blanc, et al. 2011; Wenning et al., 2009; Wang et al., 2019).

Integrase Inhibitors (INI) are a promising new class of ARV. Raltegravir (RAL) is a first-class integrase inhibitor (INI) with good efficacy and is well tolerated, but it needs to be used twice a day. Elvitegravir presents pharmacokinetic characteristics that requires the use of a booster and increases the occurrence of drug interactions, limiting its use in clinical practice. Dolutegravir (DTG) has lowered concentrations when coadministered with RMP, so studies recommend dosing it twice daily when RMP is being administered (Wang et al., 2019; Raffi et al., 2013).

In addition, INI are associated with a rapid viral load decrease and increased CD4 T lymphocyte count, especially in patients with counts below 200 cells. Their rapid effects play a significant role in the development of IRIS, characterised by increased signs and symptoms and/or radiographic TB signs (Wijting et al. 2019; Zimba et al., 2021; Lawn et al. 2005; Kolakowska et al. 2019).

The World Health Organization has recently recommended the use of INI as the preferred first-line treatment regimen for PLHIV/AIDS in the initial therapy for ART (WHO, 2015). However, studies on the efficacy, effectiveness, and safety of these drugs in PLHIV/AIDS coinfection with TB are scarce.

Therefore, the aim of this study was to systematically review the literature and evaluate the efficacy, effectiveness, and safety of INI in the treatment of HIV/AIDS in patients coinfected with active TB.

2. Methodology

The systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement (Page et al., 2021). The protocol was registered in PROSPERO by Resende et al. 2020 (registration number: CRD 42020185240).

Eligibility criteria:

Based on the question, the strategy for defining the population (P), intervention (I), comparator (C), outcomes (O) and Study type (S) (PICOS) was defined (Methley et al., 2014). Thus, the question for the research was: In experimental primary or observational studies patients receiving treatments for TB and HIV/AIDS (P), using integrase inhibitors (I), present which efficacy, effectiveness and safety outcomes (O)?

Studies that evaluated integrase inhibitors in adult patients with TB and HIV/AIDS were included, in which the evaluated outcomes were efficacy, effectiveness and/or safety. Review articles were excluded. Duplicates and articles published in languages other than English, Spanish, and Portuguese were excluded.

Search strategy and information sources:

Details of the search strategies are available in table 1. The searches were conducted in the MEDLINE, EMBASE, Latin American and Caribbean Literature on Health Sciences (LILACS), COCHRANE, Web of Science, Scopus, and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases, comprising studies published until May 2021 (table 1). The searches were conducted comprising studies published until August 2019. The search strategy was updated in May 2021 by using filters for publications published from 2019 (figure1).

To identify any relevant published studies not captured by the initial search strategy, the grey literature was searched using the following databases: ProQuest Dissertations & Theses Global, CAPES Bank of Thesis and Dissertations, UFMG Digital Library of Thesis and Dissertations, and conference proceedings in HIV studies (Conference on Retroviruses and Opportunistic Infections-CROI, International AIDS Society - IAS, and European AIDS Conference - EACS). In addition, a

manual search was performed in the references of the included studies.

Table 1 - Search strategies according to the database.

Base de dados	Estratégia de busca
MEDLINE	((((((((((((((((((HIV[MeSH Terms]) OR HIV[Text Word]) OR Human Immunodeficiency Virus[Text Word]) OR Immunodeficiency Virus, Human[Text Word]) OR Immunodeficiency Viruses, Human[Text Word]) OR Virus, Human Immunodeficiency[Text Word]) OR Viruses, Human Immunodeficiency[Text Word]) OR Human Immunodeficiency Viruses[Text Word]) OR AIDS Virus[Text Word]) OR AIDS Viruses[Text Word]) OR Virus, AIDS[Text Word]) OR Viruses, AIDS[Text Word]) OR Acquired Immune Deficiency Syndrome Virus[Text Word]) OR Acquired Immunodeficiency Syndrome Virus[Text Word])) OR ((((((((((((((((Acquired Immunodeficiency Syndrome[MeSH Terms]) OR Acquired Immunodeficiency Syndrome[Text Word]) OR Immunologic Deficiency Syndrome, Acquired[Text Word]) OR Acquired Immune Deficiency Syndrome[Text Word]) OR Acquired Immuno-Deficiency Syndrome[Text Word]) OR Acquired Immuno Deficiency Syndrome[Text Word]) OR Acquired Immuno-Deficiency Syndromes[Text Word]) OR Immuno-Deficiency Syndrome, Acquired[Text Word]) OR Immuno-Deficiency Syndromes, Acquired[Text Word]) OR Syndrome, Acquired Immuno-Deficiency[Text Word]) OR Syndromes, Acquired Immuno-Deficiency[Text Word]) OR Immunodeficiency Syndrome, Acquired[Text Word]) OR Acquired Immunodeficiency Syndromes[Text Word]) OR Immunodeficiency Syndromes, Acquired[Text Word]) OR Syndrome, Acquired Immunodeficiency[Text Word]) OR Syndromes, Acquired Immunodeficiency[Text Word]) OR AIDS[Text Word])) AND ((((((((((Tuberculosis[MeSH Terms]) OR Tuberculosis[Text Word]) OR Tuberculoses[Text Word]) OR Koch's Disease[Text Word]) OR Koch Disease[Text Word]) OR Kochs Disease[Text Word]) OR Mycobacterium tuberculosis Infection[Text Word]) OR Infection, Mycobacterium tuberculosis[Text Word]) OR Infections, Mycobacterium tuberculosis[Text Word]) OR Mycobacterium tuberculosis Infections[Text Word]))) AND ((((((((((((Raltegravir Potassium[MeSH Terms]) OR Raltegravir Potassium[Text Word]) OR Potassium, Raltegravir[Text Word]) OR Raltegravir[Text Word]) OR MK 0518[Text Word]) OR 0518, MK[Text Word]) OR MK0518[Text Word]) OR MK-0518[Text Word]) OR Isentress[Text Word])) OR ((((((((((dolutegravir[MeSH Terms]) OR dolutegravir[Text Word]) OR (4R,9aS)-5-hydroxy-2-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid- 2,4 difluorobenzylamide[Text Word]) OR dolutegravir sodium[Text Word]) OR S-GSK1349572[Text Word]) OR GSK-1349572[Text Word]) OR dolutegravir sodium monohydrate[Text Word]) OR Tivicay[Text Word]) OR GSK 1349572A[Text Word]) OR GSK1349572A[Text Word])) OR (((((((((JTK 303[MeSH Terms]) OR JTK 303[Text Word]) OR JTK303[Text Word]) OR JTK-303[Text Word]) OR Vitekta[Text Word]) OR eoslvitegravir[Text Word]) OR GS 9137[Text Word]) OR GS9137[Text Word]) OR GS-9137[Text Word])) OR (((bictegravir[MeSH Terms]) OR bictegravir[Text Word]) OR GS-9883[Text Word])) OR (((Integrase Inhibitors[MeSH Terms]) OR Integrase Inhibitors[Text Word]) OR Inhibitors, Integrase[Text Word]))
Lilacs	(tw:((tw:((tw:((tw:(Vírus da AIDS)) OR (tw:(Vírus da Imunodeficiência Humana)) OR (tw:(Vírus de Imunodeficiência Humana)) OR (tw:(VIH)) OR (tw:(Virus de Inmunodeficiencia Humana)) OR (tw:(Virus de la Inmunodeficiencia Humana)) OR (tw:(Virus del SIDA)) OR (tw:(HIV)) OR (tw:(Human Immunodeficiency Virus)) OR (tw:(Immunodeficiency Virus, Human)) OR (tw:(Immunodeficiency Viruses, Human)) OR (tw:(Virus, Human Immunodeficiency)) OR (tw:(Viruses, Human Immunodeficiency)) OR (tw:(Human Immunodeficiency Viruses)) OR (tw:(AIDS Virus)) OR (tw:(AIDS Viruses)) OR (tw:(Virus, AIDS)) OR (tw:(Viruses, AIDS)) OR (tw:(Acquired Immune Deficiency Syndrome Virus)) OR (tw:(Acquired Immunodeficiency Syndrome Virus)))) OR (tw:((tw:(Síndrome de Imunodeficiência Adquirida)) OR (tw:(SIDA)) OR (tw:(Síndrome da Deficiência Imunológica Adquirida)) OR (tw:(Síndrome da Imunodeficiência Adquirida)) OR (tw:(Síndrome de Deficiência Imunológica Adquirida)) OR (tw:(Síndrome de Inmunodeficiencia Adquirida)) OR (tw:(Síndrome de Deficiencia Inmunológica Adquirida)) OR (tw:(Síndrome de la Inmunodeficiencia Adquirida)) OR (tw:(Acquired Immunodeficiency Syndrome)) OR (tw:(Immunologic Deficiency Syndrome, Acquired)) OR (tw:(Acquired Immune Deficiency Syndrome)) OR (tw:(Acquired Immuno-Deficiency Syndrome)) OR (tw:(Acquired Immuno Deficiency Syndrome)) OR (tw:(Acquired Immuno-Deficiency Syndromes)) OR (tw:(Immuno-Deficiency Syndrome, Acquired)) OR (tw:(Immuno-Deficiency Syndromes, Acquired)) OR (tw:(Syndrome, Acquired Immuno-Deficiency)) OR (tw:(Syndromes, Acquired Immuno-Deficiency)) OR (tw:(Immunodeficiency Syndrome, Acquired)) OR (tw:(Acquired Immunodeficiency Syndromes)) OR (tw:(Immunodeficiency Syndromes, Acquired)) OR (tw:(Syndrome, Acquired Immunodeficiency)) OR (tw:(Syndromes, Acquired Immunodeficiency)) OR (tw:(AIDS)))))) AND (tw:((tw:(Tuberculose)) OR (tw:(Infecção por Mycobacterium tuberculosis)) OR (tw:(Pneumologia Sanitária)) OR (tw:(TB)) OR (tw:(Infección por Mycobacterium tuberculosis)) OR (tw:(Tuberculosis)) OR (tw:(Tuberculoses)) OR (tw:(Koch's Disease)) OR (tw:(Koch Disease)) OR (tw:(Kochs Disease)) OR (tw:(Mycobacterium tuberculosis Infection)) OR (tw:(Infection, Mycobacterium tuberculosis)) OR

Base de dados	Estratégia de busca	
	(tw:(Infections, Mycobacterium tuberculosis)) OR (tw:(Mycobacterium tuberculosis Infections)))))) AND (tw:((tw:((tw:(Raltegravir Potásico)) OR (tw:(Raltegravir Potássico)) OR (tw:(Raltegravir Potassium)) OR (tw:(Potassium, Raltegravir)) OR (tw:(Raltegravir)) OR (tw:(MK 0518)) OR (tw:(0518, MK)) OR (tw:(MK0518)) OR (tw:(MK-0518)) OR (tw:(Isentress)))) OR (tw:((tw:(Dolutegravir)) OR (tw:((4R,9aS)-5-hydroxy-2-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid- 2,4 difluorobenzylamide)) OR (tw:(dolutegravir sodium)) OR (tw:(S-GSK1349572)) OR (tw:(GSK-1349572)) OR (tw:(dolutegravir sodium monohydrate)) OR (tw:(Tivicay)) OR (tw:(GSK 1349572A)) OR (tw:(GSK1349572A)))) OR (tw:((tw:(JTK 303)) OR (tw:(JTK303)) OR (tw:(JTK-303)) OR (tw:(Vitekta)) OR (tw:(elvitegravir)) OR (tw:(GS 9137)) OR (tw:(GS9137)) OR (tw:(GS-9137)))) OR (tw:((tw:(Bictegravir)) OR (tw:(GS-9883)))) OR (tw:((tw:(Inhibidores de Integrasa)) OR (tw:(Inibidores de Integrase)) OR (tw:(Integrase Inhibitors)) OR (tw:(Inhibitors, Integrase)))))	
The Cochrane Library	#1	MeSH descriptor: [HIV] explode all trees
	#2	HIV (Word variations have been searched)
	#3	Human Immunodeficiency Virus (Word variations have been searched)
	#4	Immunodeficiency Virus, Human (Word variations have been searched)
	#5	Immunodeficiency Viruses, Human (Word variations have been searched)
	#6	Virus, Human Immunodeficiency (Word variations have been searched)
	#7	Viruses, Human Immunodeficiency (Word variations have been searched)
	#8	Human Immunodeficiency Viruses (Word variations have been searched)
	#9	AIDS Virus (Word variations have been searched)
	#10	AIDS Viruses (Word variations have been searched)
	#11	Virus, AIDS (Word variations have been searched)
	#12	Viruses, AIDS (Word variations have been searched)
	#13	Acquired Immune Deficiency Syndrome Virus (Word variations have been searched)
	#14	Acquired Immunodeficiency Syndrome Virus (Word variations have been searched)
	#15	{OR #1-#14}
	#16	MeSH descriptor: [Acquired Immunodeficiency Syndrome] explode all trees
	#17	Acquired Immunodeficiency Syndrome (Word variations have been searched)
	#18	Immunologic Deficiency Syndrome, Acquired (Word variations have been searched)
	#19	Acquired Immune Deficiency Syndrome (Word variations have been searched)
	#20	Acquired Immuno-Deficiency Syndrome (Word variations have been searched)
	#21	Acquired Immuno Deficiency Syndrome (Word variations have been searched)
	#22	Acquired Immuno-Deficiency Syndromes (Word variations have been searched)
	#23	Immuno-Deficiency Syndrome, Acquired (Word variations have been searched)
	#24	Immuno-Deficiency Syndromes, Acquired (Word variations have been searched)
	#25	Syndrome, Acquired Immuno-Deficiency (Word variations have been searched)
	#26	Syndromes, Acquired Immuno-Deficiency (Word variations have been searched)
	#27	Immunodeficiency Syndrome, Acquired (Word variations have been searched)
	#28	Acquired Immunodeficiency Syndromes (Word variations have been searched)
	#29	Immunodeficiency Syndromes, Acquired (Word variations have been searched)
	#30	Syndrome, Acquired Immunodeficiency (Word variations have been searched)
	#31	Syndromes, Acquired Immunodeficiency (Word variations have been searched)
	#32	AIDS (Word variations have been searched)
	#33	{OR #16-#32}
	#34	MeSH descriptor: [Tuberculosis] explode all trees
	#35	Tuberculosis (Word variations have been searched)
	#36	Tuberculoses (Word variations have been searched)
	#37	Koch's Disease (Word variations have been searched)
	#38	Koch Disease (Word variations have been searched)
	#39	Kochs Disease (Word variations have been searched)

Base de dados	Estratégia de busca	
	#40	Mycobacterium tuberculosis Infection (Word variations have been searched)
	#41	Infection, Mycobacterium tuberculosis (Word variations have been searched)
	#42	Infections, Mycobacterium tuberculosis (Word variations have been searched)
	#43	Mycobacterium tuberculosis Infections (Word variations have been searched)
	#44	{OR #34-#43}
	#45	MeSH descriptor: [Raltegravir Potassium] explode all trees
	#46	Raltegravir Potassium (Word variations have been searched)
	#47	Potassium, Raltegravir (Word variations have been searched)
	#48	Raltegravir (Word variations have been searched)
	#49	MK 0518 (Word variations have been searched)
	#50	0518, MK (Word variations have been searched)
	#51	MK0518 (Word variations have been searched)
	#52	MK-0518 (Word variations have been searched)
	#53	Isentress (Word variations have been searched)
	#54	{OR #45-#53}
	#55	dolutegravir (Word variations have been searched)
	#56	dolutegravir sodium (Word variations have been searched)
	#57	S-GSK1349572 (Word variations have been searched)
	#58	GSK-1349572 (Word variations have been searched)
	#59	dolutegravir sodium monohydrate (Word variations have been searched)
	#60	Tivicay (Word variations have been searched)
	#61	GSK 1349572A (Word variations have been searched)
	#62	GSK1349572A (Word variations have been searched)
	#63	{OR #55-#62}
	#64	JTK 303 (Word variations have been searched)
	#65	JTK303 (Word variations have been searched)
	#66	JTK-303 (Word variations have been searched)
	#67	Vitekta (Word variations have been searched)
	#68	elvitegravir (Word variations have been searched)
	#69	GS 9137 (Word variations have been searched)
	#70	GS9137 (Word variations have been searched)
	#71	GS-9137 (Word variations have been searched)
	#72	{OR #64-#71}
	#73	Bictegravir (Word variations have been searched)
	#74	GS-9883 (Word variations have been searched)
	#75	{OR #73-#74}
	#76	MeSH descriptor: [Integrase Inhibitors] explode all trees
	#77	Integrase Inhibitors (Word variations have been searched)
	#78	Inhibitors, Integrase (Word variations have been searched)
	#79	{OR #76-#78}
	#80	#15 OR #33
	#81	#80 AND #44
	#82	#54 OR #63 OR #72 OR #75 OR #79
	#83	#81 AND #82
EMBASE	S12	S11 AND S10
	S11	S8 OR S7 OR S6 OR S5 OR S4
	S10	S9 AND S3
	S9	S2 OR S1
	S8	(EMB.EXACT.EXPLODE("integrase inhibitor"))

Base de dados	Estratégia de busca
	S7 EMB.EXACT.EXPLODE("bictegravir")
	S6 EMB.EXACT.EXPLODE("elvitegravir")
	S5 EMB.EXACT.EXPLODE("dolutegravir")
	S4 EMB.EXACT.EXPLODE("raltegravir")
	S3 EMB.EXACT.EXPLODE("tuberculosis")
	S2 (EMB.EXACT.EXPLODE("acquired immune deficiency syndrome"))
	S1 (EMB.EXACT.EXPLODE("Human immunodeficiency virus"))
	SECOND SEARCH (portal Capes)
	#15 #12 AND (2019:py OR 2021:py)
	#14 #12
	#13 #12 AND 2019:py
	#12 #10 AND #11
	#11 #4 OR #5 OR #6 OR #7 OR #8
	#10 #3 AND #9
	#9 #1 OR #2
	#8 'integrase inhibitor'/exp
	#7 'bictegravir'/exp
	#6 'elvitegravir'/exp
	#5 'dolutegravir'/exp
	#4 'raltegravir'/exp
	#3 'tuberculosis'/exp
	#2 'acquired immune deficiency syndrome'/exp
	#1 'human immunodeficiency virus'/exp
CINAHL	(((HIV OR Human Immunodeficiency Virus OR Immunodeficiency Virus, Human OR Immunodeficiency Viruses, Human OR Virus, Human Immunodeficiency OR Viruses, Human Immunodeficiency OR Human Immunodeficiency Viruses OR AIDS Virus OR AIDS Viruses OR Virus, AIDS OR Viruses, AIDS OR Acquired Immune Deficiency Syndrome Virus OR Acquired Immunodeficiency Syndrome Virus) OR (Acquired Immunodeficiency Syndrome OR Immunologic Deficiency Syndrome, Acquired OR Acquired Immune Deficiency Syndrome OR Acquired Immuno-Deficiency Syndrome OR Acquired Immuno Deficiency Syndrome OR Acquired Immuno-Deficiency Syndromes OR Immuno-Deficiency Syndrome, Acquired OR Immuno-Deficiency Syndromes, Acquired OR Syndrome, Acquired Immuno-Deficiency OR Syndromes, Acquired Immuno-Deficiency OR Immunodeficiency Syndrome, Acquired OR Acquired Immunodeficiency Syndromes OR Immunodeficiency Syndromes, Acquired OR Syndrome, Acquired Immunodeficiency OR Syndromes, Acquired Immunodeficiency OR AIDS)) AND (Tuberculosis OR Tuberculoses OR Koch's Disease OR Koch Disease OR Kochs Disease OR Mycobacterium tuberculosis Infection OR Infection, Mycobacterium tuberculosis OR Infections, Mycobacterium tuberculosis OR Mycobacterium tuberculosis Infections)) AND ((Raltegravir Potassium OR Potassium, Raltegravir OR Raltegravir OR MK 0518 OR 0518, MK OR MK0518 OR MK-0518 OR Isentress) OR (Dolutegravir OR (4R,9aS)-5-hydroxy-2-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid- 2,4 difluorobenzylamide OR dolutegravir sodium OR S-GSK1349572 OR GSK-1349572 OR dolutegravir sodium monohydrate OR Tivicay OR GSK 1349572A OR GSK1349572A) OR (JTK 303 OR JTK303 OR JTK-303 OR Vitekta OR elvitegravir OR GS 9137 OR GS9137 OR GS-9137) OR (Bictegravir OR GS-9883) OR (Integrase Inhibitors OR Inhibitors, Integrase))
SCOPUS	(((ALL ("HIV" OR "Human Immunodeficiency Virus" OR "Immunodeficiency Virus, Human" OR "Immunodeficiency Viruses, Human" OR "Virus, Human Immunodeficiency" OR "Viruses, Human Immunodeficiency" OR "Human Immunodeficiency Viruses" OR "AIDS Virus" OR "AIDS Viruses" OR "Virus, AIDS" OR "Viruses, AIDS" OR "Acquired Immune Deficiency Syndrome Virus" OR "Acquired Immunodeficiency Syndrome Virus")) OR (ALL ("Acquired Immunodeficiency Syndrome" OR "Immunologic Deficiency Syndrome, Acquired" OR "Acquired Immune Deficiency Syndrome" OR "Acquired Immuno-Deficiency Syndrome" OR "Acquired Immuno Deficiency Syndrome" OR "Acquired Immuno-Deficiency Syndromes" OR "Immuno-Deficiency Syndrome, Acquired" OR "Immuno-Deficiency Syndromes, Acquired" OR "Syndrome, Acquired Immuno-Deficiency" OR "Syndromes, Acquired Immuno-Deficiency" OR

Base de dados	Estratégia de busca
	"Immunodeficiency Syndrome, Acquired" OR " Acquired Immunodeficiency Syndromes" OR "Immunodeficiency Syndromes, Acquired" OR "Syndrome, Acquired Immunodeficiency" OR "Syndromes, Acquired Immunodeficiency" OR "AIDS"))) AND (ALL ("Tuberculosis OR Tuberculoses" OR "Koch's Disease" OR "Koch Disease" OR "Kochs Disease" OR "Mycobacterium tuberculosis Infection" OR "Infection, Mycobacterium tuberculosis" OR "Infections, Mycobacterium tuberculosis" OR "Mycobacterium tuberculosis Infections"))) AND ((ALL ("Raltegravir Potassium" OR "Potassium, Raltegravir" OR "Raltegravir" OR "MK 0518" OR "0518, MK" OR "MK0518" OR "MK-0518" OR "Isentress")) OR (ALL ("Dolutegravir" OR "(4R,9aS)-5-hydroxy-2-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid- 2,4 difluorobenzylamide" OR "dolutegravir sodium" OR "S-GSK1349572" OR "GSK-1349572" OR "dolutegravir sodium monohydrate" OR "Tivicay" OR "GSK 1349572A" OR "GSK1349572A")) OR (ALL ("JTK 303" OR "JTK303" OR "JTK-303" OR "Vitekta" OR "elvitegravir" OR "GS 9137" OR "GS9137" OR "GS-9137")) OR (ALL ("Bictegravir" OR "GS-9883")) OR (ALL ("Integrase Inhibitors" OR "Inhibitors, Integrase")))
Web of Science	#12 #11 AND #10 Tipo de documento=Todos os tipos de documentos; Idioma=todos os idiomas; #11 #8 OR #7 OR #6 OR #5 OR #4 Tipo de documento=Todos os tipos de documentos; Idioma=todos os idiomas; #10 #9 AND #3 Tipo de documento=Todos os tipos de documentos; Idioma=todos os idiomas; #9 #2 OR #1 Tipo de documento=Todos os tipos de documentos; Idioma=todos os idiomas; #8 ALL=(Integrase Inhibitors OR Inhibitors, Integrase) Tipo de documento=Todos os tipos de documentos; Idioma=todos os idiomas; #7 ALL=(Bictegravir OR GS-9883) Tipo de documento=Todos os tipos de documentos; Idioma=todos os idiomas; #6 ALL=(JTK 303 OR JTK303 OR JTK-303 OR Vitekta OR elvitegravir OR GS 9137 OR GS9137 OR GS-9137) Tipo de documento=Todos os tipos de documentos; Idioma=todos os idiomas; #5 ALL=(Dolutegravir OR dolutegravir sodium OR S-GSK1349572 OR GSK-1349572 OR dolutegravir sodium monohydrate OR Tivicay OR GSK 1349572A OR GSK1349572A) Tipo de documento=Todos os tipos de documentos; Idioma=todos os idiomas; #4 ALL=(Raltegravir Potassium OR Raltegravir OR MK 0518 OR MK0518 OR MK-0518 OR Isentress) Tipo de documento=Todos os tipos de documentos; Idioma=todos os idiomas; #3 ALL=(Tuberculosis OR Tuberculoses OR Koch's Disease OR Koch Disease OR Kochs Disease OR Mycobacterium tuberculosis Infection OR Mycobacterium tuberculosis Infections) Tipo de documento=Todos os tipos de documentos; Idioma=todos os idiomas; #2 ALL=(Acquired Immunodeficiency Syndrome OR Immunologic Deficiency Syndrome, Acquired OR Acquired Immune Deficiency Syndrome OR Acquired Immuno-Deficiency Syndrome OR Acquired Immuno Deficiency Syndrome OR Acquired Immuno-Deficiency Syndromes OR Acquired Immunodeficiency Syndromes OR AIDS) Tipo de documento=Todos os tipos de documentos; Idioma=todos os idiomas; #1 ALL=(HIV OR Human Immunodeficiency Virus OR Human Immunodeficiency Viruses OR AIDS Virus OR AIDS Viruses OR Acquired Immune Deficiency Syndrome Virus OR Acquired Immunodeficiency Syndrome Virus) Tipo de documento=Todos os tipos de documentos; Idioma=todos os idiomas;

Abbreviations: LILACS= Literatura Latino-Americana em Ciências da Saúde. CINAHL=Cumulative Index to Nursing and Allied Health Literature. Source: Own authorship.

Selection process:

The software EndNote X7® was used to identify and exclude duplicates. The studies were evaluated using the inclusion and exclusion criteria by a pair of independent reviewers, with disagreements resolved with the support of a third

reviewer, in two stages: (i) evaluation of titles and abstracts; (ii) full reading of the articles pre-selected in the previous step. The Rayyan® (Ouzzani et al., 2016) platform was used to select the studies.

Data collection process:

Data extraction was performed after the careful reading of the selected studies. It was performed by means of an instrument developed by the authors themselves. The authors of the studies were contacted for additional information or in cases where further clarification was needed.

The extracted data covered (i) study characteristics: objective, setting, year, country of study, design, losses, biases, or limitations reported in the text; (ii) population characteristics: number of participants, age, sex, comorbidities, treatment regimens used, type of diagnosis, treatment time, efficacy, and safety outcomes.

Evaluation of the methodological quality of the included studies

The methodological quality of the included studies was analysed by a pair of independent reviewers using scales according to the design of each study: (i) Version 2 of the Cochrane Risk-of-Bias tool (RoB 2) (Sterne et al., 2019) for randomised trials; (ii) Newcastle Ottawa Scale (Wells et al., 2014) for cohort studies. A third reviewer resolved the cases of disagreement.

The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) (Balshem et al., 2011) considerations were used to assess the certainty of the evidence for the efficacy, effectiveness, and safety outcomes of integrase inhibitors in the treatment of HIV in patients coinfected with TB. The evidence tables were reproduced using the GRADE pro software tool (www.gradepro.org/).

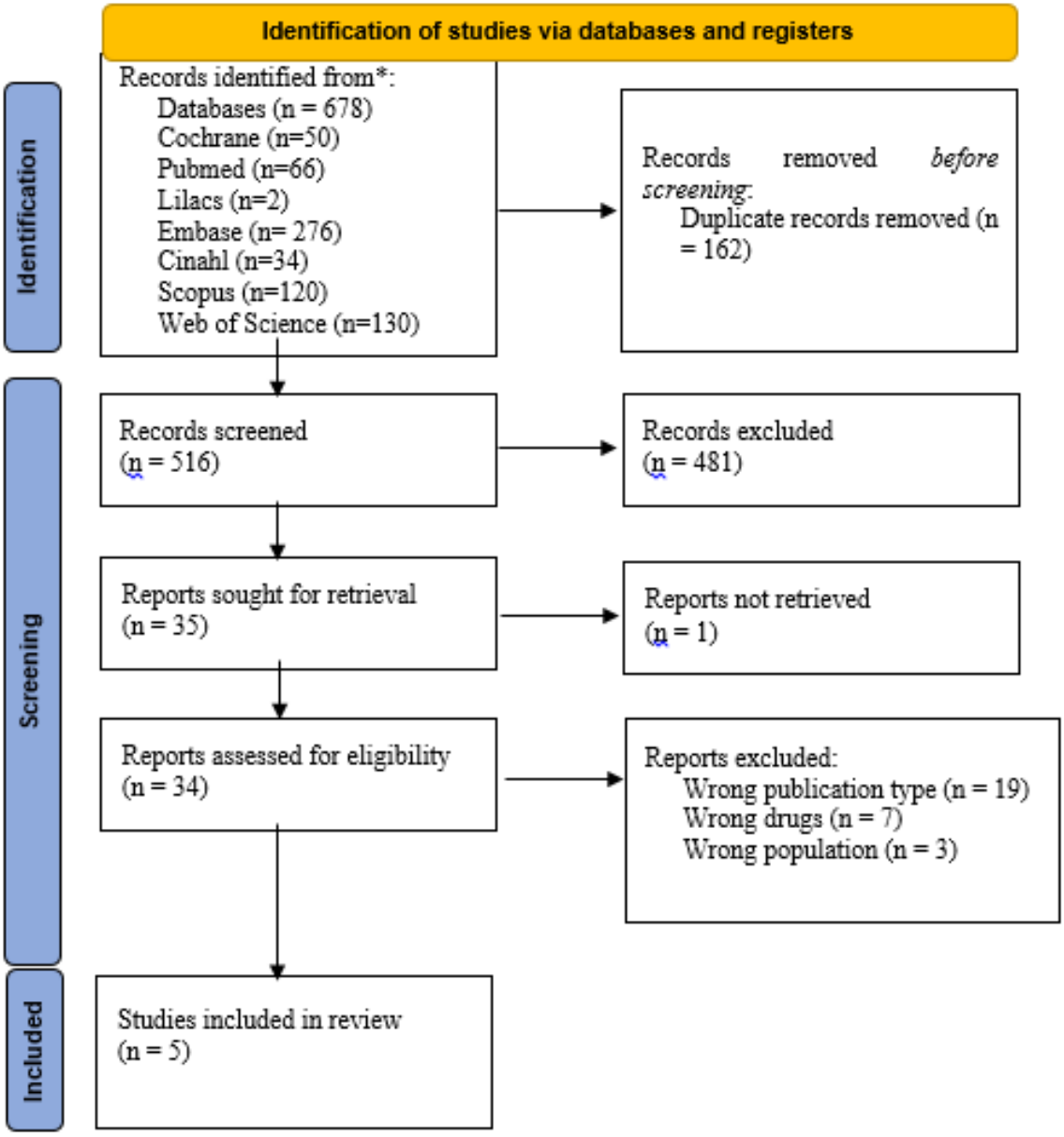
Statistical analysis

All analyses were conducted using the Review Manager Version 5.4.1 (Cochrane Collaboration). For dichotomous outcomes, the relative risks were calculated. The median and interquartile range were converted into the mean and standard deviation (Luo D, Wan X, Liu J & Tong T, 2018; Wan X, Wang W, Liu J & Tong T., 2014).. 95% confidence intervals were considered. The statistical heterogeneity of the treatment effect among studies was assessed using the Cochran's Q test and the I^2 inconsistency test.

3. Results

A total of 678 studies were captured through the electronic search. After the exclusion of 162 duplicates, 516 titles and abstracts were analysed, and 35 studies were eligible for a full text reading. In this phase, 30 studies were excluded and five met the inclusion criteria (Figure 1).

Figure 1 – Flow diagram of the selection of eligible studies.



* First search: n=472; Search update: n=206.

Source: Adapted from Page, et al. (2021).

The outcomes of efficacy were cure TB and viral load suppression, defined as HIV-RNA ≤50 copies/ml.

In the evaluation of the observational study, the outcomes were TB cure and virological suppression, considering patients who reached a viral load of less than 400 copies/ml.

Four studies referring to three RCT (Grinsztejn et al., 2014, Delagreverie et al., 2020, De Castro et al., 2021 &. Dooley et al. 2020) and one cohort study were included (Modongo et al., 2019).

The REFLATE TB study is a phase II RCT that evaluated the efficacy and safety of RAL (at doses of 400 and 800 mg administered twice daily) compared with efavirenz (EFV). The data were collected between July 2009 and June 2011 in two countries (Brazil and France) (Grinsztejn et al., 2014). In the study by Delagrevie et al. (2020), which used the REFLATE TB samples, the outcomes analysed were the impact of initiating ART with two doses of RAL or EFV on the deoxyribonucleic

acid (DNA) pool size, inflammation levels, and coagulation markers.

The REFLATE TB 2 study is a phase III RCT that evaluated the efficacy and safety of RAL at a dose of 400 mg twice daily compared to EFV. Data collection was conducted between September 2015 and January 2018 in five countries (Brazil, Ivory Coast, France, Mozambique, and Vietnam). The study presented some efficacy, safety, and treatment adherence results related to this RCT (De Castro et al., 2021).

The INSPIRING RCT (International Study of Patients with HIV on Rifampicin ING) is a phase III RCT that evaluated the efficacy and safety of DTG compared with EFV, with data collection conducted between January 2015 and October 2017. It is a multicentre study including patients from 37 sites in seven countries (Argentina, Brazil, Mexico, Peru, Russia, South Africa, and Thailand) (Dooley et al., 2020).

The cohort study examined the use of treatment regimens with RMP and DTG in 97 health care facilities in Botswana. TB treatment effectiveness, viral suppression, and association were assessed in groups of patients using DTG once a day, twice a day, and in the group not using DTG. The study was conducted between July 2016 and April 2018. It determined the predictors of the two outcomes of interest, such as age, sex, antiretroviral regimen, and CD4 T lymphocyte count (Modongo et al., 2019).

The general characteristics of the included studies are summarized in Table 2.

Table 2 - General characteristics of clinical trials and cohort included.

Type	Study name	Treatment (weeks)	Included patients/ enroled patients	Experimental group (n)	Control group (n)	Female	Age (years)	Results measured
Phase II RCT	REFLATE-TB NCT00822315	48 weeks	153/179 (85%)	51 RAL 400mg 51 RAL 800mg	51 EFV	73% male	38	Efficacy and safety
Phase III RCT	INSPIRING NCT02178592	52 weeks	113/263 (43%)	69 DTG	44 EFV	59% female	33	Efficacy and safety
Phase III RCT	REFLATE-TB 2 NCT02273765	48 weeks	459/625 (74%)	230 RAL	230 EFV	40% female	35	Efficacy, adherence and safety
Restrospective cohort	It´s not applicable	Patients were reviewed monthly and 3-6 months thereafter for HIV care.	1225/1770 (69%);	739 DTG	486 no DTG	45% female	40	Effectiveness

Abbreviations: DTG=dolutegravir; EFV=efavirenz; NCT=Number Clinical Trial; RAL=raltegravir; TB=tuberculosis.
Source: Own authorship.

Methodological quality assessment

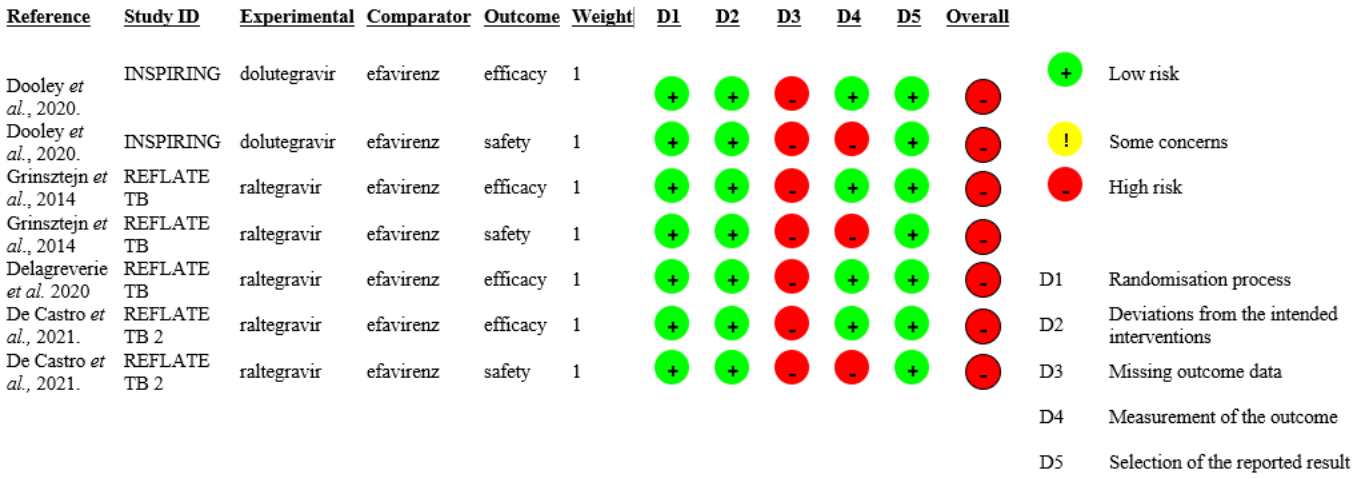
Clinical trials

All RCT outcomes assessed using RoB 2 were rated at high risk of bias in the outcome data loss domain, as missing data for the viral load laboratory tests and safety outcomes were identified in the INSPIRING, REFLATE TB, and REFLATE TB 2 studies. The protocol methodology of the studies described that unavailable viral load results were classified as non-responders (Figure 2) (National Library of Medicine [NLM], NCT00822315; NLM, NCT02178592; NLM, NCT

NCT02273765). In addition, the INSPIRING authors reported a high number of participants discontinuing treatment in the DTG arm without any specific pattern or reasons. It was not possible to know whether discontinuation was related to unreported adverse events (AE). In REFLATE TB 2, the lack of outcome data was attributed to poor treatment adherence in patients in the RAL group.

The outcome measurement domains were classified as high risk of bias for safety, since there was no masking.

Figure 2 - Assessment of the risk of bias by outcome of the included studies using the Cochrane Rob 2



Source: Cochrane Rob 2.

Cohort study

The score obtained in the analysis of the methodological quality of the cohort study was 8 stars. The sample was considered representative, using data from TB/HIV patients from 97 health facilities in Botswana. The unexposed cohort was obtained from the same population as the exposed cohort, and retrospective data were collected from the Botswana Ministry of Health database. The authors reported a protocol deviation intrinsic to the pragmatic observational studies in relation to the DTG dose provided in the national clinical protocol and the one used by patients in the cohort.

Efficacy results

The characteristics related to virologic suppression, TB treatment, CD4 T lymphocyte counts, antiretroviral resistance, and treatment outcomes are described in Table 3.

Table 3 – Characteristics related to efficacy and effectiveness in the treatment of Tuberculosis and HIV / AIDS

Reference/Study name	Tuberculosis outcomes	Change in CD4 cell count	Resistance data	HIV/aids outcomes
Grinsztejn, et al (2014) REFLATE TB	EFV: cured and treatment completed 45 (88%); death 2 (4%); default 4 (8%); RAL 400mg: cured and treatment completed 46 (90%); death 1 (2%); default 3 (6%); treatment failure 1 (2%). RAL 800mg: cured and treatment completed 45/51 (88%); death 3 (6%); default 1 (2%); treatment failure 1 (2%); transferred to different centre: 1 (2%).	EFV: 216 (IQR 87-328) RAL 400mg: 239 (IQR 160-372) RAL 800mg: 212 (IQR 130-369)	39 patients met the definition of virological failure during follow-up: 12 (24%) in the RAL 400mg group, 13 (25%) in the RAL 800mg group and 14 (27%) in the EFV group.	**Virological suppression ITT 24 weeks (HIV RNA < 50 copies per mL):** EFV: 34/51 (67%) RAL 400mg: 41/51 (80%) RAL 800mg: 39/51 (76%) Total: 114/153 (75%) **ITT 48 weeks (HIV RNA < 50 copies per mL):** EFV: 37/51 (73%) RAL 400mg: 39/51 (76%) RAL 800mg: 32/51 (63%) Total: 108/153 (71%)
Delagreverie, et al (2020) REFLATE TB	It's not reported	The median increase in CD4 cells at week 48 was similar in all three groups.	Not reported	All levels of biomarkers decreased over the course of the study. There were no differences in the reduction of biomarkers between the treatment arms.
Dooley, et al (2020) INSPIRING	DTG: cured 61 (88%); failure 0%; EFV: cured 40 (91%); failure 1%;	DTG: 220 (IQR 111, 271). EFV: 190 (IQR 104, 252).	Only the EFV-arm participant demonstrated acquired resistance mutations (to NNRTI and NRTI).	**Virological suppression ITT 24 weeks (HIV RNA < 50 copies per mL):** DTG: 56/69 (81%) EFV: 39/44 (89%) **ITT 48 weeks (HIV RNA < 50 copies per mL):** DTG: 52/69 (75%) EFV: 36/44 (82%)
De Castro, et al (2021) REFLATE TB 2	EFV cured 203/227 (89%) RAL 400mg cured 206/230 (91%)	RAL: 183 (IQR: 106 a 276) EFV: 172 (IQR: 100-258)	75 patients met the definition of virological failure during follow-up: 42 (18%) in the RAL group and 33 (15%) in the EFV group.	**ITT 24 weeks (HIV RNA < 50 copies per mL):** RAL: 133/230 (58%) EFV: 130/227 (57%) **ITT 48 weeks (HIV RNA < 50 copies per mL):** RAL 400mg: 140/230 (61%) EFV: 150/227 (66%)
Modongo, et al (2019)	DTG cured 672/739 (90,9%); failure 6 (9.0%), death 48 (71.6%). No DTG: cured 429/486 (88.3%); failure 5 (8.8%), death 35 (61.4%);	CD4 201 a 350: DTG 172 (23,3%); No DTG: 107 (22%) CD4 > 350: DTG 198 (26,8) No DTG 212 (43,6%)	Viral load> 400 copies DTG: 40 (5,4) Não DTG: 26 (5,3)	**Undetectable viral load:** DTG: 541/739 (73,2%) No DTG: 396/486 (81,5%)

Abbreviations: ART= antiretroviral therapy; DTG= dolutegravir; EFV= efavirenz; HIV-1= human immunodeficiency virus-1; RAL= raltegravir; Source: Own authorship.

The REFLATE TB study identified a total of 39/153 (25%) virologic failures distributed in the control and intervention groups (Table 2). The resistance mutations to INI were E92EQ, Y143R/C, and N155H, to nucleoside analogue reverse transcriptase inhibitors (NRTIs) were M184V/1, K65R, K70A, and other thymidine analogues, and to non-NRTIs were

K103N, V106M, and Y188L. In REFLATE TB 2, the reported mutations were: E92Q, G140C/S, Y143A/C/G/H/R/S, Q148K, N155H, and E157Q to INI, M41L, K65R, D67N, K70R, L74V/I, M184V, T215A/C to NRTI, and K101E, K103N, Y181C, Y188C, G190A to non-NRTIs. No INI-related mutations were describing in INSPIRING.

The study by Delagrevie et al. (2020) used REFLATE TB samples to measure Cell-1-associated HIV DNA blood levels in ART, systemic inflammation markers (hsCRP levels, IL-6 levels, sCD14 levels, and D-dimer levels), and viral suppression in ART. All three treatment arms had significant reductions in the four inflammation markers.

In the REFLATE TB 2 study, factors associated with virologic suppression were identified. A multivariate analysis identified an association of the female sex [odds ratio (OR) 1.77, 95% confidence interval (CI95%) 1.16–2.72), HIV-1 RNA < 100,000 copies/ml (OR 2.29, CI95% 1.33–3.96), and HIV-1 RNA from 100,000–500,000 copies/ml (OR 1.62, CI95% 1.02–2.57) versus > 500,000 copies/ml with virologic suppression. Adherence measured by the proportion of pill count > 95% was also associated with virologic suppression (OR 2.38, CI95% 1.56–3.52).

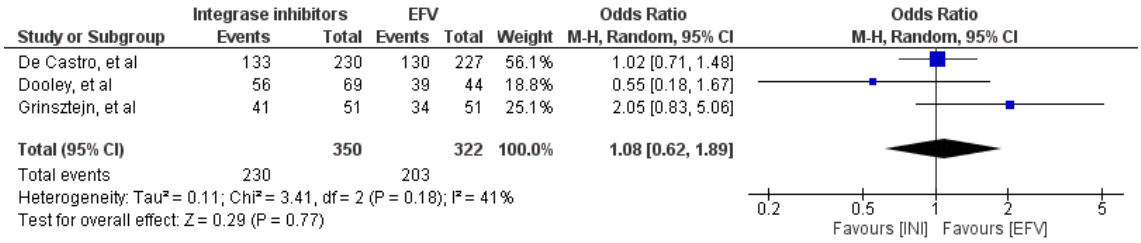
The INSPIRING study measured DTG and EFV plasma levels. Measurements occurred during concomitant TB treatment [week 8: DTG 870 ng/ml (CI90% 208–2,340) and week 24: DTG 964 ng/ml (CI90% lower limit of quantification–3,380)] and HIV/AIDS treatment alone [week 36: DTG 854 ng/ml (CI90% 64.7–3,310) and week 48: DTG 881 ng/ml (CI90% 47.1–3,310)].

Virological suppression

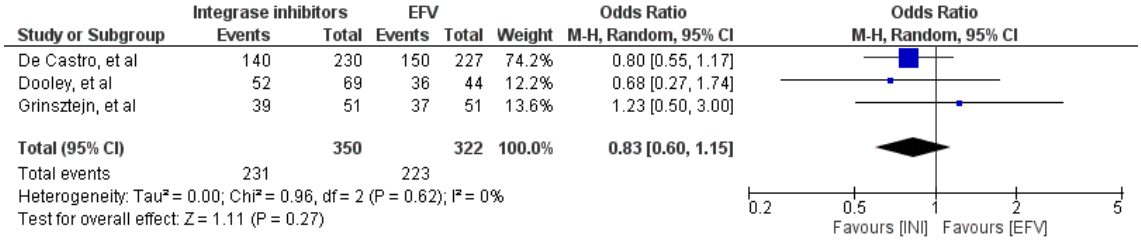
The three selected RCTs investigated virologic suppression (defined as a viral load < 50 copies/ml) for treatment-naïve patients at the 24-week and 48-week follow-up, with a total of 322 adult subjects evaluated. The intention-to-treat analysis showed no statistically significant difference in the virologic suppression between the efavirenz and INI arms (OR 1.08, CI95% 0.62–1.89). However, high heterogeneity was observed at the 24-week assessment (I^2 = 41%), which was impacted by the REFLATE TB, which favoured the EFV arm (Figure 3).

Figure 3: Meta-analysis of efficacy outcomes of 3 RCTs with integrase inhibitor and efavirenz

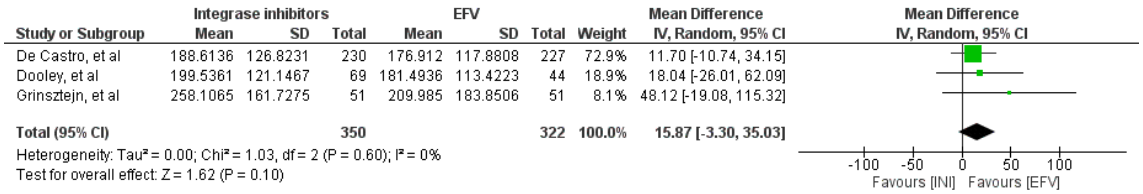
A Viral suppression (24 weeks)



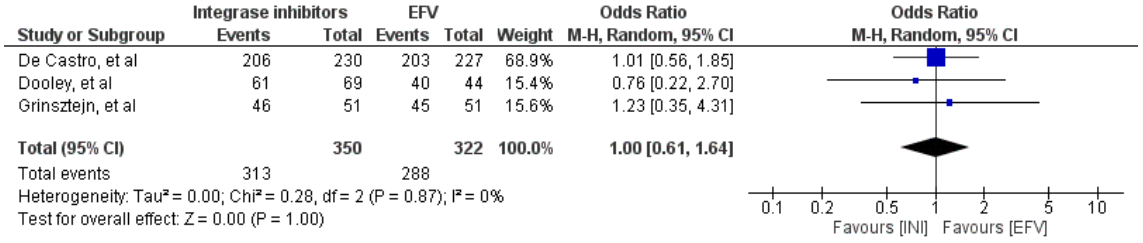
B Viral suppression (48 weeks)



C CD4+ cell count



D Tuberculosis treatment success (cured or treatment completed)



Source: Review Manager Version 5.4.1 (Cochrane Collaboration).

CD4 cell count

Baseline changes in the CD4+ T lymphocyte counts (cells/ml) were described using the median increase in counts, and all three RCTs contributed to the calculation of this outcome from the beginning of the follow-up until week 48. The INSPIRING results did not show a normal distribution relative to the other clinical trials, and no statistical significance was observed regarding the two treatment arms (mean difference 15.87, CI95% -3.30–35.03).

Tuberculosis treatment outcome

There was no statistical difference between the groups evaluated at the end of follow-up (OR 1.00, CI95% 0.61 - 1.64), and the confidence intervals were overlapping, although extended.

Effectiveness results:

In the study by Modongo et al. (2019), the ARV treatment effectiveness was greater than 70% in both treatment arms (Table 2). Of the patients who received the DTG-based regimen, 44% received one daily dose and 53% received two daily doses.

The TB treatment outcomes in patients on DTG and non-DTG regimens were 90.9% and 88.3%, respectively.

Treatment with DTG showed independent association with favourable TB treatment outcomes (OR 1.56, CI95% 1.06–2.31) after adjustments for age, sex, and CD4 counts. When administered once Daily, DTG was also associated with successful TB treatment outcomes (OR 1.93, CI95% 1.16–3.23). Similar viral suppression rates were identified in patients on once daily versus twice daily DTG regimens during TB treatment. However, DTG showed no independent association with viral suppression after the adjustment for covariates.

Safety results

Adverse events

The adverse events (AE) profile of the studies included in the review are described in Table 4.

Cutaneous rash to RAL 800mg and one participant with increased gamma-glutamyltransferase in REFLATE TB RCT

(Grinsztejn et al., 2014) was described.

The psychiatric serious adverse event described in the INSPIRING RCT (Dooley et al. 2020) was suicidal ideation, which was considered unrelated to the study drug and was resolved the same day. There were four (6%) participants in the DTG arm and 4 (9%) participants in the EFV arm that met the criteria for TB-associated IRIS. There were two participants in the DTG arm that met the criteria for non-TB IRIS: one with strongyloidiasis (also met TB IRIS criterion mentioned above) and one with herpes zoster. Thus, there was a total of five participants (7%) with any IRIS. Any AE leading to drug discontinuation represent hypersensitivity to EFV and one participant with increased gamma-glutamyltransferase.

In REFLATE TB 2 RCT (De Castro et al., 2021), nine (4%) of 230 patients in the efavirenz group and nine (4%) of 229 patients in the raltegravir group had hepatotoxicity, and seven (3%) of 230 patients in the efavirenz group had renal failure.Nine (4%) of 230 patients in the efavirenz group and nine (4%) of 229 patients in the raltegravir group had hepatotoxicity, and seven (3%) of 230 patients in the efavirenz group had renal failure.

Table 4 - Safety results of studies included in the systematic review.

Reference/ Study name	n	Any AE	SAE related to ART	Any AE leading to drug discontinuation	IRIS	Death
Grinsztejn, et al (2014) REFLATE TB	EFV: 51 RAL 400mg: 51 RAL 800mg: 51	EFV: 46 (90%) RAL 400mg: 46 (90%) RAL 800mg: 47 (92%)	EFV: 10 (20%) RAL 400mg: 6 (12%) RAL 800mg: 8 (16%)	EFV: 3 (6%) RAL 400mg: 0 (0%) RAL 800mg: 3 (6%) a	EFV: 5 (10%) RAL 400mg: 2 (4%) RAL 800mg: 4 (8%)	EFV: 2 RAL 400mg: 1 RAL 800mg: 3
Dooley, et al (2020) INSPIRING	EFV: 44 DTG: 69	EFV: 40 (91%) DTG: 52 (75%)	EFV: 1 (2%) DTG: 0 (0%)	EFV: 2 (5%) DTG: 0	EFV: 4 (9%) DTG: 5 (7%)	EFV: 0 DTG: 0
De Castro, et al (2021) REFLATE TB 2	EFV: 230 RAL 400mg: 229	It's not reported	EFV: 30 (13%) RAL 400mg: 25 (11%)	EFV: 3 (1%) RAL 400mg: 2 (1%)	EFV: 38 (17%) RAL 400mg: 25 (11%)	EFV: 14 (6%) RAL 400mg: 12 (5%)

Abbreviations: AE=Adverse Event; ART=Antiretroviral Therapy; DTG=Dolutegravir; EFV=Efavirenz; IRIS=Immune Reconstitution Inflammatory Syndrome; SAE=serious adverse events. RAL=raltegravir. Source: Own authorship.

In the REFLATE TB study, the occurrence of serious AEs was similar in all groups (mean of 35%) but was lower in the 400 mg RAL group than in the 800 mg RAL group. The AEs leading to treatment discontinuation included hepatotoxicity, skin rash, gynaecomastia, and pregnancy. None of these AEs occurred in the 400 mg RAL group. Immune Reconstitution Inflammatory Syndrome occurred in all treatment arms and the causes of deaths described were not related to ARV treatment (meningitis, septic shock, TB worsening, and unknown causes).

Severe AEs were rare in INSPIRING. The most common mild AEs were headaches, upper respiratory tract infections, diarrhoea, vomiting, dizziness, arthralgia, and gastroenteritis.

In REFLATE TB 2 (De Castro et al., 2021), few data regarding safety were available. Adverse events leading to treatment discontinuation were < 1% in both groups.

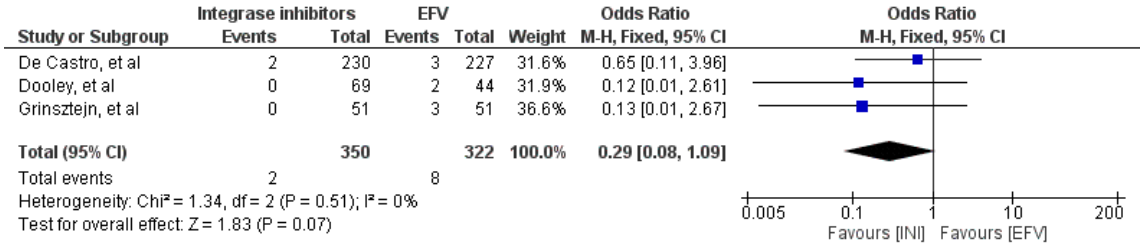
Safety outcomes were not assessed in the cohort study conducted in Botswana.

As for AEs leading to treatment discontinuation, there were few events of grade III AEs, grade IV AEs, and IRIS in

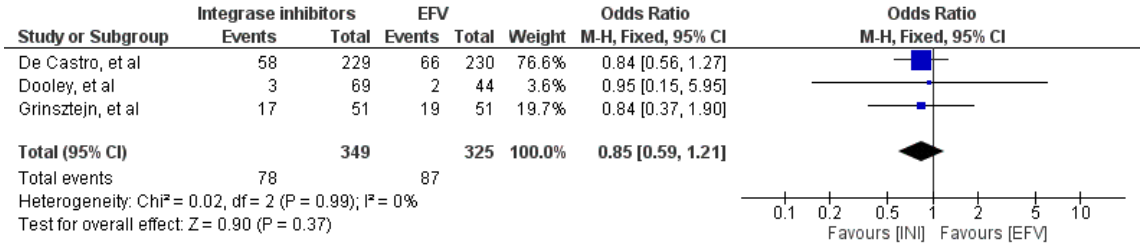
relation to the total, which directly impacted the confidence interval. In addition, there was no statistical difference among the study arms regarding AEs that led to treatment discontinuation and grade III and IV AEs. In this study, a significant difference was observed only in relation to IRIS, favouring the arm that used INI (p = 0.04) (Figure 4).

Figure 4: Meta-analysis of safety outcomes of 3 RCTs with integrase inhibitor and efavirenz.

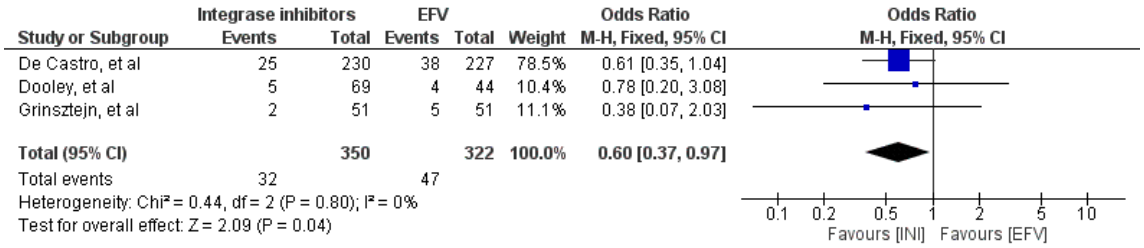
A Any AE leading to drug discontinuation.



B Grade 3-4 Adverse Event



C Immune Reconstitution Inflammatory Syndrome



Source: Review Manager Version 5.4.1 (Cochrane Collaboration).

Certainty of evidence

The evaluation of the certainty of evidence through GRADE classified outcome efficacy and safety as a low or extremely low certainty. The domains that most impacted the evaluation were risk of bias, inconsistency, and imprecision, since there were no differences between the groups assessed and large confidence intervals in the meta-analysis results. The outcome of virologic suppression at week 24 showed a high heterogeneity that was impacted by the REFLATE TB study (Grinsztejn et al., 2014), which favoured the EFV arm.

As for safety outcomes, such as IRIS, grades III and IV AEs, and treatment discontinuation due to drugs, there was a large imprecision due to the low baseline risk, with few events observed in relation to the total number of participants.

In the evaluation of the observational study, the outcomes were TB cure and virological suppression, considering patients who reached a viral load of less than 400 copies/ml. They were classified with low certainty of evidence.

Table 5: Summary of findings: Efficacy, effectiveness, and safety of integrase inhibitors in the treatment of HIV/AIDS in patients with tuberculosis

Integrase Inhibitor compared to others antiretrovirals for tuberculosis and HIV/aids

Patient or population: Tuberculosis and HIV/aids

Setting: Efficacy, effectiveness, and safety of integrase inhibitors in the treatment of HIV/AIDS in patients with tuberculosis

Intervention: Integrase Inhibitor

Comparison: other antiretrovirals

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
				Difference		
Virological supression (24 weeks) № of participants: 672 (3 RCTs)	**OR 1.08** (0.62 to 1.89)	63.0%	**64.8%** (51.4 to 76.3)	**1.8% more** (11,6 fewer to 13,3 more)	⨁◯◯◯ VERY LOW [a,b]	
Virological supression (48 weeks) № of participants: 672 (3 RCTs)	**OR 0.83** (0.60 to 1.15)	69.3%	**65.2%** (57.5 to 72.1)	**4.1% fewer** (11,8 fewer to 2,9 more)	⨁⨁◯◯ LOW [a]	
Treatment success (cured and treatment completed) № of participants: 672 (3 RCTs)	**OR 1.00** (0.61 to 1.64)	89.4%	**89.4%** (83.8 to 93.3)	**0.0% fewer** (5,7 fewer to 3,8 more)	⨁⨁◯◯ LOW [a]	
CD4 cell count № of participants: 672 (3 RCTs)	-	The mean CD4 cell count was **0**	-	MD **15.87 higher** (3.3 lower to 35.03 higher)	⨁⨁◯◯ LOW [a]	
Any AE leading to drug discontinuation № of participants: 672 (3 RCTs)	**OR 0.29** (0.08 to 1.09)	2.5%	**0.7%** (0.2 to 2.7)	**1.8% fewer** (2,3 fewer to 0,2 more)	⨁◯◯◯ VERY LOW [a,c,d]	

Table 5: Summary of findings: Efficacy, effectiveness, and safety of integrase inhibitors in the treatment of HIV/AIDS in patients with tuberculosis

Integrase Inhibitor compared to others antiretrovirals for tuberculosis and HIV/aids

Patient or population: Tuberculosis and HIV/aids

Setting: Efficacy, effectiveness, and safety of integrase inhibitors in the treatment of HIV/AIDS in patients with tuberculosis

Intervention: Integrase Inhibitor

Comparison: other antiretrovirals

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
				Difference		
Grade 3-4 AE № of participants: 674 (3 RCTs)	**OR 0.85** (0.59 to 1.21)	26.8%	**23.7%** (17.7 to 30.7)	**3.1% fewer** (9 fewer to 3,9 more)	⊕◯◯◯ VERY LOW [a,c,d]	
IRIS № of participants: 672 (3 RCTs)	**OR 0.60** (0.37 to 0.97)	14.6%	**9.3%** (5.9 to 14.2)	**5.3% fewer** (8,6 fewer to 0,4 fewer)	⊕◯◯◯ VERY LOW [a,c,d]	
Successful TB treatment № of participants: 1225 (1 observational study)	**OR 1.56** (1.06 to 2.31)	88.3%	**92.2%** (88.9 to 94.6)	**3.9% more** (0,6 more to 6,3 more)	⊕⊕◯◯ LOW	
Virological supression № of participants: 797 (1 observational study)	**OR 1.64** (0.86 to 3.12)	93.8%	**96.1%** (92.9 to 97.9)	**2.3% more** (0,9 fewer to 4,1 more)	⊕⊕◯◯ LOW	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

Table 5: Summary of findings: Efficacy, effectiveness, and safety of integrase inhibitors in the treatment of HIV/AIDS in patients with tuberculosis

Integrase Inhibitor compared to others antiretrovirals for tuberculosis and HIV/aids

Patient or population: Tuberculosis and HIV/aids

Setting: Efficacy, effectiveness, and safety of integrase inhibitors in the treatment of HIV/AIDS in patients with tuberculosis

Intervention: Integrase Inhibitor

Comparison: other antiretrovirals

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Certainty	What happens
				Difference		

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. High risk of bias due to high loss to follow-up.

b. High statistical heterogeneity (I^2=41%), due to Grinsztejn et al (2014) study.

c. Downgraded because of three randomized trial, all did not blind patients and caretakers.

d. The studies include few participants and have low basal risk, demonstrated as few events during the study.

Source: GRADE pro software tool (www.gradepro.org/).

4. Discussion

This systematic review with a meta-analysis showed that it is necessary to expand phase III studies and follow up coinfected patients using INI in a real-world setting. In general, patients coinfected with TB and HIV/AIDS showed a good response to INI treatment compared to other RCT in which the INI efficacy and safety were evaluated in patients with HIV/AIDS (Venter et al. 2021, Havlir et al. 2011, Bonnet et al. 2013, Rockstroh et al. 2013, Lennox et al. 2009).

According to the guidelines currently used, INI can be used as an alternative ARV to EFV in the coinfected population (WHO, 2018); however, RCTs designed with greater methodological robustness and with an expanded number of participants are needed. These measures are essential to improve the quality of evidence regarding INI in this population, as only three RCTs with small sample sizes and one cohort study were identified.

The highly selective populations examined in the context of RCT are often not comparable with the more heterogeneous populations in real-world clinical practice, where drugs are administered to patients with varying genetic

compositions who have different comorbidities or already receive different medications for other morbidities. Consequently, new drugs submitted for authorisation and commercialisation are accompanied by safety data as well as efficacy results with extremely high internal validity, but whose results may not be easily generalisable to a broader, heterogeneous population (Freemantle et al. 2010). In REFLATE TB, Grinsztejn et al. (2014) reported as a limitation the fact that liver toxicity was underestimated in the study because only patients with alanine aminotransferase concentrations up to 2.5-fold the normal limit were evaluated, which represented one of the justifications for conducting REFLATE TB 2, a phase III study. In that study, the AE rates were similar in the RAL and EFV arms. In REFLATE TB 2 (De Castro et al., 2021), EFV was not inferior to RAL in treating HIV/AIDS in TB patients. Efavirenz has a well-known efficacy and safety standard in clinical practice, but the effects of the long-term use of integrase inhibitors are not known, despite the profile of high genetic barriers and faster viral suppression.

Despite the controlled conditions of the RCTs, this population presents treatment adherence problems. In the study by Castro et al. (2021), the non-inferiority of RAL 400 mg compared with EFV at week 48 was not demonstrated, and the explanation for this finding was associated with non-adherence to treatment. In the study by Dooley et al. (2020), the loss was also large for reasons unrelated to treatment and the authors justified the difficulty in selecting patients, which took almost two years, representing the challenge of following up coinfected patients. According to the authors, INSPIRING would require a sample equivalent to 536 patients for comparison between the arms, and REFLATE TB was only an estimation study not designed for a formal comparison of the efficacies of RAL and EFV.

In addition, masking was not performed in any of the clinical trials identified, leading to a detection bias for safety outcomes, since masking avoids the tendency for subjects to change their behaviour because they are targets of interest and special attention, eliminating the effect of different expectations regarding the treatment (Dirk & Elston, 2021). The certainty of evidence was low or extremely low for the efficacy and safety outcomes, indicating that any effect estimate is very uncertain or that future research is likely to have a major impact on this estimate.

Both clinical trials and observational studies with a population of TB and HIV/AIDS patients are scarce. This can be explained by the fact that the incorporation of INI as a treatment alternative is recent and by the difficulty in obtaining coinfected patient volunteers who meet the eligibility criteria to participate in clinical trials (Wong, Trustman & Yalong, 2016).

The population of coinfected patients included in the studies consisted mainly of young adults, mostly men, from countries in different geographic regions and with different levels of socioeconomic development. These findings corroborate previous studies that investigated coinfection (Lemos et al. 2016; Rosetto et al. 2019, Mariano, Magnabosco & Orfão,2021) and identified that in both TB and HIV/AIDS infection, the male population is the most vulnerable and prevalent for coinfection, with a higher concentration in the economically active age group (15–50 years) (Lemos et al. 2016; Rosetto et al. 2019, Mariano, Magnabosco & Orfão,2021).

TB is an opportunistic infection with the highest death rate in HIV patients, and these patients need special pharmacotherapy follow-up, since when they discover the diagnosis, most patients are already in an advanced phase of the disease (associated with CD4 T lymphocyte values < 200) and may present characteristics that make them ineligible for inclusion in the clinical trials evaluated. The main factor behind TB mortality in PLHIV is the late diagnosis (WHO, 2021). No variation in baseline characteristics of patients was found in the studies evaluated individually, with low CD4 levels and a similar mean increase between the arms analysed. These results corroborate the SPRING study, which evaluated DTG versus RAL with once daily administration in mono-infected patients, with a median increase of 230 cells/µl at week 48 (Raffi et al. 2013).

RMP is an enzymatic inducer of cytochrome P450 and whose concomitant use with INI can lead to sub-therapeutic drug concentrations and treatment ineffectiveness, contributing to the emergence of viral resistance and increased healthcare costs (Wenning et al. 2009, Wang et al., 2019). The study by Dooley (2020) reported that the mean minimum DTG concentrations of 50 mg twice daily were similar to the minimum concentrations when 50 mg DTG was administered once daily without TB treatment, but previous pharmacokinetic studies identified a 56% reduction in the plasma concentration of the drug and thus recommended twice daily use (Calmy et al. 2020, Wang et al. 2019). Efavirenz concentrations were not significantly affected by RMP, which is a major advantage in a first-line ART regimen (Havlir et al. 2011, Bonnet et al. 2013).

In the cohort study conducted in Botswana, the effectiveness of ART with DTG was greater than 70%, although there was a deviation from the national recommendations regarding the DTG dosage used, representing a bias and deviation from the protocol to pragmatic observational studies. However, these results were not conclusive, with the recommendation to use DTG 50 mg twice daily during HIV/AIDS treatment in TB patients remaining (Calmy et al. 2020, Wang et al. 2019, Dooley et al. 2013). New clinical trials are underway to evaluate the reduced-dose DTG strategy in TB coinfected patients (Nabisere et al. 2020, Griesel et al. 2021).

Although studies comparing different ART regimens in PLHIV without TB suggest that viral suppression is achieved more frequently and more rapidly with INI-containing regimens compared with those with EFV, there is a difference between the INSPIRING results and real-life studies. Efavirenz replacement with DTG is greatly important in coinfected patients with EFV resistance mutations or significant intolerance (Pinho et al., 2020).

Concerns about ART resistance were also assessed in the REFLATE TB and INSPIRING studies. There were no reports of HIV resistance to DTG, characterising its potential for greater genetic barriers. The identified RAL-related mutations were in genes E92EQ, Y143R/C, and N155H, representing primary and secondary resistance (Nunes, 2016, da Silva et al 2010). New real-life studies are underway to evaluate DTG resistance and the impact of different INIs on immune system activation in treatment naïve patients (NLM, NCT04453436; NLM, NCT03280940).

The INI toxicity profiles include neurological and gastrointestinal symptoms and weight gain (Kolakowska et al. 2019). In the studies evaluated, INIs were safe in the treatment of coinfection, presenting a safety profile compatible with the one described in HIV treatment. It is important to emphasise the implications of a small sample size and follow-up losses.

Immune Reconstitution Inflammatory Syndrome was an AE described in the studies included in this review, which in the meta-analysis favoured the INI group (Grinsztejn et al. 2014, Delagreverie et al. 2020, De Castro et al. 2021 &. Dooley et al. 2020), but its association with INIs is controversial (Walmsley et al. 2013, Namale et al. 2015, Uthman et al. 2015). Further studies including more high-risk patients are needed to assess whether INIs increase the risk of TB-IRIS. The study by Delagreverie et al. (2020) reported that TB and HIV/AIDS treatments were successful with a limited number of INIs. Compared with other ARV classes, INIs result in a faster HIV RNA decrease and increased CD4 cell count, both of which were associated with an increased risk of IRIS (Walmsley et al. 2013). However, a systematic review reported that a faster HIV RNA decrease was not consistently associated with an increased risk of TB (Namale et al. 2015). A meta-analysis showed that early ART (defined as one to four weeks after anti-TB therapy) doubled the risk of TB-IRIS compared with late ART (defined as eight to 12 weeks after anti-TB therapy). TB-IRIS occurs more frequently in patients with CD4 count < 50 cells (Uthman et al. 2015).

This systematic review addressed a timely and relevant clinical question regarding the efficacy, effectiveness, and safety of INI in TB and HIV/AIDS coinfection. To minimise the risks of bias, a comprehensive search was conducted in seven databases and also in major scientific meeting websites on HIV/AIDS studies. The limitation of this review is the inclusion studies with small numbers of participants and/or that were underpowered. These aspects were considered when analyzing the

methodological quality of all studies.

The results of this systematic review improve the understanding of clinical outcomes related to the use of INIs in patients coinfected with TB and HIV/AIDS. The preparation of a comprehensive and sensitive search allowed the identification of the available evidence and improved the knowledge available on the subject.

5. Conclusion

Integrase inhibitors in patients co-infected with TB and HIV/AIDS appear to be effective, well tolerated and constitute an alternative to efavirenz in clinical protocols. However, the use of this drug twice a day compromises adherence to treatment. The role of these drugs should be better determined by further observations of good methodological quality studies to assess their long-term efficacy, effectiveness and safety.

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