Comparative evaluation of the applicability of fixed-dose combined drugs in HIV therapy

Avaliação comparativa da aplicabilidade de drogas combinadas em dose fixa na terapia do HIV

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Luciana Ferreira Mattos Colli
Mestrado - UFRJ
Instituição: Faculty of Pharmacy – Federal University of Rio de Janeiro – RJ- Brazil
Endereço: Av Carlos Chagas Filho, 373, CCS, Bloco Lss, sala 20 Cidade Universitária - RJ
E-mail: colli.luciana@gmail.com

Thiago Pereira de Abreu
Doutorado - UFRJ
Instituição: Faculty of Pharmacy – Federal University of Rio de Janeiro – RJ- Brazil
Endereço: Av Carlos Chagas Filho, 373, CCS, Bloco Lss, sala 20 Cidade Universitária - RJ
E-mail: thiagoabreu0704@hotmail.com

Guacira Corrêa de Matos
Doutorado - UFRJ
Instituição: Faculty of Pharmacy – Federal University of Rio de Janeiro – RJ- Brazil
Endereço: Av Carlos Chagas Filho, 373, CCS, Bloco Lss, sala 20 Cidade Universitária - RJ
E-mail: guacira@pharma.ufrj.br

Letícia Coli Louvisse de Abreu
Doutorado - IFRJ
Instituição: Faculty of Pharmacy – Federal University of Rio de Janeiro – RJ- Brazil
Federal Institute of Rio de Janeiro – RJ- Brazil
Endereço: Av. República do Paraguai, 120 - Vila Sarapui, Duque de Caxias - RJ
E-mail: leticialouvisse@gmail.com

Carlos Rangel Rodrigues
Doutorado - UFRJ
Instituição: Faculty of Pharmacy – Federal University of Rio de Janeiro – RJ- Brazil
Endereço: Av Carlos Chagas Filho, 373, CCS, Bloco Lss, sala 20 Cidade Universitária - RJ
E-mail: rangelfarmacia@gmail.com

Valéria Pereira de Sousa
Doutorado - UFRJ
Instituição: Faculty of Pharmacy – Federal University of Rio de Janeiro – RJ- Brazil
Endereço: Av Carlos Chagas Filho, 373, CCS, Bloco Lss, sala 20 Cidade Universitária - RJ
E-mail: valeria@pharma.ufrj.br

Lucio Mendes Cabral
Doutorado - UFRJ
Instituição: Faculty of Pharmacy – Federal University of Rio de Janeiro – RJ- Brazil
Endereço: Av Carlos Chagas Filho, 373, CCS, Bloco Lss, sala 20 Cidade Universitária - RJ
E-mail: lmcabral@pharma.ufrj.br

ABSTRACT
The principal global pandemic is Acquired Immunodeficiency Syndrome (AIDS), the early diagnosis and the premature treatment is the main current strategies in combating the development and spread of the disease. Antiretroviral therapy is effective and safe, what is sought nowadays is compliance and convenience for the patient. Different countries adopt different combinations of antiretroviral drugs when using the fixed-dose combination (FDC). The study design was a meta-analysis with clinical trials, patients experienced and naïve of treatment. The Pubmed, Scopus, Embase, Web of Science and Cochrane databases were searched for studies reporting AIDS treatment. The primary outcome was viral load and another outcome is adverse events. The results of the main analysis included 5224 patients. Since there was significant heterogeneity between studies, random effects were selected, and they showed an event rate of 0.67 (95%CI from 0.57 to 0.77). The exploratory analysis showed the general drug effects are not consistently significant along time, and treatments of longer times are more efficient. Specifically, the random analyses of 6 months and 1 year did not show significant drug effects on viral load, while a significant effect of 71% (95% CI from 0.61 to 0.80) in a very heterogeneous analyses (I^2>96%). First, d4T-3TC-NVP showed a mean rate of only 21% efficacy and the second, EFV-TDF-FTC did not reach statistical significance (p=0.07). This meta-analysis shows that fixed-dose combination therapy is tolerability, safety and effective, occurred viral load suppression between patients on FDC.

Keywords: acquired immunodeficiency syndrome, aids, human immunodeficiency virus, antiretroviral, fixed-dose combination.

RESUMO
A principal pandemia global é a Síndrome de Imunodeficiência Adquirida (AIDS), o diagnóstico precoce e o tratamento prematuro são as principais estratégias atuais para combater o desenvolvimento e a propagação da doença. A terapia anti-retroviral é eficaz e segura, o que se busca hoje em dia é o cumprimento e a conveniência para o paciente. Diferentes países adotam diferentes combinações de medicamentos anti-retrovirais ao utilizar a combinação em dose fixa (FDC). O desenho do estudo foi uma meta-análise com ensaios clínicos, pacientes experientes e ingênuos de tratamento. Os bancos de dados Pubmed, Scopus, Embase, Web of Science e Cochrane foram pesquisados para estudos que relatavam o tratamento da AIDS. O resultado primário foi a carga viral e outro resultado foram os eventos adversos. Os resultados da análise principal incluíram 5224 pacientes. Como havia uma heterogeneidade significativa entre os estudos, os efeitos aleatórios foram selecionados e mostraram uma taxa de eventos de 0,67 (95%CI de 0,57 a 0,77). A análise exploratória mostrou que os efeitos gerais da droga não são consistentemente significativos ao longo do tempo, e os tratamentos de tempos mais longos são mais eficientes. Especificamente, as análises aleatórias de 6 meses e 1 ano não mostraram efeitos medicamentosos significativos sobre a carga viral, enquanto um efeito significativo de 71% (IC 95% de 0,61 a 0,80) em análises muito heterogêneas (I2>96%). Primeiro, d4T-3TC-NVP mostrou uma taxa média de eficácia de apenas 21% e o segundo, EFV-TDF-FTC não alcançou significância estatística (p=0,07). Esta meta-análise mostra que a terapia de combinação em dose fixa é tolerável, segura e eficaz, ocorreu supressão de carga viral entre pacientes com FDC.

Palavras-chave: síndrome de imunodeficiência adquirida, aids, vírus de imunodeficiência humana, antiretroviral, combinação de dose fixa.

1 INTRODUCTION

Acquired Immunodeficiency Syndrome (AIDS) is still a pandemic, with global consequences. At the end of 2019, 38 million people lived with the human immunodeficiency virus (HIV) worldwide [1]. The World Health Organization (WHO) recommends that any individual at risk of HIV contamination get tested. The widely disseminated campaigns on HIV infection and the development of AIDS are essential to advise patients on the importance of early diagnosis. The HIV virus destroys CD4 cells, leading to a failure of the immune system, and consequently, several opportunistic diseases may occur. Individuals infected with HIV that reach a CD4 count below200 cells are considered to have developed AIDS from de HIV viral infection [2,3]. Therefore, early diagnosis and monitoring of viral load are important treatment strategies for AIDS patients.

Antiretroviral therapy (ART) drugs are some of the most important treatments for AIDS. Besides, ART drugs decrease the viral load, helping prevent transmission as individuals with undetectable viral loads do not transmit HIV [1,4]. Antiretroviral drugs have been developed with similar profiles of commonly used drugs for AIDS treatments, such as nucleoside and nucleotide reverse transcriptase inhibitor (NRTIs), non-nucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (PIs), andintegrase-strand transfer inhibitors (INSTIs) [5].

The first-line treatment for AIDS ,currently recommended for adult, naive of treatment patients,is the combination of the ART Dolutegravir with an NRTI. As a second-line treatment, a low-dose of Efavirenz is recommended in combination with an NRTI[5]. Despite these recommendations, several countries have their own therapy campaigns prescribing specific combinations of treatments for AIDS. Also, combinations of drugs have been tested in clinical studies, which have used the monitoring of the viral load as the main outcome of drug efficiency[6].

Despite the success of ART, treatment failure may occur when the viral load rises again mainly due to patient non-adherence to treatment[7,8]. Some of the main factors for non-adherence include the occurrence of adverse events and the need to use several pills a day[9,10]. These factors point out as an advantage on the use of combined fixed-dose drugs for the treatment of AIDS patients [11–13].

2 METHODS

2.1 SEARCH STRATEGY

The databases used to obtain the research articles were Pubmed, Scopus, Embase, Web of Science (WOS) and Cochrane. For the Pubmed search, the terms applied were((“FDC”[tiab] AND ("lamivudine"[mh] OR lamivudine[tiab] OR "tenofovir"[mh] OR tenofovir[tiab] OR "efavirenz” [Supplementary Concept] OR efavirenz[tiab]) OR (“efavirenz, lamivudine, tenofovir disoproxil fumarate drug combination”[Supplementary Concept] OR “Efavirenz, Emtricitabine, Tenofovir Disoproxil Fumarate Drug Combination”[mh])). For the Scopus search the terms were (TITLE-ABS-KEY(“FDC”) AND (TITLE-ABS-KEY("lamivudine")) OR (TITLE-ABS-KEY(lamivudine)) OR (TITLE-ABS-KEY("tenofovir")) OR (TITLE-ABS-KEY(tenofovir)) OR (TITLE-ABS-KEY("efavirenz”)) OR (TITLE-ABS-KEY("efavirenz")) OR (TITLE-ABS-KEY(“efavirenz, lamivudine, tenofovir disoproxil fumarate drug combination”)) OR (TITLE-ABS-KEY (“Efavirenz, Emtricitabine, Tenofovir Disoproxil Fumarate Drug Combination”)). The database Pubmed search was conducted November 3rd of 2020, and the other databases were searched on November 6th of 2020. The references were imported and transferred to the Rayyan – QCRI web online reference manager[14]. This software was used for the management of the research data, including the presence of duplicate articles. Two experienced researchers assessed the quality of the articles and selected the relevant articles simultaneously, but were unaware of each other selection.

The inclusion criteria were: research articles published between 2005 and 2020 as clinical trials, using ART for virgins and experienced patients, aged over 18 years. The main outcome used to evaluate the efficiency of the ART were the viral load and CD4 cell counts. The thresholds for these variables were a viral load more than 450 copies, and CD4 less than 350 cells. The ART regimens were combined fixed dose or comparison of combined with multiple daily doses. Only studies with outcome measures in comparable format were included (n / N, mean, standard deviation, N or median and inter-quartile range). The variables adherence to therapy, efficacy, safety, tolerability, and cost were evaluated to compare the availability of drugs nationally and internationally.

The guidelines of systematic reviews and meta-analyzes (PRISMA) and the “PICOS principle” (patient, intervention, comparator, outcomes and study design) were used for the design of the study [15].The data extraction process was year of publication, first author, study type, population, sample size and outcomes. The exclusion criteria were: literature reviews, meta-analysis, case reports, patients with comorbidities and adverse effects of treatment. Also, viral loads less than 450 copies, CD4 counts of more than 350 cells, failure of another treatment

for AIDS, children, pregnant, and different scope were excluded. This search was submitted to PROSPERO with registration number of CRD42021228582.

2.2 STATISTICAL ANALYSIS

The meta-analysis was performed using Comprehensive Meta-Analysis (CMA) software, version 3.3.070. The main meta-analysis tested the mean rate of individuals (and 95% confidence interval) with viral load lower than 50 copiesml^{-1} within the overall patients that received ART. When there was significant heterogeneity ($p \leq 0.05$), we calculated the randomized effect, and when there was no significant heterogeneity ($p > 0.05$) we used fixed effects. Studies considering individuals under 20 copiesml^{-1} and 20-50 copiesml^{-1} in different subgroups were combined in one unique group named <50 copiesml^{-1} to avoid sample overlapping.

Furthermore, when the studies reported different time points of analysis, we selected only the 24weeksfor the main analysis. For subgroup analysis, the comparison between the different drug effects was also tested considering only one subgroup of each study, based on the same criteria (<50 copiesml^{-1} and 24weeks when more than one time point exists). To explore the different time effects, we compared each of the subgroups included in the studies. To this end, we clustered the studies within the following subgroups: 6months (24 to 26weeks of intervention), 1 year (48 to 52 weeks of intervention) and more than 1 year (76 to 104 weeks of intervention). An inconsistency between studies above 75% was considering high. Publication bias was analyzed by the Egger test and a p-value ≤ 0.05 was considered significant.

3 RESULTS

3.1 RESULTS ARTICLES TRIALS

The literature search in all databases showed 178 citations, of which 5 were duplicated and discarded, resulting in 142 articles. The subsequent step was to read the abstracts, which resulted in the exclusion of 111 articles. Of these, 31 articles followed for complete reading of the text, where two were discarded; the first because it was a meta-analysis and the two others had no focus on AIDS pharmacotherapy.

A total of 29 articles were elected to perform data extraction, and 19 articles were excluded because they did not detail the outcomes or did not measure viral load [16–28], were studies in children [18,27], in pregnant women[29], without a focus on pharmacotherapy[30] and did not have the same focus on ART treatment[31–34] . The PRISMA flow is in Figure 1.

Figure 1: PRISMA flow diagram describing the selection of studies

Study name	Subgroup (drug type, viral load cut-off point, weeks of drug treatment)	Statistics for each study					
		Event rate	Lower limit	Upper limit	p-Value	Total	Relative weight
Rossi 2019 [34]	FDC <50 24	0.225	0.147	0.329	0.000	18 / 80	5.87
Rossi, 2019 [34]	MTR, <50, 24	0.301	0.235	0.375	0.000	49 / 163	6.14
Rockstroh, 2013 [33]	EFV-TDF-FTC, <50, 24	0.998	0.972	1.000	0.000	282 / 282	1.97
Rockstroh, 2013 [33]	RAL-TDF-FTC, <50, 24	0.993	0.972	0.998	0.000	279 / 281	4.07
Manosuthi, 2008 [19]	d4T-3TC-NVP,<50,24	0.571	0.488	0.651	0.092	80 / 140	6.14
Triyono,2019 [39]	TDF-3TC-EFV, <50, 24	0.002	0.000	0.033	0.000	0 / 236	1.97
Mukherjee, 2014 [24]	FDC 30 *	0.310	0.170	0.497	0.047	9 / 29	5.38
Mukherjee, 2014 [24]	FDC 6 - d4T-3tC-NVP, =47, 12	0.690	0.503	0.830	0.047	20 / 29	5.38
Manosuthi, 2007 [20]	d4T-3TC-NVP, <50,18	0.050	0.023	0.107	0.000	6 / 120	5.31
Velvanathan,2016 [41]	TDF-FTC-EFV - FDC, <20, 6	0.992	0.882	0.999	0.001	60 / 60	1.96
Li, 2019 [46]	ATV/r - TDF-FTC, <20, 104	0.775	0.727	0.816	0.000	258 / 333	6.22
Li, 2019 [46]	DRV/r -TDF-FTC, <20, 104	0.695	0.645	0.741	0.000	244 / 351	6.25
Li, 2019 [46]	DTG-ABC-3TC, <20, 104	0.828	0.788	0.862	0.000	332 / 401	6.22
Li, 2019 [46]	EFV-TDF-FTC, <20, 104	0.884	0.864	0.901	0.000	1026 / 1161	6.28
Li, 2019 [46]	EVG/c-TAF-FTC, <20, 104	0.828	0.782	0.867	0.000	256 / 309	6.18
Li, 2019 [46]	EVG/c-TDF-FTC, <20, 104	0.744	0.706	0.779	0.000	410 / 551	6.27
Li, 2019 [46]	RPV-TDF-FTC, <20, 104	0.807	0.770	0.839	0.000	397 / 492	6.25
Reynes, 2013 [32]	LPV/r - RAL, <40, 96	0.624	0.526	0.713	0.014	63 / 101	6.06
Reynes, 2013 [32]	LPV/r - TDF-FTC, <40, 96	0.667	0.571	0.750	0.001	70 / 105	6.05
Summarized effects	**LPV/r - TDF-FTC, <40, 96**	**0.672**	**0.561**	**0.766**	**0.003**	**3859 / 5224**	**100**

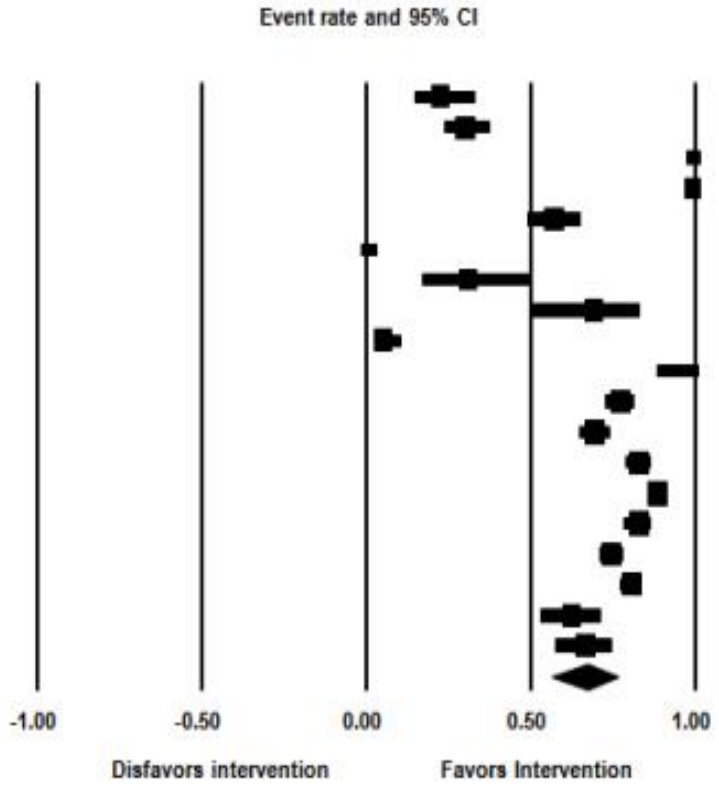


Table 1 Studies included in Qualitative Evidence Synthesis.

Study	Study type	Intervention	Comparator	Population	Sample size	Outcomes	Included in Meta-Analysis
Calmy et al.[17] (2006).	Cohort	D4t/3TC/NVP	Not	Naive of treatment	6961	Safety and Efficiency	No
Elzi et al.[18] (2012).	Prospective Cohort	TDF-FTC/EFV or TDF-FTC/LPV, TDF-FTC/ATV or ZDV-3TC /LPV or ABC-3TC/EFV	Other treatments	Naive of treatment	1957	Efficiency /adherence	No
Gyamfi et al.[19] (2020).	Retrospective/ Transversal	ZVD/3TC/EFV	ZVD/3TC/NVP	Treatment experienced	500	Safety and Efficiency	No
Hagins et al.[20] (2016).	Randomized	DTG/ABC/3TC	ATV/FTC/TDF	Naive of treatment	495	DTG/ABC/3TC	No
Natu, Daga[21] (2007).	Prospective Cohort	FDC - D4t/NVP/3TC	Not	Naive of treatment	25	Efficiency /adherence	No
O´Brien et al.[22] (2006).	Prospective Cohort	Triviro 30 - D4t/3TC/NVP	Triviro 40 - D4t/3TC/NVP	Naive of treatment / Experienced	1184	Safety and Efficiency	No
Orkin et al.[23] (2019).	Double blind	DOR/3TC/TDF or DOR/FTC/TDF or ABC/3TC	DRV+r with FTC/TDF or ABC/3TC or EFV/FTC/TDF	Naive of treatment	1494	DOR/3TC/TDF no inferior effectiveness.	No
Pujari et al.[24] (2004).	Observational	D4t/3TC	ZVD/3TC	Naive of treatment	1291	Safety and Efficiency	No
Puspitasari et al.[25] (2020).	Longitudinal observational	FDC - 3TC/TDF/EFV	Not	Naive of treatment	20	FDC change the lipid profile.	No
Sax et al.[26] (2012).	Prospective Cohort	EVG/COB/FTC/TDF	EFV/FTC/TDF	Naive of treatment	700	Safety and Efficiency	No
Taramasso et al.[27] (2018).	Prospective Cohort	TDF/FTC/EFV	TDF/FTC/RPV	Naive of treatment	1490	RPV better than EFV	No

Wiriyatanakorn, Sungkanuparph[28] (2019).	Randomized	TDF/FTC/EFV	TDF/FTC/RPV	Treatment experienced	246	The change has no impact	No
Moodley et al.[29] (2016).	Transversal	D4t/3TC/NVP	Not	Treatment experienced	2726	Safety and Efficiency	No
Susilo et al.[30] (2020).	Observational	FDC-TDF/3TC/EFV	Not	Treatment experienced	20	Safety and Efficiency	No
Bourgeois et al.[31] (2005).	Prospective Cohort	ZVD/3TC/NVP	ZVD/3TC/NVP	Treatment experienced	109	Efficiency/Equivalent therapies	No
Oyugi et al. [32] (2007).	Prospective Cohort	Triomune®	Maxivir®	Naive of treatment	97	Safety and Efficiency	No
Squires et al.[33] (2016).	Randomized	RAL/EFV/RAL	TDF/FTC	Naive of treatment	669	Safety and Efficiency	No
De Los Santos et al.[34] (2014).	Cohort Prospective	FDC-3TC/ABC and DRV/RTV	Not	Treatment experienced	76	Safety and Efficiency	No
Duse et al.[35] (2008).	Prospective Cohort	Triviro 30 - D4t/3TC/NVP	Triviro 40 - D4t/3TC/NVP	Naive of treatment	100	Safety and Efficiency	No
Manosuthi et al.[37] (2007).	Prospective Cohort	D4t/3TC/NVP	Not	Naive of treatment	140	Efficiency /dyslipidemia	Yes
Rockstroh et al.[38] (2013).	Prospective Cohort	TDF/FTC+RAL	TDF/FTC+EFV	Naive of treatment	566	TDF/FTC+ RAL better than TDF/FTC+ EFV.	Yes
Rossi et al.[39] (2019).	Prospective Cohort	Atripla® or Truvada® or Kivexa® or TDF/3TC/-EFV or TDF/3TC or	MTR	Treatment experienced	243	Efficiency / adherence of	Yes

		ABC/3TC				FDC	
Manosuthi et al.[40] (2008).	Retrospective Cohort	FDC-D4t/3TC/NVP	Not	Naive of treatment	204	Safety and Efficiency	Yes
Xiuhong Li et al.[41] (2019).	Prospective Cohort	EFV/TDF/FTC or EVG/c/TDF/FTC or LPV/TDF/FTC or DTG/ABC/3TC or DRV/r+TDF/FTC or ATV/r+TDF/FTC or EVG/c/TAF/FTC	Not	Treatment experienced	7357	Safety and Efficiency	Yes
Mukherjee et al.[42] (2014).	Cohort Transversal	FDC-6-NVP/3TC/D4t	FDC-30	Treatment experienced	79	Safety and Efficiency	Yes
Reynes et al.[43] (2012).	Randomized	LPV/r+RAL	LPV/r+TDF/FTC	Naive of treatment	206	LPV/r+RAL no impact on treatment.	Yes
Triyono et al.[44] (2019).	Transversal	TDF/3TC/EFV	D4t/3TC/EFV or D4t/3TC/NVP or TDF/3TC/NVP or TDF/FTC/EFV or TDF/FTC/NVP or ZDV/3TC/EFV or ZDV/3TC/NVP or TDF/FTC/LPV/r or TDF/3TC/LPV/r	Treatment experienced	236	Safety and Efficiency /FDC	Yes
Velvanathan et al.[45] (2016).	Randomized	FDC-FTC/TDF/EFV	FRC-FTC/TDF /EFV	Treatment experienced	120	FDC greater adherence.	Yes

ABC – abacavir, ATV – atazanavir, DOR – doravirine, DRV – darunavir, DRV+r – darunavir plus ritonavir, DTG – dolutegravir, D4t – stavudine, EFV – efavirenz, EVG – elvitegravir, EVG/r – elvitegravir/cobicistat, FDC – Fixed-dose combination, FRC – free dose combination, FTC – emtricitabine, LPV – lopinavir, MTR – multiple tablets, NVP – nevirapine, RAL – raltegravir, RTV – ritonavir, 3TC – lamivudine, TDF – tenofovir disoproxil fumarato, ZDV – zidovudine.

According to the type of study in Table 1, of the total selected studies, 13 were prospective cohorts[18,20,24–27,32–38]. In a total of 29 studies analyzed, nine studies did not compare the pharmacotherapy[17,27–30,32,35,39,40]. Additionally, considering the studies read, a total of 12 volunteers were experienced in the treatment, and exactly 17 patients were treatment naive, inferring they received first-line treatment.

3.2 RESULTS META-ANALYSIS

The main analysis to evaluate the efficiency of the ART included 5224 patients (Figure 2). A significant heterogeneity was detected between studies and therefore random effects were selected. These effects showed an average event rate of 0.67 (95%CI from 0.57 to 0.77). Thus, considering all the different drugs in the same analysis, efficacy upon viral load reached 67% of patients in a highly heterogeneous analysis (I^2= 96.85). Additionally, the p-value of 0.08 for the Egger test suggested no risk of publication bias.

Nevertheless, considering each different drug treatment individually, while most drugs were significantly efficient, two drugs had no significant effects (Table 2). First, d4T-3TC-NVP showed a mean rate of only 21% efficacy in an analysis that combined two studies of the same research group[35,39]. Second, EFV-TDF-FTC was not statistically significant (p=0.07) for the 98% mean rate due to a high variation between the studies Li et al. (2019) and Rockstroh et al.(2013) (95% CI from 0.44 to 1.00). It is noteworthy, for other drug subgroups only one study was included in each analysis, facilitating the existence of true homogeneity within these studies and consequent significant effects.

The exploratory analysis showed general drug effects are not time significant, and treatments of longer times are more efficient (Table 3). Specifically, the random analyses of 6 months and 1 year were not significant for drug effects on viral load, while with a significant effect of 71% (95% CI from 0.61 to 0.80) in a very heterogeneous analyses (I^2>96%).

Table 2. Comparison between different drug effects on individuals mean rate (and 95% confidence interval) with viral load lower than 50 copies/ml.

Subgroup	K	Event rate	LL 95 (%)	UL 95 (%)	P-value
ATV/r - TDF-FTC	1.00	0.77	0.73	0.82	**0.00**
d4T-3TC-NVP	2.00	0.21	0.01	0.87	0.42
DRV/r -TDF-FTC	1.00	0.70	0.64	0.74	**0.00**
DTG-ABC-3TC	1.00	0.83	0.79	0.86	**0.00**
EFV-TDF-FTC	2.00	0.98	0.44	1.00	0.07
EVG/c-TAF-FTC	1.00	0.83	0.78	0.87	**0.00**
EVG/c-TDF-FTC	1.00	0.74	0.71	0.78	**0.00**
FDC - fixed dose combined	1.00	0.22	0.15	0.33	**0.00**
FDC 30 *	1.00	0.31	0.17	0.50	**0.05**
FDC 6 - d4T-3tC-NVP	1.00	0.69	0.50	0.83	**0.05**
LPV/r – RAL	1.00	0.62	0.53	0.71	**0.01**
LPV/r - TDF-FTC	1.00	0.67	0.57	0.75	**0.00**
MTR - multi tablet regimen	1.00	0.30	0.24	0.38	**0.00**
RAL-TDF-FTC	1.00	0.99	0.97	1.00	**0.00**
RPV-TDF-FTC	1.00	0.81	0.77	0.84	**0.00**
TDF-3TC-EFV	1.00	0.00	0.00	0.03	**0.00**
TDF-FTC-EFV – FDC	1.00	0.99	0.88	1.00	**0.00**

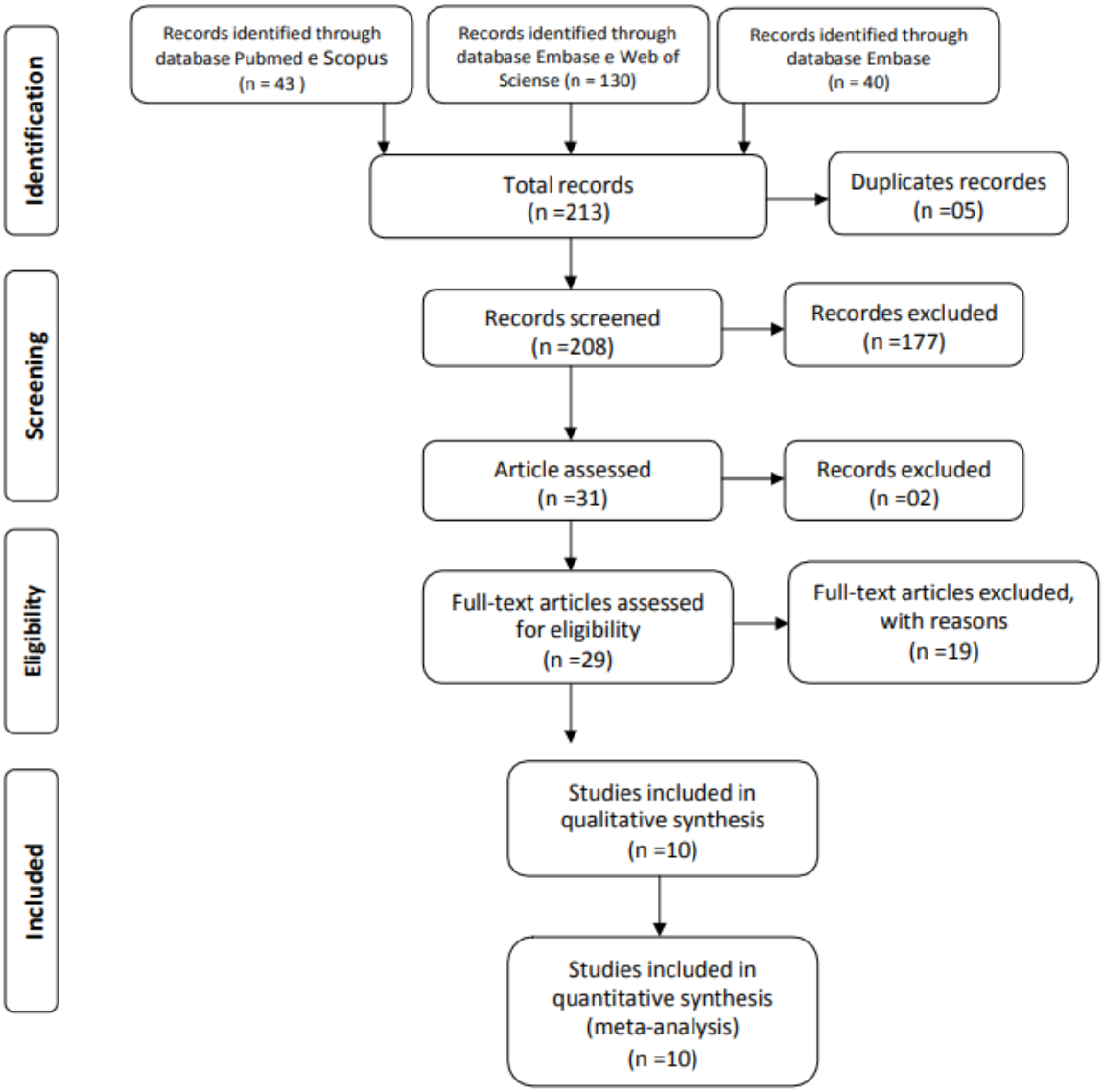
Legend: K = number of study groups included in the analysis; LL. = lower limit of 95% confidence interval; UL= upper limit of 95% confidence interval; Bold p-values = significant rate of individuals under 50 copies/ml; *Stavudine 30 mg/lamivudina 150 mg/nevirapina 200mg

Table 3. Comparison between different time points on individuals mean rate (and 95% confidence interval) with viral load lower than 50 copies/ml

Subgroup	K	Event rate	LL 95 (%)	UL 95 (%)	P-value
6 months	9.00	0.49	0.18	0.81	0.97
1 year	10.00	0.41	0.19	0.66	0.48
>1.5 years	14.00	0.71	0.61	0.80	**0.00**

Legend: K = number of study groups included in the analysis; LL. = lower limit of 95%confidence interval; UL= upper limit of 95% confidence interval; Bold p-values = significant rate of individuals under 50 copies/ml

Figure 2. Forest plot of individuals mean rate (and 95% confidence interval) with viral load lower than 50 copies/ml within the overall medicated patients.



4 DISCUSSION

Treatments for AIDS patients are usually different for each country due to technical capabilities and difficulties. According to each country clinical protocol, treatment is based on drugs like NRTIs, NNRTI, PIs and INSTIs, all of which are administered in separate formulations as multiple daily doses, or as a daily fixed-dose. The impact of whether the treatment will be in multiple or single doses may range from the pharmacokinetics of the drug to patient adherence to treatment[41,42]. However, when adopting the combined fixed-dose treatment the drugs involved perform differently and effectiveness on viral load may decrease.

Therefore, prescribing a combination of different drugs can imply in different therapeutic results from single-drug treatments.

Research involving new AIDS treatments mobilizes both private and public entities around the world. Several pharmaceutical companies apply for patents of new drugs and launch their products in order to innovate with different treatments. There is no standard of treatment with international scope for different combinations of treatments. Therefore, the efficacy of drug combination treatments in comparison with single therapy is still not established. Thus, meta-analysis studies are an interesting application to highlight whether there are discrepancies within the treatments adopted in different parts of the world.

This study has provided evidence of significant differences among the ART treatments. The main finding was that viral load suppression was statistically significantly higher in the treatments ATV/r - TDF-FTC, RV/r -TDF-FTC, DTG-ABC-3TC, EFV-TDF-FTC, EVG/c-TAF-FTC e RPV-TDF-FTC[40], and TDF-3TC-EFV[43]. A previous meta-analysis showed a comparison of fixed-dose combined and multiple tablet regimens, obtaining a positive result for the intervention with a fixed-dose combined[6]. In the present meta-analyses, most studies have evaluated fixed-dose combined regimens, with the exception of Inojosa (2019) which compared different treatment regimes. The observed in the evaluated studies is that the fixed-dose combined, in spite of issues of pharmacokinetics, dose comfort and possibility of adverse events, is effective, promoting a reduction in viral load.

Another concern was the relative weight the studies, and the principal results were of Xiuhong Li (2019), Inojosa (2019) and Mukherjee (2014)[44] with more than five, which highlights the effectiveness of the AIDS treatment using fixed-dose combined ART drugs.

5 CONCLUSIONS

This literature review and meta-analysis shows that fixed-dose combination ART is tolerable, safe and effective, promoting viral load suppression for AIDS patients on FDC. However, patients on fixed-dose combination have statistically significantly better viral load suppression. The present analysis further identified the main treatments applied in several different countries, and how it promotes patient compliance. It was possible to infer more effective treatments for HIV-positive patients with AIDS, and the associations in fixed-dose combination studied were shown to be fully effective within 48 months.

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