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Efavirenz versus Protease Inhibitors in Patients with HIV: A Systematic Review and Meta-Analysis

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Abstract

Efavirenz- and protease inhibitor (PI)-based regimens remain viable options across the globe. We conducted a meta-analysis to compare the effectiveness of efavirenz-based regimens relative to PI-based regimens. EMBASE, PubMed, Cochrane, and clinicaltrials.gov were searched for randomized controlled trials conducted between 1987 and 2018 comparing efavirenz- with PI-based regimens. This was followed by title, abstract, and full-text screens. The quality of selected studies was assessed using the Cochrane risk of bias tool. Meta-analysis of the odds of virological suppression was conducted using the robust variance estimation approach. Fifteen studies met the inclusion criteria and totaled 6712 patients (efavirenz arm = 3339; PI arm = 3373), of which 1610 (24.0%) were females. Follow-up ranged from 24 to 144 weeks. Mean/median age ranged from 33 to 44 years. Mean/median baseline CD4 count ranged from 32 to 557 cells/mL while mean/median baseline viral load ranged from log_{10} 4.5 to log_{10} 5.5 copies/mL. Meta-analysis showed that patients receiving efavirenz-based regimens had 37% higher odds of virological suppression compared to PI-based regimens (odds ratio = 1.37, 95% confidence interval = 1.06-1.77, p = 0.02). The Egger test suggested the presence of publication bias (B = 0.927, t = 2.214, p = 0.033). The main threat to the quality of evidence was attrition bias. Regarding virological suppression, efavirenz-based regimens were more effective than PI-based regimens and, therefore, might be ideal for the management of treatment naïve patients with HIV in settings where NNRTIs and PIs are used. (AIDS Rev. 2021;22:103-114)

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Key words

Highly active antiretroviral therapy. Comparative effectiveness research. HIV. Systematic review. Treatment outcomes.

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Introduction

Although there is no cure, advances in pharmacological management of HIV infection allow infected persons to live a regular life with a life expectancy that approximates the general population[1-5]. There are currently six classes of anti-HIV or antiretroviral drugs: (1) nucleoside reverse transcriptase inhibitors (NRTIs), (2) non-NRTIs (NNRTIs), (3) protease inhibitors (PIs), (4) integrase inhibitors (IIs), (5) fusion inhibitors (FIs), and (6) chemokine coreceptor 5 (CCR5) inhibitors[6]. At initiation of therapy, a typical antiretroviral regimen consists of two drugs from the NRTI class and one drug from the NNRTI, PI, or II class[7]. The two NNRTIs are referred to as the "backbone" while the third drug is the "base," with the combination resulting in highly active antiretroviral therapy (HAART).

Combination therapy with HAART became mainstream in the mid-1990s with the base consisting of either an NNRTI or a PI, as the first II was not approved until 2007[8]. Efavirenz is often the preferred NNRTI, mainly because of its relatively low toxicity profile[9]. With the exception of ritonavir, the other PIs are generally recommended as bases with atazanavir and darunavir having been shown from post-marketing studies to have lower risk of metabolic side effects[10-12].

Efavirenz- and PI-based regimens remain viable options across the globe. Efavirenz-based HAART is recommended as first-line treatment for HIV in Canada and in countries where the WHO guidelines are adopted[9,13]. PIs are also recommended in Canada and Europe[13,14]. Several studies have assessed the comparative effectiveness of NNRTI- and PI-based HAART regimens, with at least three meta-analyses reported in the literature[15-17]. However, no study has compared efavirenz, specifically, with PIs in a meta-analysis. The current study is a systematic literature review and meta-analysis of clinical trials comparing efavirenz- versus PI-based HAART regimens.

Materials and methods

Search strategy

Using the Population-Intervention-Comparator-Outcome search strategy and searching from January 1987 to June 2018, the following databases were searched in consultation with a medical librarian: EMBASE, PubMed, Cochrane, and clinicaltrials.gov databases. A trial run on PubMed showed that a combination of Intervention and Comparator search terms optimized search results. Adding the Population search terms, "HIV infection OR HIV seropositivity," gave slightly fewer results and were, therefore, excluded from the final combination. The search terms used were ([efavirenz] AND [(PIs) OR ([atazanavir OR darunavir OR fosamprenavir OR indinavir OR lopinavir OR ritonavir OR nelfinavir OR saquinavir OR tipranavir])]/filter: clinical trial).

Eligibility criteria

Studies were included if they were met the following criteria: (1) used a randomized controlled study design; (2) included and reported results for treatment-naïve patients; (3) included patients who were 13 years or older; (4) had at least an efavirenz-based HAART arm and a PI-based HAART arm; and (5) had the same NRTI backbone in both treatment arms. Studies were excluded if they employed/included: (1) a non-randomized trial or observational study design; (2) treatment-experienced patients; (3) patients with hepatitis or tuberculosis infection; and (4) efavirenz and PI arms with different NRTI backbones.

Study selection, quality assessment, and data extraction

A title screen was conducted for records identified with the search terms to determine if they qualified for further screening. This was followed by abstract and full-text screening based on the inclusion and exclusion criteria. Publications included after the full-text screen were assessed for risk of bias using the Cochrane risk of bias tool, which uses the following five bias domains: selection, performance, detection, attrition, and reporting[18]. After the quality assessment, the following data were extracted for meta-analysis: outcome of interest (virologic suppression and limit of detection), regimen (NRTI backbone and PI type), study sample size, race/ethnicity, gender, baseline CD4 count, baseline viral load, age, and follow-up period. Virologic suppression was operationalized as the proportion of patients with HIV viral load below the limit of detection of the assay used in the individual studies. If the study included intent-to-treat outcomes, on-treatment outcomes, and/or outcomes based on the number of patients at risk, intent-to-treat outcomes were preferentially extracted. The title, abstract, and full-text screens as well as data extraction were conducted by two reviewers and compared after each step. Discordant results were resolved by discussion.

Statistical analysis

Descriptive statistics were used to summarize data. The following characteristics were pooled across studies and expressed as frequencies and percentages: race/ethnicity, gender, virological suppression, and NRTI backbone. Age, baseline CD4 count, baseline viral load, and length of follow-up were pooled across studies and expressed as means and standard deviations or medians. For individual studies, the proportion of patients who were virologically suppressed was converted to the odds ratio (OR) of being virologically suppressed between patients in the efavirenz arm versus the PI arm. The ORs were then converted to log ORs and pooled across studies using the robust variance estimation approach. We conducted subgroup analyses for the selected studies stratified by whether or not the PI was boosted and by dosing frequency. We also conducted a sensitivity analysis that excluded efavirenz-PI pairs no longer recommended by the WHO[9]. The risk of publication bias was assessed using the Egger test. The a priori alpha level of statistical significance was set at $p < 0.05$. Analysis was conducted using SPSS Statistics 26. The study was approved by the University of Texas at Austin Institutional Review Board and determined to be non-human subjects research as it involved obtaining information from publicly available data. Hence, informed consent was not required. The study was registered with PROSPERO, an international database supported by PRISMA (ID: CRD42018100296) and conducted between June and December 2018.

Results

A total of 1321 records were identified. After screening by title, 290 records were selected for abstract screen, of which 122 were excluded based on inclusion/exclusion criteria. The included records were then combined and assessed for duplication. Forty-two duplicates were identified while full text of the remaining 126 records was retrieved for detailed evaluation. Fifteen studies were included in the final selection. Figure 1 summarizes the selection and attrition processes and details reasons for exclusions.

Of the 15 included studies, four (26.7%) included sites across multiple continents[19-22]. Six (40%) were conducted in Europe[23-28], two (13.3%) in the US[29,30], and one (6.7%) each in Mexico[31], Japan[32], and South Africa[33]. Nine (60%) studies included patients who were 18 years or older[22-28,30,31], three (20%) included patients who were at least 16 years[19,21,29], while the other three included patients who were at least 20 years[32], 14 years[33], and 13 years[20]. The minimum viral load for recruiting study participants was 500 copies/mL in one (6.7%) study[20], 1000 copies/mL in two (13.3%) studies[29,31], 2000 copies/mL in two (13.3%) studies[19,21], 5000 copies/mL in two (13.3%) studies[27,30], and 10,000 copies/mL in one (6.7%) study[28]. Seven (46.7%) studies did not recruit participants using a viral load criterion[22-26,32,33]. The lower limit of viral load detection was 50 copies/mL in 14 studies[19-32] and 400 copies/mL in one[33]. Three of the studies reported viral suppression based on both limits[22,30,31] while two reported viral suppression as the proportion of patients with viral load < 50 copies/mL, < 200 copies/mL, as well as < 400 copies/mL[19,21]. The PI-based HAART treatment group was ritonavir-boosted atazanavir in six studies[19,23,26,27,29,32], boosted lopinavir in four studies[24,26,31,33], and unboosted nelfinavir in two studies[22,28]. The remaining studies had boosted indinavir[25], boosted nelfinavir[20], unboosted atazanavir[21], or boosted fosamprenavir arms[30]. One study had three treatment arms comprising efavirenz, boosted atazanavir, and boosted lopinavir[26]. The NRTI backbone added to the treatments was tenofovir/emtricitabine in four studies[19,23,26,27], zidovudine/lamivudine in four studies[21,25,28,31], abacavir/lamivudine in three studies[24,30,32], didanosine/stavudine in one study[22], and zidovudine/didanosine in one study[33]. One study had four treatment arms where participants in the first two arms received abacavir/lamivudine plus either efavirenz or a PI and those in the other two arms received tenofovir/emtricitabine plus either efavirenz or a PI[29]. In another study, participants in two arms received didanosine/stavudine plus either efavirenz or a PI while another set of participants received zidovudine/stavudine plus either efavirenz or a PI[20].

The trial arms from the 15 selected studies totaled 6712 participants of which 1610 (24.0%) were female. Of the 6712 participants, 3339 were in the efavirenz arm and 3373 were in the PI arm. Follow-up ranged from 24 weeks to 144 weeks. Average and/or median age ranged from 33 years to 44 years. Average and/or median baseline CD4 counts ranged from 32 cells/mm^3 to 557 cells/mm^3 while average and/or median baseline viral load ranged from $\log_{10}$ 4.5 copies/mL to $\log_{10}$ 5.5 copies/mL (Table 1).

Risk of bias

Table 2 summarizes the quality assessment of the 15 studies included in the meta-analysis using the

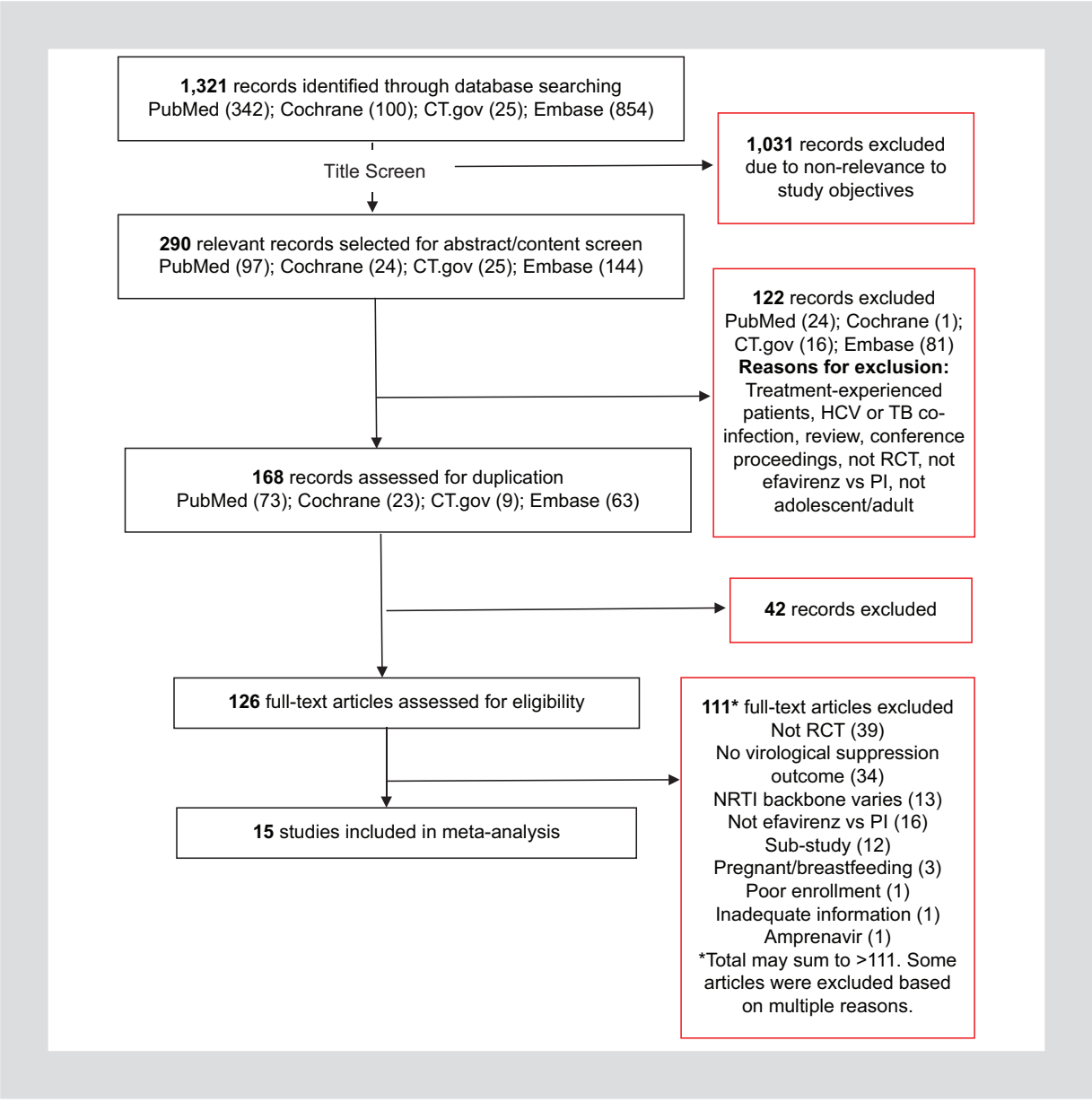

Figure 1. *Study attrition. CT.gov: Clinicaltrials.gov; HCV: hepatitis C virus; NRTI: nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; RCT: randomized clinical trial; TB: tuberculosis.*

Cochrane risk of bias tool. Regarding selection bias, eight studies provided adequate details on how study participants were randomized (computer generated list, permutated blocks, and minimization) and were determined to have low risk of bias due to random sequence generation[20-23,25,26,29,33]. The seven other studies stated that participants were randomized but did not provide details about how randomization was conducted[19,24,27,28,30-32]. These were categorized as unclear risk. Nine studies justified how allocation could have been concealed by reporting a centralized randomization process[20-23,25,26,29,31,33]. They were deemed to have low risk due to allocation concealment. Five studies did not provide details of allocation concealment and were deemed to have unclear risk[19,24,30,32]. One study was a single-center three-arm trial where patients were randomized in blocks of three[28]. This approach increases the risk of predicting which group patients would be allocated to, particularly the third patient in each block. Hence, this was determined to be high risk.

Two studies were double-blind trials[20,21]. These were categorized as low risk with respect to performance bias (participants and personnel) and unclear risk with respect to detection bias (assessors). Ten studies were open label[19,22,25,26,28,30-33]. These were classified as high risk for both performance and detection bias. For

Table 1. Characteristics of the 15 randomized controlled trials included in meta-analysis

Author, year	EFV arm (n)	PI arm (n)	NRTI backbone	Age (years) mean (SD)/median (IQR/range)	Female n (%)	CD4 count (cells/mm^3) mean (SD)/median (IQR/range)	Viral load (log^{10} copies/mL) mean (SD)/median (IQR/range)
Albini, 2012[23]	43	ATV/r (48)	TDF/FTC	43.7[a] (11·5)[b]	19 (20.9)	283.6[a] (119.5)[b]	4.6[a] (0.6)[b]
Daar, 2011[29]	465 464	ATV/r (463) ATV/r (465)	ABC/3TC, TDF/FTC	38.0[c] (31-45)[d]	322 (17.3)	230[c] (90-334)[d]	4.7[c] (4.3-5.0)[d]
Echeverria, 2010[24]	63	LPV/r (63)	ABC/3TC	38.0[a] (9.0)[b]	17 (13.5)	192[a] (NR)[b]	5.4[a] (NR)[b]
Honda, 2011[32]	36	ATV/r (35)	ABC/3TC	35.5[a] (NR)	0 (0.0)	223[c] (112-215)[e]	4.5[c] (2.8-5.4)[e]
Kumar, 2013[30]	50	FPV/r (51)	ABC/3TC	34.0[c] (18.0-79.0)[e]	32 (31.5)	(19-1,061)[e]	NR
Maggiolo, 2003[28]	34	NFV (34)	ZDV/3TC	38.3[a] (NR)	10 (14.7)	176[a] (NR)[b] (1-499)[e]	5.2[a] (NR)[b] (4.1-5.7)[e]
Miro, 2010[25]	34	IDV/r (31)	ZDV/3TC	43.0[c] (28.0-75.0)[e]	13 (20.0)	41[c] (26-67)[d]	5.5[c] (5.1-5.8)[d]
Miro, 2015[26]	29	ATV/r (30) LPV/r (30)	TDF/FTC	38.0[c] (22.0-69.0)[e]	16 (18.0)	32[c] (20-59)[d]	5.3[c] (4.8-5.7)[d]
Puls, 2010[19]	114	ATV/r (105)	TDF/FTC	36.6[a] (9.2)[b]	54 (4.7)	229[a] (115)[b]	4.7[a] (0.6)[b]
Ratsela, 2010[33]	888	LPV/r (883)	ZDV/ddI	35.4[a] (NR)	567 (32.0)	106[c] (NR)[d]	5.2[c] (NR)[d]
Robbins, 2003[20]	155 155	NFV/r (155) NFV/r (155)	ddI/d4T, ZDV/3TC	36.0[c] (30.0-42.0)[d]	118 (19.0)	280[c] (105-454)[d]	4.9[c] (4.3-5.5)[d]
Sierra-Madero, 2010[31]	95	LPV/r (94)	ZDV/3TC	35.0[c] (29.0-42.0)[d]	28 (14.8)	56[c] (25-117)[d]	NR
Squires, 2004[21]	401	ATV (404)	ZDV/3TC	33.0[c] (18.0-73.0)[e]	283 (35.0)	282[c] (64-1,424)[e]	4·9[c] (2.2-5.9)[e]
Yeni, 2006[22]	297	NFV (311)	ddI/d4T	38.6[a] (10.1)[b]	129 (21.2)	223[a] (176)[b]	4.9[a] (0.7)[b]
NCT02246998[27]	16	ATV/r (16)	TDF/FTC	35.0[a] (8.3)[b]	2 (3.0)	557[a] (198)[b]	NR

[a]Mean; [b]standard deviation (SD); [c]median; [d]interquartile range (IQR); [e]range.
3TC: lamivudine; ABC: abacavir; ATV: atazanavir; d4T: stavudine; ddI: didanosine; FPV: fosamprenavir; FTC: emtricitabine; IDV: indinavir; LPV: lopinavir; NFV: nefinavir; NRTI: nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; r: ritonavir; TDF: tenofovir; ZDV: zidovudine.

Table 2. Quality assessment summary table of studies included in meta-analysis

Author, year	Study name	Selection bias		Performance bias		Detection bias	Attrition bias	Reporting bias
		Random sequence generation[a]	Allocation concealment[a]	Blinding of participants[a]	Blinding of personnel[a]	Blinding of assessor[a]	Incomplete outcome data[a]	Selective reporting[a]
Albini 2012[23]	N/A	+	+	?	?	?	+	+
Daar 2011[29]	A5202	+	+	<	-	?	-	+
Echeverria 2010[24]	Lake study	?	?	?	?	?	-	+
Honda 2011[32]	N/A	?	?	-	-	-	+	+
Kumar 2013[30]	Support	?	?	-	-	-	-	+
Maggiolo 2003[28]	N/A	?	-	-	-	-	-	+
Miro 2010[25]	Advanz	+	+	-	-	-	-	+
Miro 2015[26]	Advanz-3	+	+	-	-	-	+	+
Puls 2010[19]	Altair study	?	?	-	-	-	+	+
Ratsela 2010[33]	Project Phidisa	+	+	-	-	-	+	+
Robbins 2003[20]	ACTG 384	+	+	+	+	?	-	+
Sierra-Madero 2010[31]	N/A	?	+	-	-	-	+	+
Squires 2004[21]	N/A	+	+	+	+	?	+	+
Yeni 2006[22]	Initio	+	+	-	-	-	-	+
NCT02246998[27]	N/A	?	?	-	-	-	+	+

[a]Key: low risk (+); moderate risk (<); high risk (-); unclear risk (?).

one study, the NRTI backbone was blinded to "everyone except the pharmacists"[29]. However, the main comparators, efavirenz and PI, were open label. It was categorized as moderate risk for personnel, high risk for participants, and unclear risk for detection bias. Two studies did not indicate if the trials were open label or blinded and were deemed to have unclear risk[23,24].

All studies reported patient disposition at end of study, which aided in assessing attrition bias. Studies were categorized as low risk if < 20% of patients had missing outcome data and high risk if more than 20% had missing outcome data. In eight studies, < 20% of participants withdrew consent, discontinued treatment, or were lost to follow-up[19,21,23,26,27,31-33]. In the other seven studies, attrition rate was over 25%[20,22,24,25,28-30].

Regarding reporting bias, six studies reported virological suppression as the primary outcome[21,22,24,28,31,32]. Eight studies reported virological suppression as a predefined secondary outcome[19,20,25-27,29,30,33] and one reported this outcome *post hoc*[23]. However, there was no evidence of selective reporting. The Egger test suggested the presence of publication bias (B = 0.927, standard error [SE] = 0.419, t = 2.214, p = 0.033).

Outcome – virological suppression

The calculated OR of virological suppression of efavirenz-based HAART regimens compared to PI-based HAART regimens ranged from 0.59 to 4.82 for the individual studies (Fig. 2). When the results were pooled, efavirenz was significantly more effective than PIs (coefficient = 0.314, SE = 0.118, p = 0.02). The odds of achieving virological suppression were 37% higher among those receiving efavirenz-based HAART compared to those receiving a PI-based HAART regimen (OR = 1.37, 95% confidence interval [CI] = 1.06-1.77). Tau square at rho = 0.70 was 0.091 and ranged between 0.089 and 0.092 when rho was varied from 0.0 to 1.0. In the analysis stratified by PI boosting, efavirenz was significantly more effective than boosted PIs (coefficient = 0.308, SE = 0.137, p = 0.046) (Fig. 3). The odds of achieving virological suppression were 36% higher among those receiving efavirenz-based HAART compared to those receiving a HAART regimen with boosted PI (OR = 1.36, 95% CI = 1.01-1.84). Tau square at rho = 0.70 was 0.086 and ranged between 0.082 and 0.088 when rho was varied from 0.0 to 1.0. On the other hand, there was no significant difference in virological suppression between those receiving either efavirenz-based HAART regimen or a HAART regimen with unboosted PI (coefficient = 0.402, SE = 0.319, OR = 1.49, 95% CI = 0.38-5.91, p = 0.046). In the analysis stratified by dosing frequency, seven and three studies, respectively, were identified that compared once a day and twice-daily efavirenz-PI pairs (Fig. 4). There was no significant difference between efavirenz- and PI-based HAART for once a day and twice-daily dosing frequency. For the sensitivity analysis, two studies were excluded because they compared efavirenz-PI pairs with either zidovudine/didanosine or didanosine/stavudine NRTI backbones[22,33] with two of four arms excluded from a third study[20]. The remaining 13 studies showed the results of the main analysis to be robust (coefficient = 0.376, SE = 0.167, p = 0.04) (Appendix 1). The odds of achieving virological suppression in the sensitivity analysis were 46% higher among those receiving efavirenz-based HAART compared to those receiving a PI-based HAART regimen (OR = 1.46, 95% CI = 1.01-2.10). Tau square at rho = 0.70 was 0.180 and ranged between 0.176 and 0.182 when rho was varied from 0.0 to 1.0.

Discussion

This study pooled the results of 15 randomized controlled trials comparing efavirenz- with PI-based HAART regimens in a meta-analysis using the robust variance estimation approach. In this meta-analysis, patients receiving efavirenz-based regimens had significantly higher odds of virological suppression compared to those receiving PI-based regimens (PIs) (OR = 1.37, 95% CI = 1.06-1.77, p = 0.02). This finding is similar to that of Chou et al. who compared NNRTIs (efavirenz or nevirapine) with PIs[15]. They found that patients who received NNRTI-based HAART had 60% higher odds of virological suppression. The present study differs in that the NNRTI under consideration is efavirenz only, multiple effect sizes were pooled per study, and most of the selected trials were more recent. Five of the trials pooled in the current study were also selected for inclusion in the meta-analysis by Chou et al. A more recent meta-analysis conducted by Borges et al. (2016), which had nine of 18 selected trials that were also included in the present study, found no significant difference between NNRTI- and PI-based regimens[17]. The risk ratio of virological suppression at week 48 for the nine common trials (i.e., those also included in the present study) ranged from 0.90-1.33 (NNRTI vs. PI). Three of the other trials selected by Borges et al. included patients treated with nevirapine and the risk ratio of virological suppression for these three trials ranged between 0.85 and 1.01. Hence, the poor effect of nevirapine on virological suppression contributed to reduce the effect size

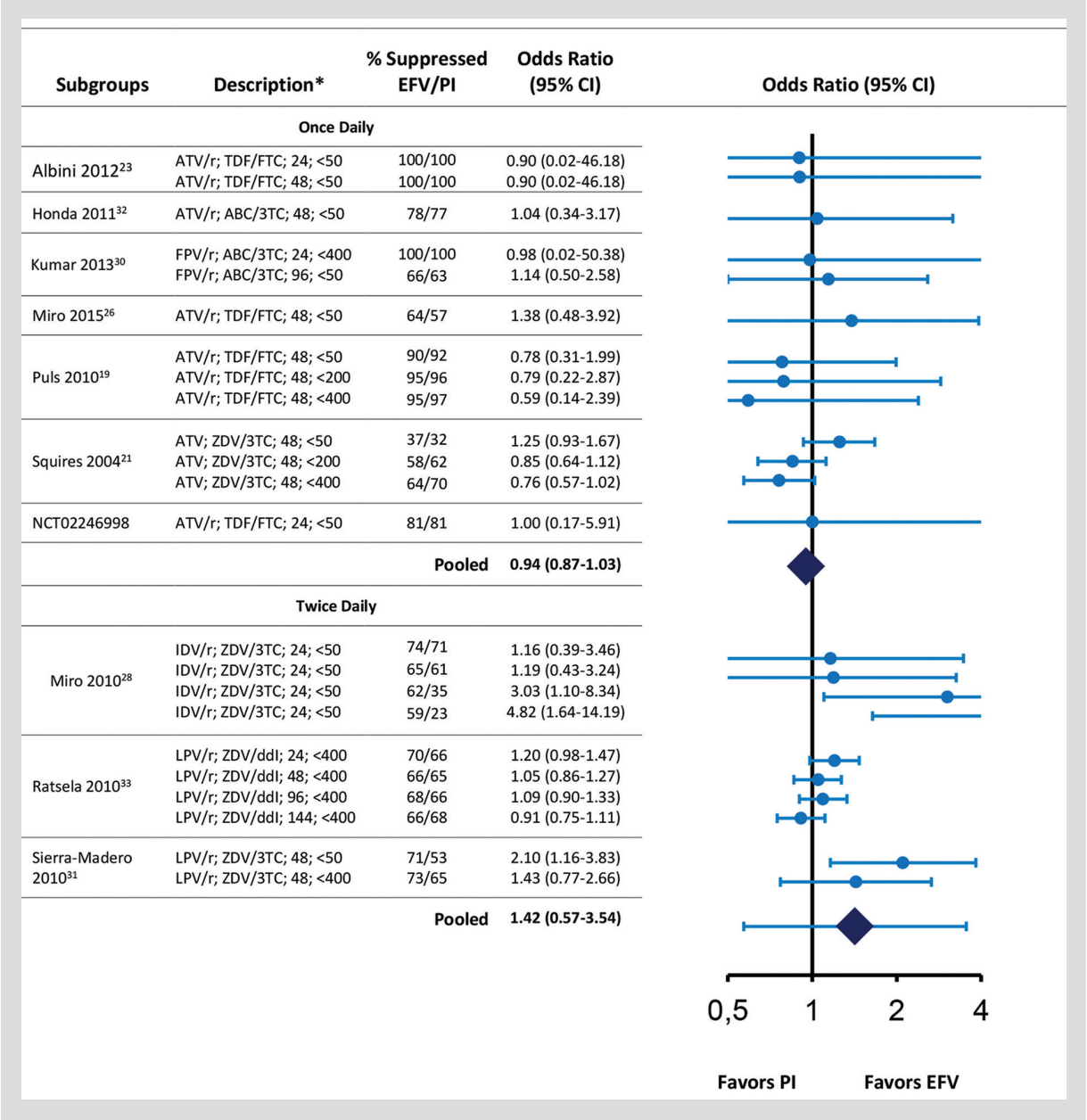

Figure 2. *Efficacy of efavirenz versus protease inhibitors on virological suppression.*
**PI; NRTI backbone; follow-up (weeks); viral load detection limit. 3TC: lamivudine; ABC: abacavir; ATV: atazanavir; d4T: stavudine; ddI: didanosine; FPV: fosamprenavir; FTC: emtricitabine; IDV: indinavir; LPV: lopinavir; NFV: nefinavir; NRTI: nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; r: ritonavir; TDF: tenofovir; ZDV: zidovudine.*

of the pooled results, thereby explaining why there was no significant difference between the NNRTI group and the PI group in their study.

Other meta-analyses compared NNRTI- and PI-based regimens through indirect meta-analyses and found PIs to be superior for virological suppression[15,16]. However, those studies included studies with two-drug regimens which were older and which ceased to be recommended after 1998; thus, the results are not comparable to the current study.

Our findings were robust even after limiting the meta-analysis to comparison arms with NRTI backbones of current clinical relevance[9] and stratifying by whether the PI was boosted with ritonavir. However, the lack of significance for unboosted PI may have been due to lack of power. Stratified analysis by dosing frequency also suggested that PIs may be equivalent to efavirenz with once-daily regimens. This may be related to improved adherence in both treatment arms resulting from reduced burden to patients[34]. Although

Subgroups	Description*	% Suppressed EFV/PI	Odds Ratio (95% CI)
Boosted Protease Inhibitor			
Albini 2012[23]	ATV/r; TDF/FTC; 24; <50	100/100	0.90 (0.02-46.18)
	ATV/r; TDF/FTC; 48; <50	100/100	0.90 (0.02-46.18)
Daar 2011[29]	ATV/r; ABC/3TC; 48; <50	87/78	1.89 (1.33-2.67)
	ATV/r; ABC/3TC; 96; <50	91/85	1.78 (1.19-2.68)
	ATV/r; TDF/FTC; 48; <50	90/84	1.71 (1.16-2.54)
	ATV/r; TDF/FTC; 96; <50	91/90	1.12 (0.72-1.74)
Echeverria 2010[24]	LPV/r; ABC/3TC; 48; <50	57/63	0.76 (0.37-1.56)
Honda 2011[32]	ATV/r; ABC/3TC; 48; <50	78/77	1.04 (0.34-3.17)
Kumar 2013[30]	FPV/r; ABC/3TC; 24; <400	100/100	0.98 (0.02-50.38)
	FPV/r; ABC/3TC; 96; <50	66/63	1.14 (0.50-2.58)
Miro 2010[28]	IDV/r; ZDV/3TC; 24; <50	74/71	1.16 (0.39-3.46)
	IDV/r; ZDV/3TC; 24; <50	65/61	1.19 (0.43-3.24)
	IDV/r; ZDV/3TC; 24; <50	62/35	3.03 (1.10-8.34)
	IDV/r; ZDV/3TC; 24; <50	59/23	4.82 (1.64-14.19)
Miro 2015[26]	ATV/r; TDF/FTC; 48; <50	64/57	1.38 (0.48-3.92)
	LPV/r; TDF/FTC; 48; <50	64/52	1.68 (0.59-4.78)
Puls 2010[19]	ATV/r; TDF/FTC; 48; <50	90/92	0.78 (0.31-1.99)
	ATV/r; TDF/FTC; 48; <200	95/96	0.79 (0.22-2.87)
	ATV/r; TDF/FTC; 48; <400	95/97	0.59 (0.14-2.39)
Ratsela 2010[33]	LPV/r; ZDV/ddI; 24; <400	70/66	1.20 (0.98-1.47)
	LPV/r; ZDV/ddI; 48; <400	66/65	1.05 (0.86-1.27)
	LPV/r; ZDV/ddI; 96; <400	68/66	1.09 (0.90-1.33)
	LPV/r; ZDV/ddI; 144; <400	66/68	0.91 (0.75-1.11)
Robbins 2003[20]	NFV/r; ddI/d4T; 24; <50		2.09 (1.22-3.60)
	NFV/r; ZDV/3TC; 24; <50		3.75 (1.82-7.73)
Sierra-Madero 2010[31]	LPV/r; ZDV/3TC; 48; <50	71/53	2.10 (1.16-3.83)
	LPV/r; ZDV/3TC; 48; <400	73/65	1.43 (0.77-2.66)
NCT02246998	ATV/r; TDF/FTC; 24; <50	81/81	1.00 (0.17-5.91)
		Pooled	1.36 (1.01-1.84)
Unboosted Protease Inhibitor			
Maggiolo 2003[28]	NFV; ZDV/3TC; 32; <50	79/50	3.72 (1.28-10.75)
	NFV; ZDV/3TC; 52; <50	77/40	3.42 (1.20-9.77)
Squires 2004[21]	ATV; ZDV/3TC; 48; <50	37/32	1.25 (0.93-1.67)
	ATV; ZDV/3TC; 48; <200	58/62	0.85 (0.64-1.12)
	ATV; ZDV/3TC; 48; <400	64/70	0.76 (0.57-1.02)
Yeni 2006[22]	NFV; ddI/d4T,24, <50		1.44 (1.05-1.99)
	NFV; ddI/d4T,48, <50		1.65 (1.19-2.28)
	NFV; ddI/d4T; 144, <50		1.64 (1.19-2.27)
	NFV; ddI/d4T; 144; <400		1.61 (1.02-2.53)
		Pooled	1.49 (0.38-5.91)

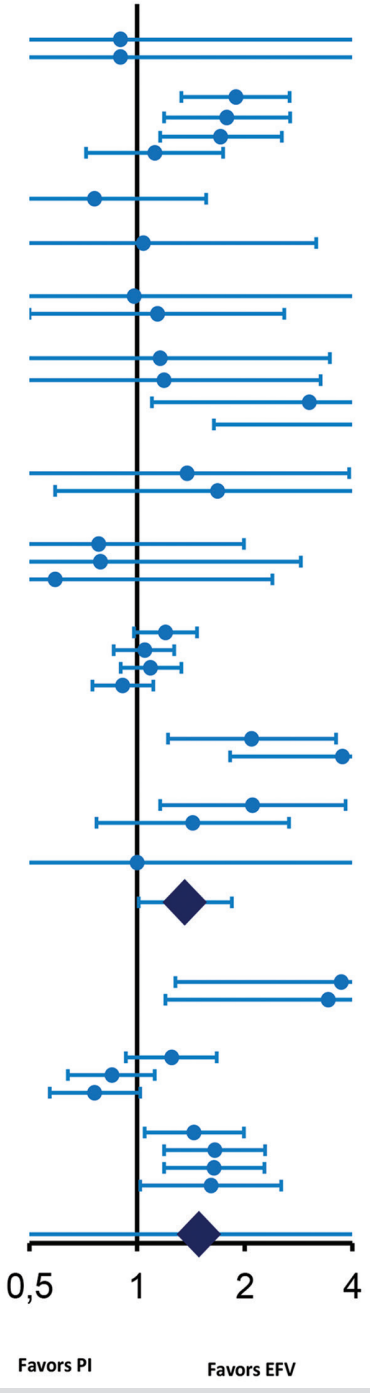

Figure 3. *Meta-Analysis of the Efavirenz versus Protease Inhibitors on Virological Suppression – Subgroup Analysis by Boosted or Unboosted Protease Inhibitor.*
**PI; NRTI backbone; follow-up (weeks); viral load detection limit. 3TC: lamivudine; ABC: abacavir; ATV: atazanavir; d4T: stavudine; ddI: didanosine; FPV: fosamprenavir; FTC: emtricitabine; IDV: indinavir; LPV: lopinavir; NFV: nefinavir; NRTI: nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; r: ritonavir; TDF: tenofovir; ZDV: zidovudine.*

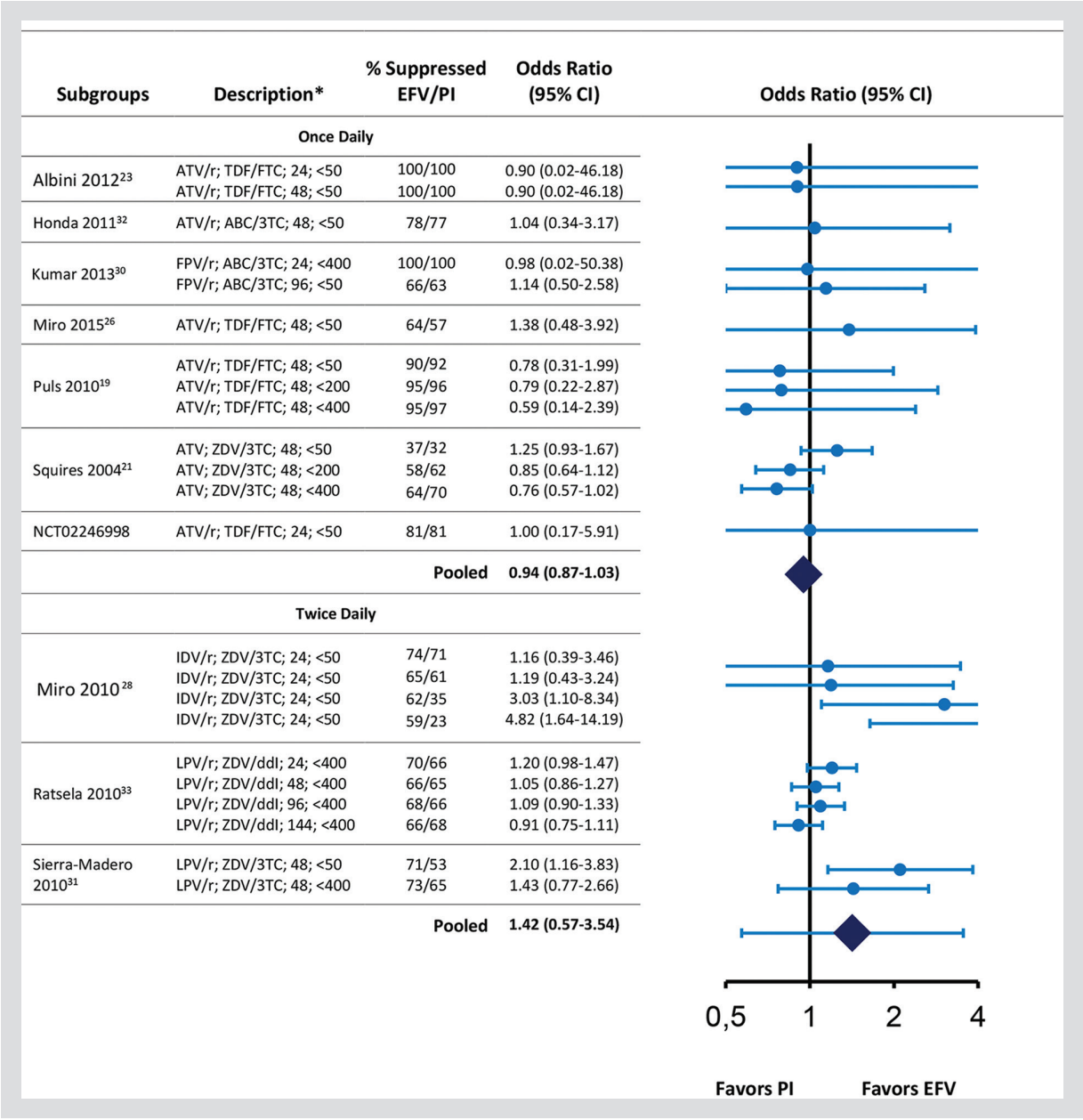

Figure 4. *Meta-Analysis of the Efavirenz versus Protease Inhibitors on Virological Suppression – Subgroup Analysis by Dosing Frequency. *PI; NRTI backbone; follow-up (weeks); viral load detection limit. 3TC: lamivudine; ABC: abacavir; ATV: atazanavir; d4T: stavudine; ddI: didanosine; FPV: fosamprenavir; FTC: emtricitabine; IDV: indinavir; LPV: lopinavir; NFV: nefinavir; NRTI: nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; r: ritonavir; TDF: tenofovir; ZDV: zidovudine.*

the analysis comparing efavirenz-PI arms with twice-daily regimen was not significant, it lacked sufficient power to allow for interpretation of the pooled results.

Quality of evidence

In this meta-analysis, 43% (7 of 15) of included trials had unclear or high level of risk regarding selection bias due to non-reporting of how randomization was conducted or allocation was concealed. In addition, 80% (12 of 15) of included trials were either open label or lacked information regarding blinding. Savovic et al. showed that inadequate or unclear sequence generation (ratio of OR [ROR] = 0.89, 95% credible interval [95% CrI] = 0.82-0.96), allocation concealment (ROR = 0.93, 95% CrI = 0.87-0.99), and blinding

(ROR = 0.87, 95% CrI = 0.79-0.96) are associated with 11%, 7%, and 13% exaggeration of intervention effects[35]. However, these exaggerations were non-significant for objective outcomes (sequence generation: ROR = 0.99, 95% CrI = 0.84-1.16; allocation concealment: ROR = 0.97, 95% CrI =0.85-1.10; and blinding: ROR = 0.93, 95% CrI = 0.73-1.18). In our study, the outcome of interest was virological suppression, which is measured by laboratory tests and may be considered an objective outcome. Hence, the effect of inadequacies in sequence generation, allocation concealment, and blinding on the current meta-analysis may be minimal.

Only 53% of included studies had drop-out rates < 20%, which was considered the cutoff below which attrition may not seriously affect outcomes[36]. Although analysis of data based on an intent-to-treat basis is recommended to address incomplete outcome data[18], this approach is not without issues. Considering that almost all studies reported intent-to-treat outcomes where missing data were considered failure, the high attrition rate is likely to underestimate the virological suppression outcome. This bias is especially problematic if attrition differs between treatment groups. One of the included studies reported differential attrition rate (PI vs. efavirenz = 60% vs. 23%). However, sample size was small (n = 65) and unlikely to have much impact on the pooled data.

All but one study specified virological suppression as a primary or secondary outcome. The last study reported virological suppression ***post hoc***. However, this report did not seem out of place as it was an interesting observation that patients in both treatment groups were 100% virologically suppressed. Hence, reporting bias does not pose a threat to the quality of the current meta-analysis.

One limitation of this study is that only one outcome, virological suppression, was assessed. Other outcomes have been assessed in other meta-analyses including CD4 count, AIDS diagnosis, and death. However, this is the first meta-analysis of antiretroviral therapy in treatment-naïve HIV patients to focus on efavirenz- and PI-based HAART regimens, making this study different from previous meta-analyses. Furthermore, although change in viral load as an outcome tends to overestimate clinical benefits in the long term[37], it is considered a reliable surrogate marker of clinical progression to AIDS and death, particularly in the short term[38]. The generalizability of our study results to women of child-bearing potential is limited as most of the included studies excluded pregnant or breastfeeding women, with at least three requiring the use of contraceptives to prevent pregnancy. This exclusion may likely have been due to concerns about the safety of efavirenz in pregnancy (category D). Bearing in mind that there are important limitations in the quality of evidence of the included studies, our results suggest that PIs may be less efficacious than efavirenz in scenarios where treatment assignment is known. Although there is currently a shift toward II-based HAART regimens for treatment initiation, efavirenz and PIs are still relevant in countries where treatment guidelines recommend them. At the time of this writing, no generic versions of IIs were available, which positions generic efavirenz and PI-based regimens as medications that are more accessible to low- and middle-income countries.

Attrition bias posed a threat to the quality of evidence. However, this was minimized by extracting data based on an intent-to-treat basis. Although the Egger test suggested the presence of publication bias, the test has not been validated for meta-analysis where there are multiple outcomes per study.

Conclusions

The use of the now preferred integrase-based HAART regimens may not always be feasible as they are often cost-prohibitive or unavailable in selected parts of the world or for selected populations. Guidelines still support the use of efavirenz or PIs as a base for HAART. This meta-analysis supports the use of efavirenz-based HAART regimens over PI-based HAART regimens in treatment-naïve adults and adolescents in settings where IIs are either cost-prohibitive or unavailable.

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Supplementary data

Supplementary data are available at AIDS Reviews online (http://www.aidsreviews.com/). These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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