Comparison of 48-Week Efficacies of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide and Nucleoside/Nucleotide Reverse Transcriptase Inhibitor-Sparing Regimens: A Systematic Review and Network Meta-Analysis

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48-WEEK EFFICACY OF ELVITEGRAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE RELATIVE TO NRTI-SPARING REGIMENS: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

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Abstract

BACKGROUND: Nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) based combination antiretroviral therapy (cART) are effective treatment regimens in HIV-1 infected adults but lifetime exposure is associated with safety issues, including renal and bone toxicity for tenofovir disoproxil fumarate (TDF) based regimens and potential cardiovascular risk for abacavir based regimens. Alternatives include NRTI-sparing combinations and new treatment options like tenofovir alafenamide (TAF)-based combinations that are associated with a more favorable renal and bone safety profile. However, no comparative data regarding efficacy is available for these alternative regimen. In this context, we performed a network meta-analysis (NMA) in order to provide estimates of relative efficacy between NRTI-sparing and TAF-based regimens.

METHODS: A systematic literature review (SLR) was performed to identify phase 3/4 randomized controlled clinical trials evaluating the efficacy of commonly used cART that include a NRTI backbone or NRTI-sparing regimen. A Bayesian random-effect model was used to compare virological suppression rates at 48 weeks for NRTI-free regimens compared to elvitegravir/cobistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF).

RESULTS: Twenty-three studies in treatment-naïve patients identified by the SLR were included in the NMA including four studies assessing NRTI-sparing regimens. In naïve patients, the probability of achieving virological suppression at 48 weeks was between 40% and 60% higher with ECFTAF compared to NRTI-sparing strategies. The difference was significant compared to RVR / r + RAL. In the subgroup of naïve patients with viral load < 100,000 copies/mL, no statistical difference was found between NRTI sparing treatments and E/C/F/TAF. Studies in treatment-experienced patients were too heterogeneous to allow for an NMA.

CONCLUSION: The NMA results suggest that E/C/F/TAF represents a more effective alternative than NRTI-sparing regimens in terms of 48-week efficacy in treatment-naïve patients. Furthermore, TAF pharmacological properties, as well as tolerability results in clinical studies suggest similar safety profile than NRTI-sparing regimens..Thus, TAF-based combination might represent a more appropriate alternative than NRTI sparing regimen with a favorable safety profile, while maintaining similar efficacy levels to currently used combination for initiation of cART.

Introduction

Combination antiretroviral therapy (cART) including two nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) associated with a third agent, is the currently recommended first-line treatment strategy for HIV-1 infected patients (1, 2). Third agents include Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI), boosted Protease Inhibitors (PI) and Integrase Inhibitors (INI). cART including the newest available drugs from the INI class (i.e dolutegravir (DTG), or cobicistat boosted-elvitegravir (EVG/COBI) achieve high levels of efficacy with up to 90% virological suppression at 48 weeks. Nevertheless, lifelong exposure to cART have been associated with severe drug-related toxicity including renal toxicity, bone fractures resulting from osteoporosis and increased cardiovascular risk. In particular, Tenofovir Disoproxil Fumarate (TDF), one of the most widely used NRTI has been associated with a significantly higher renal dysfunction risk as well as greater bone mineral density losses and higher risk of osteoporotic fractures than other antiretroviral therapies.(3-8) Similarly, Abacavir (ABC), another commonly used NRTI, has been found to be a risk factor for cardiovascular disease (CVD) although the association has proven inconsistent.(9) Therefore, NRTI-sparing regimens have gained a wide attention, since these combinations could avoid the NRTI-associated toxicity.

A number of studies assessing the efficacy and safety of NRTI-sparing regimens have been carried out (10-13). The NEAT001 study was a large randomized, open label, non-inferiority trial conducted in 805 treatment-naive adults. Included patients either received a standard cART containing Ritonavir-boosted Darunavir (DRV/r) associated with TDF and Emtricitabine (FTC) or a NRTI-sparing regimen combining DRV/r and raltegravir (RAL) (14). The study showed that the NRTI-sparing regimen had a higher proportion of failure at 96 weeks although the difference was not significant. Another study comparing the same regimen in 83 patients also showed that DRV/r + RAL had a significantly inferior efficacy at 48 weeks (12). Similarly, the GARDEL study compared Ritonavir-boosted Lopinavir (LPV/r) + TDF/FTC to LPV/r + RAL in 206 treatment-naive adults and showed a trend for lower efficacy of the NRTI-sparing regimen.(15) Thus, although NRTI-sparing regimens could be associated with reduced long-term toxicity, clinical studies suggest that they come with an efficacy trade-off.

In this setting, Tenofovir Alafenamide (TAF) is a promising alternative that might allow sparing cART toxicity while preserving its efficacy. TAF is a tenofovir (TFV) prodrug than can achieve higher intracellular concentrations of TFV-DP than those obtained with TDF, with much lower TFV exposure in plasma, reducing renal and bone toxicity risks. TAF-based cART has shown similar efficacy in treatment-naïve HIV-1 patients than TDF-based cART in several randomized studies with evidence of a more favourable renal and bone safety profile (16).

However, TAF-based cART which appears to have reduced renal and bone consequences in lifelong exposure with similar efficacy compared to TDF-based cART, has not been compared in head-to-head studies to alternative NRTI-sparing regimens. Thus, the objective of this study is to compare the efficacy of NRTI-sparing regimen with a TAF-based cART, elvitegravir/cobistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF), based on a systematic literature review and a Bayesian network meta-analysis (NMA).

Methods

Systematic Literature Review

Two separate literature reviews were performed. The first review identified randomized controlled trials (RCTs) evaluating the efficacy of currently recommended cART that include a NRTI backbone either FTC/TDF or ABC+lamivudine (3TC). The second review identified RCTs assessing the efficacy of NRTI-sparing regimens (IP/r monotherapies, dual therapies and NRTI-sparing integrase inhibitors based regimens).

PubMed/MEDLINE, Embase, and Cochrane databases were systematically searched (up to March 2016) to identify clinical studies of cART in HIV-1 patients. Terms and keywords used are presented in Supplementary Table 1. In addition, the 2013 through March 2016 conference proceedings for the following organizations were searched (where available) for relevant abstracts. Conferences included the International AIDS Conference, IAS Conference of HIV Pathogenesis and Treatment, Conference on Retroviruses and Opportunistic Infections, European AIDS Conference, HIV Drug Therapy, Interscience Conference of Antimicrobial Agents and Chemotherapy (ICAAC). The clinical trial registry (ClinicalTrials.gov) was hand-searched for unpublished trials and unpublished data to assess publication biases and identifying upcoming results.

Clinical studies were included if they met the predefined inclusion and exclusion criteria. For the NRTI-sparing regimens: RCTs performed in treatment-naïve or experienced adults infected with HIV-1, with or without progression to AIDS and reporting efficacy results expressed as proportion of patients virologically supressed was considered for the NMA. More restrictive criteria were applied for recommended NRTI-based regimens, further restricting the selection to studies with at least one study arm consisting in a regimen that contains either emtricitabine (FTC) and TDF, lamivudine (3TC) and ABC or FTC and TAF.

Initial screening for relevant studies was based on the abstract and title. Full-texts were re-screened to ensure their eligibility for inclusion in the systematic review. Relevant data from the studies included in the systematic literature reviews were extracted into a preformatted template and were independently verified. Extracted study outcomes included year of the first inclusion, virological suppression at 48 weeks defined as viral load <50 copies. Patients' characteristics including CD4 cell count and viral load at inclusion were extracted as well.

Network Meta-Analysis

The network meta-analysis methodology was implemented as per the NICE Decision Support Unit recommendations for Bayesian network meta-analysis (16). A logit model for the rate of virological suppression at 48 weeks was fitted to the data via Bayesian Markov Chain Monte Carlo (MCMC) methods (specifically Gibbs sampling) using WinBUGs, a valid and common approach for synthesizing clinical trial data(17).

Fixed and random-effect models were tested. Adjustment on mean CD4 cell count at inclusion and years of study initiation were also tested as these variables were considered as potential confounders for treatment efficacy. Indeed, both of these variables are associated with changes in treatment guidelines that may result in heterogeneity in patients inclusion and selection criteria. These include: viral load and CD4 cell count cut-offs for patient selection, screening for HLA-B*5701 allele to prevent risk of ABC hypersensitivity reaction (HSR) and definitions of virological response (<50 or <200 or <500 copies/mL depending on studies). Similarly, viral load at inclusion was considered for adjustment. However, given the large quantitative interaction with treatment differences seen in the NEAT001 study, a stratified analysis was deemed more appropriate.(14) Thus, a subgroup analysis was performed in patients with viral load <100,000 copies per mL at inclusion where DRV/r+RAL showed a very similar efficacy to DRV/r+TDF/FTC in the NEAT001 study(14). This analysis was based on the 48 weeks data from the NEAT001 study, obtained from the main investigator.

The most appropriate model was selected based on the Deviance Information Criterion (DIC) and total residual deviance. Quality of the model fit was based on visual inspection of convergence, absence of autocorrelations for posterior distribution means and variance, inspection of posterior densities (normal-shaped and unimodal) and Monte-Carlo error (<1% of the standard deviation of the posterior distribution). Consistency was assessed by comparing the posterior mean deviance of individual data points between the full model and an inconsistency model.(18)

Treatment effects were estimated as risk ratios (RR) of virological suppression at 48 weeks relative to E/C/F/TAF. Uncertainty around point estimates was measured using 95% confidence intervals (CI) that represent the given range within which the outcome estimate falls with a 95% probability. Credible intervals of RRs excluding 1 are considered, “statistically significant.”

Estimation was based on 70,000 replications after a discarded burn-in of 30,000.

Results

Literature review

Overall, a total of 1,282 unique records were found through the database and conference abstracts searching for recommended (with FTC/TDF or ABC/3TC backbone) treatment regimens. Based on title and abstract, 443 were selected for full text review and 350 publications, including 70 conference abstracts were finally included for data extraction. TDF/ABC-sparing treatment regimen literature research returned 228 unique results, of which 30 were selected based on title and abstract. 26 articles and conference abstracts/posters were extracted after full text selection. In total 117 unique RCTs were identified (Figure 1), 75 of which in the treatment-naïve population.

A total of 23 of the 75 RCTs in treatment-naïve patients identified by the systematic literature review (SLR) were included in the NMA including four studies assessing NRTI-sparing regimens. Main reasons for excluding a study from the NMA was a lack of reported outcomes at the time point of interest (i.e. 96 weeks instead of 48 weeks), specific study population (resource-limited settings or CCR5-tropic HIV-1), absence of a connected arm including comparison of different regimen formulations with equivalent daily dosing or arms consisting in mixed backbones or third agents (Table 1). Three of the four NRTI-sparing regimen studies included in the NMA compared a ritonavir-boosted PI (2 DRV/r, 1 LPV/r) + RAL to a corresponding recommended cART (PI/r + TDF/FTC or ABC/3TC). One study assessed LPV/r monotherapy versus LPV/r + TDF/FTC. Finally, only seven of the included studies presented results for patients with <100,000 copies per mL at inclusion. These studies were included in the <100,000 subgroup analysis.

Patient characteristics at baseline for each study are described in Table 1. Mean age was 36 (range: 33 - 44). All studies included mostly male participants (69% to 100%).Six studies included patients with median viral loads equal to or above 5.0 log 10 c/mL, median viral loads of patients in all other 19 other studies were lower. Baseline CD4 cell counts were ≥350 cells/mm3 in 7 and <200 in 3 studies, none of which included an NRTI-sparing regimen arm. Publication dates ranged from 2003 up to February 2015. A single study had fewer than 100 participants (Table 1).

Figure 2 presents the network of included studies. Bold lines show studies with results available in patients with viral load <100,000 copies/mL.

Study heterogeneity among treatment-experienced patients did not allow to build a network connecting E/C/F/TAF to NRTI-sparing regimens. In particular, most studies compared pursuing the current treatment regimen vs. switching to a new regimen. This was notably true for the RCT assessing the efficacy of E/C/F/TAF in experienced patients (GS-US-292-0109). Thus, performing a NMA in this population would have required to assume that “current regimen” arms were similar across trials, despite the fact that the reported treatments pursued by the patients and their distributions differed drastically.

Similarly, too few NRTI-sparing regimens studies reported additional outcomes such as change in CD4 cell count from baseline or all-cause discontinuation rates appropriately and in a comparable way. Therefore, it was not possible to build a network connecting E/C/F/TAF to NRTI-sparing regimens for this outcome.

Table 2 shows the Deviance Information Criterion (DIC) and total residual deviance obtained from the tested models. The Fixed-Effect (FE) and Random-Effect (RE) showed similar DIC. However, the RE model was associated with a lower total residual deviance of 50.9 compared to 54.6 for the FE for 54 data points. Adjusting on CD4 cell count at the baseline or on a year of first patient inclusion in the study did not improve the models as shown by higher DIC values compared to the RE model. These adjustments were thus discarded. Therefore, the RE model was chosen for the base case analysis. The model converged in a satisfactory manner: the model history trace plots showed good convergence, no autocorrelation was present and density plots showed that the posterior density functions of each parameter of interest were globally unimodal and symmetric. Finally, the size of the Monte Carlo (MC) error was less than 1% of the standard deviation of the posterior distribution for each parameter. The inconsistency model was run to look at inconsistency across the whole network and using as many studies as possible. The CLASS trial comparing fosamprenavir (FPV)/r to efavirenz (EFV) in combination with ABC/3TC led to different results between the consistent and inconsistent models, although its exclusion from the network did not produce significantly different results.

In patients with viral load <100,000 copies per mL, the RE showed better fitting than the FE. It was associated with lower total residual deviance (16.44 vs. 18.53) and almost identical DIC (106.0 vs. 105.9) (table 2). Similarly to the full population analysis, RE showed good convergence. Inconsistency could not be tested in the absence of “loops” in the network.

Mean relative risks (RR) of 48 weeks viral suppression and 95% confidence interval (95%CI) of recommended first-line treatments and NRTI-sparing regimens versus E/C/F/TAF are presented in Figure 3. A tendency for lower 48 weeks viral suppression rates compared to E/C/F/TAF (mean RR <1) was shown for all treatments with the exception of DTG+ABC/3TC that showed similar efficacy. However, only DRV/r + RAL regimen was associated with a significantly inferior efficacy. Similar efficacy results versus E/C/F/TAF were obtained with DRV/r + RAL for the <100,000 subgroup with mean RR comparable for the full population analysis but because of large 95%CI no treatment was associated with significant efficacy differences.

Discussion

Overall our network meta-analysis from a systematic literature review shows that NRTI-sparing regimens are associated with a lower risk ratio of virological suppression at 48 weeks compared to E/C/F/TAF in treatment-naïve adult patients ans this difference was significant in one specific study (NEAT001). These results are consistent with findings of clinical studies assessing TAF-based and NRTI-sparing regimens. E/C/F/TAF was found comparable to other recommended TDF-or- ABC-based regimens (16, 19), while NRTI-sparing regimens were associated with a trend for lower efficacy in most clinical trials compared to other recommended TDF/ABC-based regimens(8, 11, 13, 14, 20, 21). Results in patients with viral load inferior to 100,000 copies/mL are coherent with the full analysis and show similar mean RR with non-significant differences, likely due to the smaller number of studies that increases the uncertainty and the corresponding CI.

Lastly, the feasibility of performing NMA for treatment-experienced patients or for other endpoints than virological response at week 48 was assessed. Although, this population might be the most concerned by NRTI-sparing regimens considering their exposure to NRTI-toxicity that might lead practitioners to consider a treatment simplification, studies in this population were too heterogeneous in terms of reported outcomes and overall methodology to build a network and perform a NMA in these patients.

Our results indicate that E/C/F/TAF represents a more effective alternative than NRTI-sparing regimens and particularly DRV/r+RAL as it is associated with a significantly better viral suppression rate at 48 weeks. Furthermore, TAF pharmacological properties, as well as clinical studies of E/C/F/TAF suggest much lower long-term toxicity issues than TDF-based regimens. In treatment-naïve patients, E/C/F/TAF was shown to lead to smaller reductions in estimated glomerular filtration rate and more favourable changes in proteinuria and tubular biomarkers than a TDF-based equivalent treatment. Specific markers of proximal renal tubular dysfunction significantly favoured the TAF over the TDF group.(16) The same study showed that TAF-based regimen resulted in significantly smaller reductions in bone mineral density at both the hip and the lumbar spine. In the NEAT study, the safety profile has been reported during 96 weeks of therapy (22). The decrease of bone mineral density among patients treated with TAF at the hip (-0.67%) and spine (-0,96%) (16) were similar to those seen with DRV/r+RAL (-1,57%) and -0,43% respectively (14)), and no differences in term of renal outcome..

Currently, numerous trials evaluated 2-drug regimens to reduce toxicities, both in treatment naive or pretreated patients (15, 23-33). The benefit of an NRTI-sparing regimen regarding E/C/F/TAF must be balanced against potential detriments: disrupting single-tablet regimen increasing the number of pills and drug intakes (34), changes in lipid parameters that may necessitate additional monitoring or treatment, persistence of viral replication in reservoir sites such as the central nervous system (CNS) (24, 35), absence of activity against HBV. It is therefore advisable to encourage comparative clinical trials between E/C/F/TAF and 2-drug regimens, especially NRTI-sparing regimen.

Our analysis presents some limitations, generally due to the lack of appropriate and sufficient data. First, it was not possible to perform the NMA for virological suppression on a longer time horizon than 48 weeks. Furthermore, our analysis does not allow the comparison of treatment-effects relatively to other important outcomes: resistance rate, CD4 cell count increase and tolerance outcomes were not reported consistently enough. Second, E/C/F/TAF being the only TAF-based regimen assessed in clinical studies in the naïve patients population, it was not possible to assess other TAF-based regimen or to compare NRTI-sparing regimens independently of the third agent. However, DRV/r+RAL, an NRTI-sparing regimen studied in our network is based on a commonly used INI with non-inferior-efficacy compared to EVG/COBI (16, 36, 37) Also, the subgroup analysis performed in patients with a viral load <100,000 c/mL at inclusion is based on a limited number of studies, limiting the significance and interpretation of our results, although they are coherent with findings of Raffi *et al.* 2014, suggesting an interest for NRTI-sparing regimens in patients initiating treatment with low viral load levels(14). At last our network metaanalysis was unable to perform in treatment-experienced patients due to study heterogeneity, reinforcing the value of having new clinical trial data.

In conclusion, our systematic literature review and network meta-analysis suggest that E/C/F/TAF regimen has high rates of virological suppression in HIV-1 naïve patients through 48 weeks of therapy compared to NRTI-sparing regimens. The safety profile of E/C/F/TAF seems at least equivalent to NRTI-sparing regimens in term of renal and bone toxicity. Thus, recourse to TAF based cART regimens may decrease interest of NRTI-sparing regimen in first line therapies.

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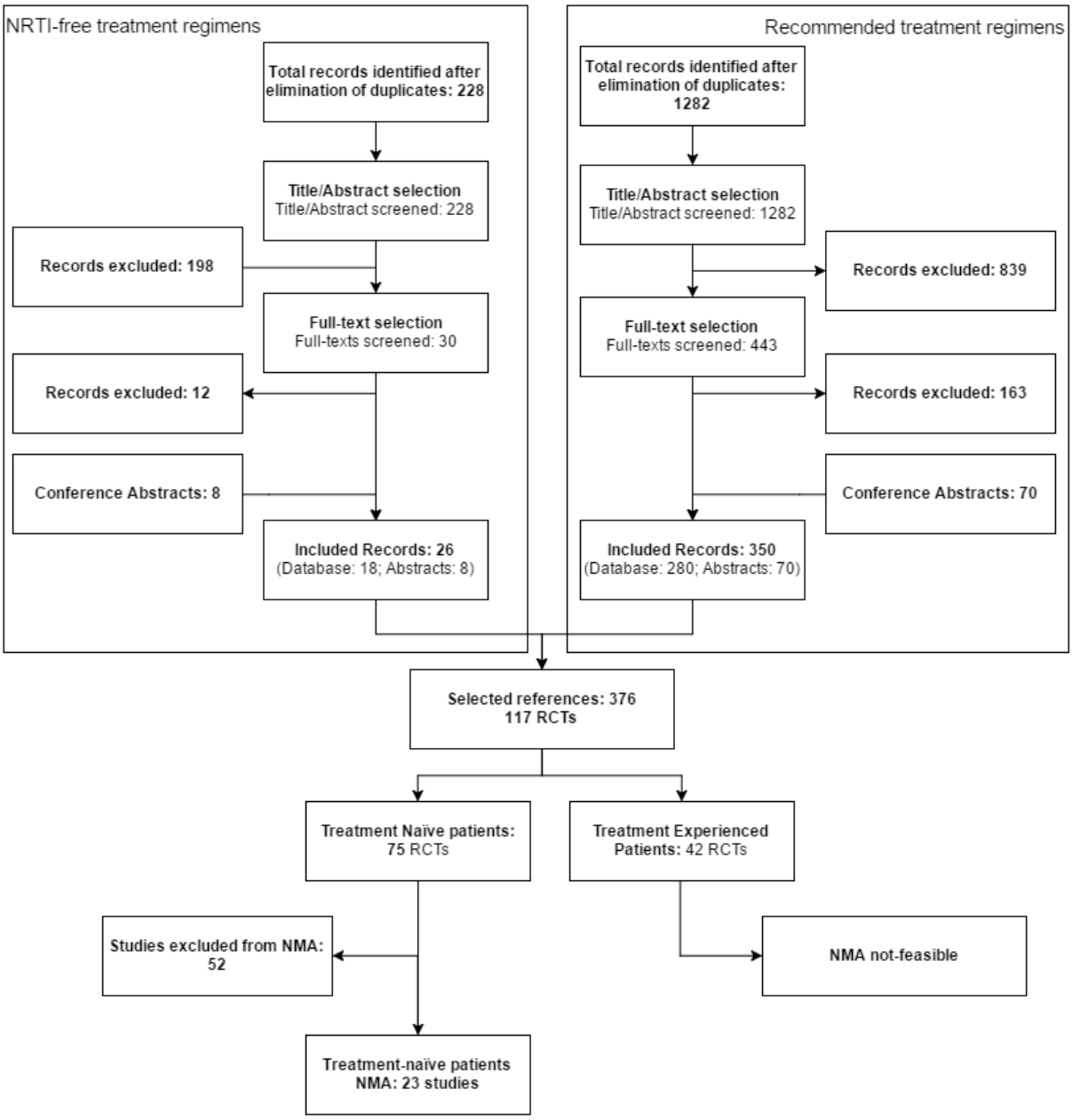

Figure 1 Flow Chart of included studies

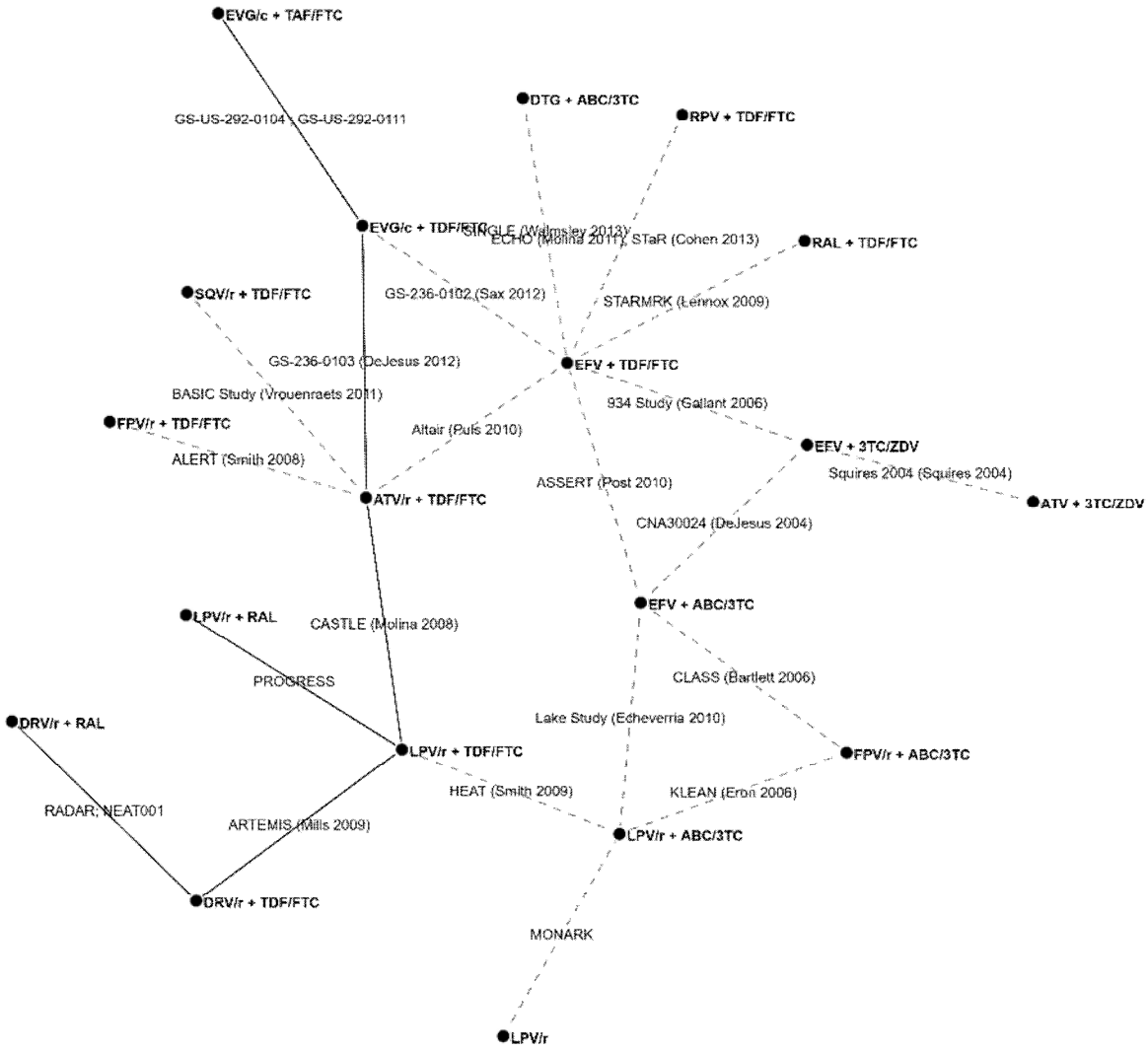

Figure 2 Study Network for 48 weeks viral suppression rate included in the NMA

Bold lines: network in patients with viral load <100,000 copies/mL

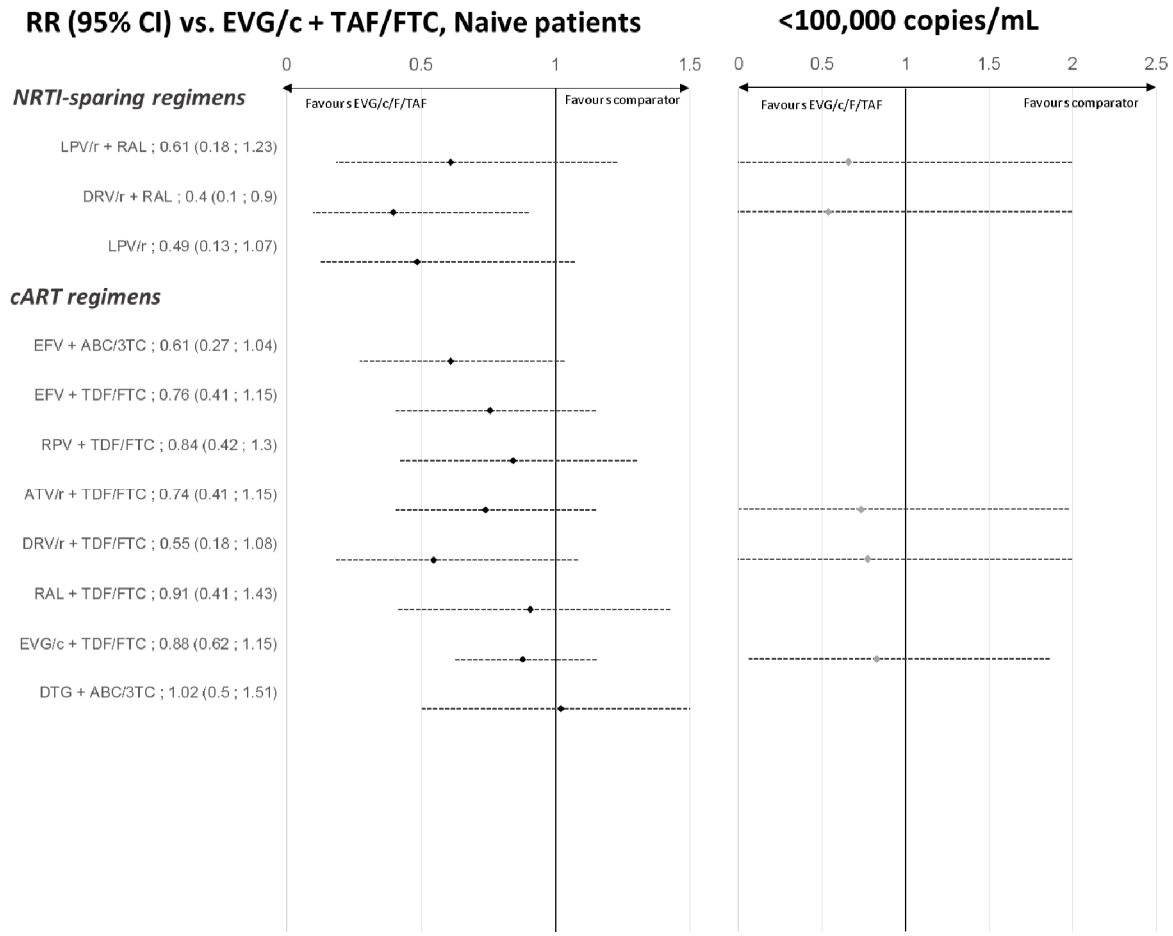

Figure 3 Relative Risk (RR) and 95% confidence intervals of 48 weeks virological suppression versus EVG/c+TAF/TDF in naïve patients (Gray points: <100,000 subgroup)

NRTI: Nucleoside/nucleotide reverse transcriptase inhibitors; cART: combination antiretroviral therapy; LPV/r: Ritonavir-boosted lopinavir; DRV/r: Ritonavir-boosted Darunavir; EVF: Efavirenz; ABC: Abacavir; 3TC: Lamivudine; TDF: Tenofovir disoproxil fumarate; FTC: Emtricitabin; ATV/r: Ritonavir-boosted atazanavir; RAL: Raltegravir; RPV: Rilpivirine; EVG/c: Cobicistat-boosted elvitegravir; DTG: DOlutegravir; TAF: Tenofovir alafenamide

Table 1 Studies and study results included in the NMA

Study Name	Year (first inclusion)	Treatments	N ° subjects	Age	% Men	Median CD4 (cells/mm3)	Median VL (log 10 c/mL)	Virological suppression rate at 48 wks (all patients)	Virological suppression rate at 48 wks patients with VL (<100,000c/mL)
GS-US-292-0111 (Sax 2015)(16)	2013	EVG/c + TAF/FTC	431	35	86%	414	4.5	92%	93%
		EVG/c + TDF/FTC	435	36	84%	431	4.5	89%	88%
GS-US-292-0104 (Sax 2015)(16)	2012	EVG/c + TAF/FTC	435	35	84%	437	4.6	93%	95%
		EVG/c + TDF/FTC	432	36	87%	426	4.6	92%	93%
GS-236-0102 (Sax 2012)(37)	2011	EFV + TDF/FTC	352	38	90%	382	4.8	84%	NR
		EVG/c + TDF/FTC	348	38	88%	391	4.7	88%	NR
GS-236-0103 (DeJesus 2012)(38)	2011	EVG/c + TDF/FTC	353	38	92%	351	4.8	90%	93%
		ATV/r + TDF/FTC	355	39	89%	366	4.8	87%	85%
SINGLE (Walmsley 2013)(39)	2011	DTG + ABC/3TC	414	36	84%	334.5	4.7	88%	NR
		EFV + TDF/FTC	419	35	85%	339	4.7	81%	NR
NEAT001(14)	2010	DRV/r + RAL	401	37	88%	340	4.8	89%	88%
		DRV/r + TDF/FTC	404	39	89%	325	4.8	91%	92%
RADAR(12)	2009	DRV/r + RAL	40	44	90%	249	4.7	62%	77%
		DRV/r + TDF/FTC	43	39	95%	201	4.9	84%	96%
ECHO (Molina 2011)(40)	2008	EFV + TDF/FTC	344	36	80%	257	5	82%	NR
		RPV + TDF/FTC	346	36	77%	240	5	82%	NR
PROGRESS(13)	2008	LPV/r + RAL	101	40	87%	289	4.2	83%	88%
		LPV/r + TDF/FTC	105	39	82%	297	4.3	85%	92%

Altair (Puls 2010)(41)	2007	ATV/r + TDF/FTC	105	37	71%	235	4.8	89%	NR
		EFV + TDF/FTC	114	37	79%	227	4.7	85%	NR
ASSERT (Post 2010)(42)	2007	EFV + ABC/3TC	192	38	83%	240	5	59%	NR
		EFV + TDF/FTC	193	36	80%	230	5.1	71%	NR
BASIC Study (Vrouenraets 2011) (43)	2006	ATV/r + TDF/FTC	61	38	87%	249	4.8	79%	NR
		SQV/r + TDF/FTC	57	39	82%	234	4.7	75%	NR
STARMRK (Lennox 2009)(44)	2006	EFV + TDF/FTC	282	37	82%	217.4	5	82%	NR
		RAL + TDF/FTC	281	38	81%	218.9	5	86%	NR
ALERT (Smith 2008)(45)	2005	ATV/r + TDF/FTC	53	40	89%	188	4.9	83%	NR
		FPV/r + TDF/FTC	53	40	79%	161	4.9	75%	NR
ARTEMIS (Mills 2009)(46)	2005	DRV/r + TDF/FTC	346	35	70%	218	4.8	80%	86%
		LPV/r + TDF/FTC	343	36	70%	228	4.9	84%	85%
CASTLE (Molina 2008)(47)	2005	ATV/r + TDF/FTC	440	34	69%	205	5	78%	82%
		LPV/r + TDF/FTC	443	36	69%	204	5	76%	81%
HEAT (Smith 2009)(48)	2005	LPV/r + ABC/3TC	343	38	84%	214	4.9	63%	NR
		LPV/r + TDF/FTC	345	38	80%	193	4.8	61%	NR
Lake Study (Echeverria 2010)(49)	2005	EFV + ABC/3TC	63	39	86%	193	5.4	57%	NR
		LPV/r + ABC/3TC	63	37	87%	191	5.3	63%	NR
KLEAN (Eron 2006)(50)	2004	FPV/r + ABC/3TC	444	37	78%	194	5.1	65%	NR
		LPV/r + ABC/3TC	434	38	78%	188	5.1	66%	NR
MONARK(11)	2003	LPV/r	83	37	71%	244	4.4	67%	NR
		LPV/r + ABC/3TC	53	35	57%	233	4.3	75%	NR
Squires 2004(51)	2001	ATV + 3TC/ZDV	404	33	64%	286	4.9	32%	NR

		EFV + 3TC/ZDV	401	33	66%	280	4.9	37%	NR
STaR (Cohen 2013)(52)	2001	EFV + TDF/FTC	392	35	93%	385	4.8	82%	NR
		RPV + TDF/FTC	394	37	93%	396	4.8	86%	NR
934 Study (Gallant 2006)(53)	2000	EFV + 3TC/ZDV	254	38	87%	241	5	68%	NR
		EFV + TDF/FTC	255	38	86%	233	5	77%	NR
CLASS (Bartlett 2006)(54)	2000	EFV + ABC/3TC	97	37	82%	307	4.9	75%	NR
		FPV/r + ABC/3TC	96	36	86%	306	4.9	59%	NR
CNA30024 (DeJesus 2004)(55)	1999	EFV + 3TC/ZDV	325	35	82%	258	4.8	69%	NR
		EFV + ABC/3TC	324	35	80%	267	4.8	70%	NR

Table 2 Model fit statistics

Model	DIC	Total Res. Dev.
Fixed-Effect (FE)	364.0	54.6
Random-Effect (RE)	364.0	50.2
RE adjusted on CD4 count	365.1	50.9
RE adjusted on year	364.2	51.0
FE <100,000 copies	106.0	18.5
RE <100,000 copies	105.9	16.4

DIC : Deviance information criterion, RE : Random Effect, FE : Fixed effect. Total Res. Dev.: Total Residual Deviance. DIC and Total Residual Deviance are smaller in patients with < 100,000 copies due to the smaller number of studies with results available in this population.

Supplementary Table: Search strategies PubMed/MEDLINE

Term group	Query	Search Terms	Tags
Disease	#1	HIV Infection	MESH
	#2	HIV	MESH
	#3	Sexually Transmitted Disease, Viral	MESH,NoExp
	#4	HIV	TIAB
	#5	HIV-1*	TIAB
	#6	HIV-2*	TIAB
	#7	HIV1	TIAB
	#8	HIV2	TIAB
	#9	HIV infect*	TIAB
	#10	Human Immunodeficiency Virus	TIAB
	#11	Human Immunedeficiency Virus	TIAB
	#12	Human Immuno-deficiency Virus	TIAB
	#13	Human Immune-deficiency Virus	TIAB
	#14	Acquired Immunodeficiency Syndrome	TIAB
	#15	Acquired Immunedeficiency Syndrome	TIAB
	#16	Acquired Immuno deficiency Syndrome	TIAB
	#17	Acquired Immune deficiency Syndrome	TIAB
	#18	AIDS	TIAB
	#19	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18	
cART regimens	#20	truvada* OR "TDF/FTC" OR "FTC/TDF"	TIAB
	#21	tenofovir OR viread* OR TDF OR TAF	TIAB
	#22	emtricitabine OR emtriva* OR coviracil OR FTC	TIAB
	#23	#21 AND #22	
	#24	#20 OR #23	
	#25	kivexa* OR epzicom* OR "ABC/3TC" OR "3TC/ABC"	TIAB
	#26	lamivudine OR epivir* OR heptodin* OR heptovir* OR inhavir* OR ladiwin* OR lamidac* OR lamivir* OR zeffix* OR zefix* OR 3TC	TIAB
	#27	abacavir OR ziagen* OR filabac* OR zepril* OR ABC	TIAB
	#28	#26 AND #27	
	#29	#25 OR #28	
	#30	#24 OR #29	

RCT	#31	Randomized Controlled Trial	Publication Type
	#32	"Randomized control trial"	All fields
	#33	Clinical Trials, phase III as topic	MESH
	#34	"Phase 3"	All fields
	#35	"Phase III"	All fields
	#36	#31 OR #32 OR #33 OR #34 OR #35	
	#37	Clinical Trial	Publication type
	#38	Clinical Trials as Topic	MESH
	#39	Clinical Trial	All fields
	#40	#37 OR #38 OR #39	
	#41	Phase AND 3	All fields
	#42	#40 AND #41	
	#43	#36 AND #42	
Adults	#44	Adult*	TIAB
	#45	Adult	MESH
	#46	#44 OR #45	
NRTI-sparing regimens	#47	Protease Inhibitors OR Protease Antagonists OR Peptidase Inhibitors	All Fields
	#48	Saquinivir OR Invirase* Indinavir OR Crixivan*	All Fields
	#49	Nelfinavir OR Viracept*	All Fields
	#50	Amprenavir OR Fosamprenavir OR Agenerase* OR Lexiva*	All Fields
	#51	Lopinavir OR Kaletra*	All Fields
	#52	Atazanavir OR Reyataz*	All Fields
	#53	Darunavir OR Prezista*	All Fields
	#54	#47 OR #48 OR #49 OR #50 OR #51 OR #52 or #53	
	#55	monotherapy OR "mono therapy" OR mono-therapy	All Fields
	#56	"dual therapy" OR dual-therapy OR bitherapy OR bi-therapy	All Fields
	#57	#55 OR #56	
	#58	#54 AND #57	
	#59	Integrase inhibitors	All Fields
	#60	Raltegravir OR Isentress*	All Fields
	#61	Dolutegravir OR Tivicay*	All Fields

	#62	Elvitegravir OR Vitekta*	All Fields
	#63	#59 OR #60 OR #61 OR #62	All Fields
	#64	#58 OR #63	
RCT cART regimens	**#65**	**#19 AND #30 AND #46 AND #30**	
RCT NRTI sparing regimens	**#66**	**#19 AND #30 AND #46 AND #64**	