NETWORK META-ANALYSIS OF POSTEXPOSURE PROPHYLAXIS RANDOMIZED CLINICAL TRIALS.

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Short title: PEP randomized clinical trials

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Abstract

Objective: We performed a network meta-analysis of PEP randomized clinical trials to evaluate the best regimen.

Methods: After MEDLINE/Pubmed search, studies were included if: 1) were randomized, 2) comparing at least 2 PEP three-drug regimens and, 3) reported completion rates or discontinuation at 28 days. Five studies with 1105 PEP initiations were included and compared ritonavir-boosted lopinavir (LPV/r) versus [1 atazanavir (ATV), 1 cobicistat-boosted elvitegravir (EVG/c), 1 raltegravir (RAL), or 2 maraviroc (MVC)]. We estimated the probability of each treatment of being the best based on the evaluation of 5 outcomes: PEP non-completion at day 28, PEP discontinuation due to adverse events, PEP switching due to any cause, lost to follow-up and adverse events.

Results: Participants were mostly men who have sex with men (n=832, 75%) with non-occupational exposure to HIV (89.86%). Four-hundred fifty-four (41%) participants failed to complete their PEP course for any reason. The Odds Ratio (OR) for PEP non-completion at day 28 in each antiretroviral compared to LPV/r was: ATV 0.95 (95% CI 0.58-1.56; EVG/c: OR 0.65 95% CI 0.30-1.37; RAL: OR 0.68 95% CI 0.41-1.13; and MVC: OR 0.69 95% CI 0.47-1.01. In addition, the rankogram showed that EVG/c had the highest probability of being the best treatment for the lowest rates in PEP non-completion at day 28, switching, lost to follow-up or adverse events and MVC for PEP discontinuations due to adverse events.

Conclusion: Our study shows the advantages of integrase inhibitors when used as PEP, particularly EVG as a Single-Tablet Regimen.

Keywords: PEP, integrase inhibitors, completion, HIV.

Introduction

Post-exposure prophylaxis (PEP) is a well-known prevention strategy for people who have had a potential risk exposure to HIV. PEP generally consists of a combination of 3 antiretroviral drugs for 28 days. To maximize the desired preventive effect, PEP compliance seems essential. Toxicity and/or side effects leading to frequent drop-outs and lost to follow-up have been frequently described during this type of treatment. Higher rates of antiretroviral toxicity and discontinuation have been reported as a result of use of PEP regimens when compared with people living with HIV (PLWH) receiving treatment with the same antiretroviral combination. Due to ethical constrains and sample size, PEP efficacy studies cannot be performed, therefore its prescription is based on data of animal studies(1), retrospective analysis of occupational PEP(2) and on prophylaxis of maternal-fetal transmission(3).

Previous PEP regimens consisted on zidovudine (ZDV)/lamivudine (3TC) as the backbone and a third drug preferably a protease inhibitor (PI). Since tolerability was an issue with these nucleoside reverse transcriptase inhibitors (NRTI), more recent PEP combinations are based on a backbone including tenofovir (TDF)/emtricitabine (FTC). Until very recently the third recommended antiretroviral drug was ritonavir-boosted lopinavir (LPV/r) or atazanavir (ATZ/r)(4) with poor rates of PEP completion. Some studies have been conducted in the last decade searching for better tolerated regimens. Cohort single arm studies using as third drug an integrase inhibitor (INSTI)(5), the entry inhibitor Maraviroc(6), or no-nucleoside transcriptase inhibitor (NNRTI) rilpivirine(7) as third drug have been reported suggesting that these alternative regimens have better completion outcomes than PI. Updated guidelines (based on expert opinion) now recommend integrase inhibitors as first line (eg UK:- Raltegravir, USA:- Raltegravir or Dolutegravir), with boosted PIs as alternatives (8, 9).

Few randomized studies have been conducted searching for better tolerated regimens as a priority (10-14). It is not known which is the best tolerated regimen and, therefore, the recommendations of guidelines are mainly based on expert opinions (15). To evaluate which PEP regimen has the best completion rate, we performed a network meta-analysis (NMA) of 5 randomized clinical trials (RCT) comparing different PEP regimens reporting completion outcomes on 1105 PEP initiations (10-14).

Methods

We performed a systematic search (September 2019) MEDLINE/Pubmed applying the terms “HIV” AND/OR “PEP” AND/OR “post exposure prophylaxis” AND/OR “post-exposure prophylaxis” AND “randomized”. The searches were limited to English

language articles. In addition, we searched www.clinicaltrials.gov for ongoing studies. Reference lists of included studies were evaluated by the investigators to identify additional relevant studies. Studies included were all: randomized controlled studies, comparing at least 2 PEP three-drug regimens in adults and with reports on completion rates or discontinuation at 28 days follow up visit. We excluded any study that was not randomized, that compared PEP with one or two-drug regimens, that studied population were newborns or minors, had inadequate data, had duplication of data, or was available only in abstract form.

Data were extracted and verified following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines(16). Available baseline characteristics were collected and evaluated to ensure similar distribution of potencial effect modifiers. Outcome data for completion rates at 28-day, treatment discontinuation, switching, lost to follow-up and total of adverse events were collected. We accepted each study definitions for adverse events, but the different definitions of adverse events allow the comparability. Following rigorous examination, we identified 6 RCT candidates to include in the NMA. Neverthless, to meet the transitivity assumption, in the main study we excluded one trial that compared darunavir (DRV/r) vs LPV/r (17) because subjects were stratified by type of event (occupational vs. nonoccupational) and there were significantly more occupational exposures (21%) than in the other 5 trials which included manly non-occupational exposures (10-14). We assumed that the threshold of tolerance and/or risk perception of health workers and MSM exposed by sexual contact could be significantly different and, consequently, the possibility of abandoning the treatment or study may be intrinsically different between those two groups. Starting from there, we determined that it would be valid to exclude that sixth study. Three out of the 5 selected RCT compared previous standard of care (SOC) ritonavir-boosted lopinavir (LPV/r) versus a different antiretroviral (ARV) in each trial: atazanavir (ATV)(10), cobicistat-boosted elvitegravir (ELV/c) and raltegravir (RAL), and versus maraviroc (MVC) in 2 RCT. In any case, taken in account the limitations of including a study with some selection bias and despite the stratification by exposure type, we decided to perform a subanalysis including the 6 studies DRV/r is now considered the first line and best tolerated PI.

Statistical Analysis

Odds ratios (OR) with 95% confidence intervals (95% CIs) were used as a measure of the association between the treatment and each outcome: PEP non-completion at day 28, switching, lost to follow-up or adverse events and PEP discontinuation due to adverse events. ORs <1 correspond to beneficial treatment effects of the first drug relative to the second one (the comparator). Since only for comparisons that involved MVC there were more than one RCT, only the OR for MVC relative to LPV/r is a pooled

estimate. For each outcomes, the network graph, treatment rankings and relative probabilities of superiority were reported. The network graph represents a network of treatments using nodes and edges. Nodes represent the competing treatment and edges represent the available direct comparisons between pairs of treatments. Both nodes and edges were weighted according to the number of studies involved in each treatment or comparison respectively. Ranking probabilities of each treatment being at a particular order (the best, second, third, fourth and the worst) were reported tabularly and graphically with rankograms. In order to account for uncertainty in treatment order, the mean rank (the average ranking place for each treatment) and the surface under cumulative ranking area SUCRA (the relative probability of a treatment being among the best options) were also estimated. The statistical analysis was performed using Stata 15.1.

Results

A total of one-thousand one-hundred and five (n=1105) PEP initiations from 5 RCT, 4 conducted in Spain and 1 in England were included in the clinical trials analyzed (10-14). Study participants in all studies were mostly men (n=941, 85%) who have sex with men (n=832, 75%), 247 (22%) were non-Caucasian, 261 (24%) reported previous sexually transmitted infections (STI) at the moment of inclusion in the studies and 759 (69%) had a previous HIV test, also 318 (29%) had a known HIV positive sexual partner (table 1). Non-occupational exposure to HIV was the main reason for PEP (89.86%), being this an inclusion criterion in 4 studies. In the remaining study, 30 occupational exposures were described. A 3-drug regimen was prescribed in all studies, where tenofovir-disoproxil/emtricitabine was the most frequently used backbone. All studies followed European recommendations on prescription and follow-up(15).

Four-hundred and fifty-four (41%) PEP non-completion cases were reported for any reason. The OR for each ARV compared to LPV/r was: ATV 0.95 (95% CI 0.58-1.56); EVG/c 0.65 (95% CI 0.30-1.37); RAL 0.68 (95% CI 0.41-1.13) and MVC 0.69 (95% CI 0.47-1.01). Of note, two of the included trials used MVC and therefore, the presented OR is a pooled estimate. We estimated the probability of each treatment being the best (Supplementary table 1 and figure 1a). This rankogram showed that EVG/c has 46% probability of being the best treatment, followed by MVC, RAL, ATV and LPV/r. The highest relative probability of being among the best three was shared by EVG/c, MVC and RAL (SUCRA of 70%). The mean rank also supported the good performance of the EVG/c (2.2) and the other two inhibitors drugs (2.3 for both MVC and RAL). When the subanalysis was performed including DRV/r (see Supplementary Table 6), the rankogram showed that DRV/r and EVG/c has 35% and 32% probability, respectively, of being the best treatment, followed by MVC, RAL, ATV and LPV/r.

There were 35 treatment discontinuations due to adverse events reported. The OR for each ARV compared to LPV/r was: ATV 1.55 (95% CI 0.57-4.21); EVG/c 0.31 (95% CI

0.01-5.13); RAL 0.32 (95% CI 0.03-3.16), and the pooled OR for MVC was 0.18 (95% CI 0.02-1.63) (Supplementary table 2 and figure 1b). This rankogram showed that MVC has a 47% probability of being the best treatment, followed by EVG/c, RAL, ATV and LPV/r. The SUCRA was also the highest for MVC (80%) and the mean rank was the lowest (1.9).

We found 23 cases of switching, 208 lost to follow-up and 1242 adverse events. Based on these data, the rankogram showed that EVG/c has the highest probability of being the most beneficial treatment for the lowest rate of switching, lost to follow-up or adverse events (79%, 100% and 98%, respectively) (Supplementary table 3-5 and figure 1 c-e).

Discussion

To our knowledge, this is the first meta-analysis comparing different PEP regimens for the prevention of HIV infection. PEP regimens containing LPV/r as the third drug were the most used in the past 10 years, probably because they were the less expensive option particularly in resource-limited settings. Other ARV prescribed as the third drug are the non-nucleoside reverse transcriptase inhibitors (NNRTIs) such as nevirapine that have reported more acute adverse events like severe hepatotoxicity. When used as ART, integrase inhibitors or CCR5 antagonists have a better tolerability and safety profile because they have less adverse events and lower risk for drug-drug interactions than PIs. Until recently, PI have been the preferred recommended regimen third drugs in most PEP guidelines but this has changed to RAL or dolutegravir based regimens following opinion of experts(4).

Based on a meta-analysis of 5 randomized clinical trials, we found that EVG/c-based PEP was the best option considering treatment non-completion by day 28. It was followed by MVC, RAL and ATV-based combinations. LPV/r was the regimen with the highest discontinuation rate. Nevertheless, in all the PEP studies lost to follow-up rate was high, ranging from 25 to 80% in French cohorts (18), and in a meta-analysis of 2014 only a 56.6% (95%CI: 50.9% - 62.2%) of people considered eligible for PEP completed the 28 day course (19). These data suggest that if a better-tolerated drug is used, the lost to follow up rates could be lower. When a subanalysis was performed including DRV/r (17), this regimen was the best option (altogether with EVG/c) considering treatment non-completion by day 28. These data should be taken with caution given that in this study subjects were stratified by type of event (occupational vs. nonoccupational) and there were significantly more occupational exposures (21%) than in the other 5 trials which included manly non-occupational exposures (10-14). It is possible that this high number of occupational exposures could influence the non-completion rates.

We also found that TDF/FTC+EVG/c was more likely to be ranked the best option with regard to almost all of the secondary endpoints: PEP switching due to any cause, lost to follow-up and adverse events. TDF/FTC+EVG/c was administered as a single-tablet regimen (STR) and these regimens have better adherence than multiple-tablet regimens (MTRs), missing doses were frequently reported when antiretrovirals were prescribed twice daily(7). In addition, EVG/c has a good tolerability profile, lower rate of adverse events and lower rate of poor adherence when compared with MTRs(20). This safety profile could explain the good results in our meta-analysis.

MVC was the best option in discontinuation due to adverse events, and RAL and EVG/c were the second and third best options in this endpoint. Méchai F et al(6) have reported that MVC was well-tolerated as PEP. Most data about tolerance and rate of discontinuation for different PEP regimens have been reported in non-controlled retrospective and prospective studies and they have shown a non-completion rate at day 28 related to side effects rate between 11.7 and 21%(21, 22). Adverse events seem to be the principal cause of non-compliance so antiretrovirals with a good safety profile should preferably be used.

Our study has a number of limitations. First, there are only few randomized clinical trials comparing PEP regimens, so our analysis has information about 5 studies. In addition, none of the 5 include dolutegravir, despite this being considered a first line option, and also bictegravir which is undergoing evaluation (ClinicalTrials.gov Identifier: NCT03499483). Second, the number of patients included is relatively low. Therefore, more clinical trials comparing different PEP regimens should be performed in the future.

In conclusion our study compares the different regimens use for PEP and shows the advantages of integrase inhibitors over the rest of PEP-regiments. Especially EVG/c containing regiment that had the best completion rate at day 28.

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Table1. General characteristics of studied population.

Study_ author	Backbone	Arm	Cohort	Per_arm	Male	MSM	Non-caucasian	PEP*	STI§	HIV test¥	HIV partner~
Leal_MRV	TDF+FTC	LOP/r	237	117	219	197	27	25	27	106	36
Leal_MRV	TDF+FTC	MVC		120			36	26	33	109	33
Leal_RAL	TDF+FTC	LOP/r	243	121	218	196	31	28	26	109	31
Leal_RAL	TDF+FTC	RAL		122			39	31	32	107	43
Milinkovic	TDF+FTC	LOP/r	213	106	208	200	17	41	48	96	38
Milinkovic	TDF+FTC	MVC		107			15	32	33	98	60
Inciarte	TDF+FTC	LOP/r	157	38	149	143	10	10	15	31	10
Inciarte	TDF+FTC	EVG/c		119			23	38	52	103	26
Diaz_Brito	AZT+3TC	LOP/r	255	131	147	96	21	15			23
Diaz_Brito	AZT+3TC	ATV		124			28	15			18

MSM: men who have sex with men. * Previous post-exposure prophylaxis. §Previous sexually transmitted infection. ¥Previous HIV test. ~Known HIV positive sexual partner.

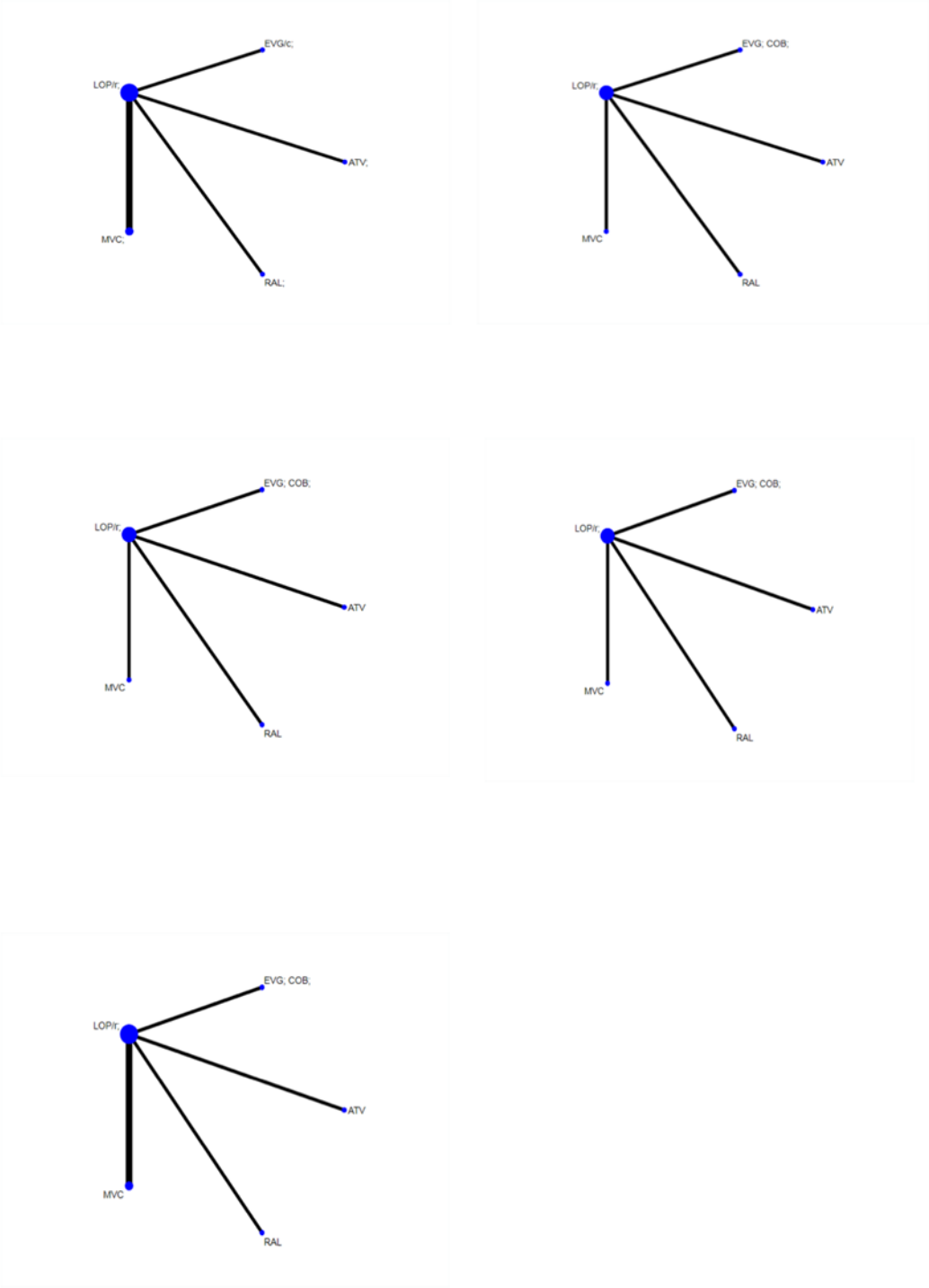

Figure 1. ***Network map for post-exposure prophylaxis.*** a. post-exposure prophylaxis completion at day 28; b. post-exposure prophylaxis discontinuation due to adverse events; c. post-exposure prophylaxis switching due to any cause; d. post-exposure prophylaxis lost to follow-up; e. post-exposure prophylaxis adverse events

Supplementary table 1. Treatment and corresponding ranking probabilities, mean rank and SUCRA for post-exposure prophylaxis non-completion at day 28.

study_id and Rank	Treatment LOP/r;	ATV;	EVG/c;	MVC;	RAL;
1					
Best	0.0	2.4	45.6	22.0	30.0
2nd	0.5	9.4	19.3	40.9	29.9
3rd	10.8	20.9	15.3	28.1	24.9
4th	43.6	30.6	9.0	7.3	9.5
Worst	45.1	36.7	10.8	1.7	5.7
MEAN RANK	4.3	3.9	2.2	2.3	2.3
SUCRA	0.2	0.3	0.7	0.7	0.7

Supplementary table 2. Treatment and corresponding ranking probabilities, mean rank and SUCRA for post-exposure prophylaxis discontinuation due to adverse events.

study_id and Rank	Treatment LOP/r;	ATV	EVG; COB;	MVC	RAL
1					
Best	0.1	0.2	29.1	47.1	23.5
2nd	4.0	2.5	30.4	29.2	33.9
3rd	28.7	8.7	19.9	16.1	26.6
4th	54.8	25.7	7.9	4.4	7.2
Worst	12.4	62.9	12.7	3.2	8.8
MEAN RANK	3.8	4.5	2.4	1.9	2.4
SUCRA	0.3	0.1	0.6	0.8	0.6

Supplementary table 3. Treatment and corresponding ranking probabilities, mean rank and SUCRA for post-exposure prophylaxis switching due to any cause.

study_id and Rank	Treatment LOP/r;	ATV	EVG; COB;	MVC	RAL
1					
Best	0.0	2.9	79.4	12.1	5.6
2nd	5.3	18.1	13.4	42.5	20.7
3rd	26.1	35.4	2.9	16.8	18.8
4th	48.2	27.1	2.4	10.1	12.2
Worst	20.4	16.5	1.9	18.5	42.7
MEAN RANK	3.8	3.4	1.3	2.8	3.7
SUCRA	0.3	0.4	0.9	0.5	0.3

Supplementary table 4. Treatment and corresponding ranking probabilities, mean rank and SUCRA for post-exposure prophylaxis lost to follow-up.

study_id and Rank	Treatment LOP/r;	ATV	EVG; COB;	MVC	RAL
2					
Best	0.0	0.0	100.0	0.0	0.0
2nd	0.2	16.3	0.0	7.2	76.3
3rd	22.7	35.8	0.0	23.5	18.0
4th	52.3	18.9	0.0	24.3	4.5
Worst	24.8	29.0	0.0	45.0	1.2
MEAN RANK	4.0	3.6	1.0	4.1	2.3
SUCRA	0.2	0.3	1.0	0.2	0.7

Supplementary table 5. Treatment and corresponding ranking probabilities, mean rank and SUCRA for post-exposure prophylaxis adverse events.

study_id and Rank	Treatment LOP/r;	ATV	EVG; COB;	MVC	RAL
1					
Best	0.0	0.9	98.4	0.0	0.7
2nd	0.0	45.7	1.6	2.8	49.9
3rd	0.1	39.1	0.0	21.5	39.3
4th	1.4	13.2	0.0	75.3	10.1
Worst	98.5	1.1	0.0	0.4	0.0
MEAN RANK	5.0	2.7	1.0	3.7	2.6
SUCRA	0.0	0.6	1.0	0.3	0.6

Supplementary table 6. Treatment and corresponding ranking probabilities, mean rank and SUCRA for post-exposure prophylaxis non-completion at day 28 including study by Fatkenheuer G et al (1) ***with darunavir/ritonavir containing regimen.***

study_id and Rank	Treatment LOP/r;	ATV;	DRV/r;	EVG/c;	MVC;	RAL;
1						
Best	0.0	2.6	34.6	32.2	13.4	17.2
2nd	0.0	5.2	19.6	20.5	27.9	26.8
3rd	1.7	10.3	16.0	17.7	28.9	25.4
4th	13.6	20.5	12.1	13.6	20.8	19.4
5th	44.7	26.1	8.0	6.6	7.2	7.4
Worst	40.0	35.3	9.7	9.4	1.8	3.8

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