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Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate for Nonoccupational HIV-1 Postexposure Prophylaxis: A Prospective Open-Label Trial (DORAVIPEP)

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Background. New regimens may provide better tolerability, convenience, and safety for nonoccupational human immunodeficiency virus (HIV) postexposure prophylaxis (PEP). For this reason, we evaluated the single-tablet regimen of doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF) for 28 days.

Methods. This was a prospective, open-label, single-arm trial including individuals with potential HIV-1 exposure within 72 hours. The primary endpoint was noncompletion of PEP at day 28. Secondary endpoints were adverse effects, adherence, and rate of seroconversion. We performed follow-up at day 7, week 4, and week 12.

Results. Between September 2019 and March 2022, the study enrolled 399 individuals. Median age was 30 (interquartile range [IQR], 27–36) years, and 91% (n = 364) were male. The mode of exposure was sex between men in 84% (n = 331) of cases; risk assessment for HIV-1 transmission was considered as "high" in 97% (n = 385) of the participants. Median time from exposure to consultation was 24 (IQR, 13–40) hours. Noncompletion of PEP was 29% (n = 114) (95% confidence interval [CI], 24%–33%) and 20% (n = 72) (95% CI, 16%–25%) per modified intention-to-treat. Main reasons for noncompletion were loss to follow-up (n = 104 [91%]) and intolerance (n = 8 [7%]). Older age was associated with a lower risk of premature discontinuation (OR, 0.94; $P < .001$). One hundred twenty-three (31%) participants reported adverse events, mostly mild and self-limited (82%); discontinuation occurred in 8 cases (2%). Adherence to PEP in the assessed users was 96%. There were no HIV seroconversions.

Conclusions. DOR/3TC/TDF is a well-tolerated option for nonoccupational PEP.

Clinical Trials Registration. NCT04233372.

Keywords. HIV-1 prevention; PEP; doravirine; postexposure prophylaxis; sexual exposure.

According to the Joint United Nations Programme on HIV/AIDS (UNAIDS), there were 1.5 million new human immunodeficiency virus (HIV) infections worldwide in 2021. This figure adds to the 38.4 million people who are currently living with HIV [1]. Clinicians administer antiretroviral therapy (ART) as secondary prevention to infection, following a situation with risk of exposure. This strategy is known as postexposure prophylaxis (PEP). It is used after occupational or nonoccupational exposure. PEP was initially provided in the occupational context [2] but it has now been implemented in nonoccupational settings, too.

Data from animal transmission models, perinatal clinical trials, and studies of healthcare workers receiving prophylaxis after occupational exposure and observational studies indicate that PEP given within 48–72 hours of a possible risk and continued for 28 days might reduce the likelihood of HIV infection [3–6]. The sooner the administration of PEP after exposure, the higher the chances of transmission prevention. The recommended guidelines in Spain and Europe for PEP consist of 2 nucleotide reverse transcriptase inhibitors that can be combined with either an integrase inhibitor or a protease inhibitor [7, 8]. PEP toxicity is the main reason for poor adherence and high treatment discontinuation rate [9]. Side effects of PEP that appear mostly in 3-drug regimens are attributable primarily to protease inhibitors. These can cause irregular compliance and dropouts, leading to lower treatment completion [10–14]. Drug–drug interaction potential, treatment-associated toxicities, and a lack of convenience (ie, bedtime dosing or calorie

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intake requirements) have prevented the use of older nonnucleoside reverse transcriptase inhibitor (NNRTI)–based regimens as PEP. There is, however, evidence concerning rilpivirine (RPV)–based regimens [15]. Indeed, recent French guidelines recommend a 28-day course of RPV/emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF) for nonoccupational and occupational exposure [16]. The prevalence of resistance rates for NNRTI might be an additional concern for the use of such regimens as PEP [17, 18].

A triple ART regimen for PEP is recommended to prevent resistance from developing in cases of seroconversion. ART combinations have been chosen for their pharmacodynamic characteristics (potency), pharmacokinetics (dosage and potential interactions), tolerance, and convenience of administration (single tablet). Nonetheless, recommended regimens for PEP frequently have issues with 1 or more of these aforementioned properties. Doravirine (DOR) is a novel NNRTI that has hit the market as a once-a-day single-tablet regimen (STR) in combination with lamivudine (3TC) and TDF. Studies in people with HIV have shown an excellent tolerability profile for this new agent [19, 20]. DOR has an in vitro resistance profile that is distinct from other NNRTIs, retaining activity against viruses containing the most commonly transmitted NNRTI mutations: K103N, E138K, Y181C, and G190A [21]. Recent studies have shown that the prevalence of DOR-associated resistance mutations was low in antiretroviral-naive and antiretroviral-experienced people with HIV in Spain and other European countries [17, 22]. Altogether, these characteristics make DOR/3TC/TDF an appealing combination choice for PEP. This study evaluated a DOR/3TC/TDF STR for nonoccupational PEP.

METHODS

We performed a phase 4, single-center, open-label, single-arm, prospective study addressing safety and tolerance of a DOR/3TC/TDF STR as PEP. We included those individuals who visited the emergency department at Hospital Clinic of Barcelona between September 2020 and March 2022 due to potential consensual exposure to HIV. PEP guidance was performed according to established indications [7, 8]. We enrolled individuals aged >18 years who had agreed to participate and signed the informed consent. Individuals who were pregnant, exhibited intolerance to the study drug, or were concurrently using medications that interacted with the study drug, were excluded from the initial enrollment as part of the exclusion criteria. Supplementary Figure 1 shows the study flowchart.

After signing informed consent, the participants reviewed the follow-up. They also obtained information and counseling about HIV transmission and prevention, ART, and PEP. They received a complete 28-day prescription, with DOR/3TC/TDF (Delstrigo) being initiated immediately (day 0). At day 7 (3–10), week 4 (3–5), and week 12 (10–14), participants had appointments to undergo blood tests that involved hematologic and biochemical analyses (for renal and hepatic functions); HIV testing; the Venereal Disease Research Laboratory test; immunoglobulin M and immunoglobulin G (IgG) antibody testing for *Treponema pallidum* (syphilis); and antibody testing for hepatitis A virus (HAV), hepatitis B virus (HBV), and hepatitis C virus (HCV). Participants received results a week after the blood tests during a follow-up visit with either the nurse or physician (Supplementary Table 1).

An infectious disease specialist carried out an initial assessment. After enrollment, information including demographics, social background, previous PEP use, previous sexually transmitted infections (STIs), drug use in the context of chemsex, past medical history, exposure characteristics, stratification for HIV acquisition, physical examination, and the time between sexual exposure and consultation was collected. We recorded HIV serostatus of the source when available.

We reported evaluations of adverse events (AEs) in 2 different ways: the number of participants who experienced an AE and the total number of AEs reported. An AE episode was defined as any occurrence of an AE, regardless of whether the same individual experienced it multiple times. AEs were evaluated at every scheduled visit, considering type, grade, causality, outcome, and prognosis according to standard medical terminology in the Medical Dictionary for Regulatory Activities (MedDRA, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use). AEs could belong to 1 of 2 groups: those that might have a causal relationship (defined as definitive, probable, and possible) and those unrelated (defined as not related, unlikely unrelated).

Adherence was measured at week 4 with the Simplified Medication Adherence Questionnaire (SMAQ). The SMAQ is a 6-item scale that measures ART adherence in people with HIV. The questionnaire considers patients as treatment adherent if they answer 4 qualitative questions correctly and respond ≤2 times and 2 days to questions 5 and 6, respectively. Patients' answers determine the adherence score, and a score <94% is considered as low adherence [23, 24].

The primary endpoint was the proportion of participants not completing the 28-day PEP regimen. PEP noncompletion was defined as either any case lost to follow-up before day 28 or PEP suspended or changed for any reason. Secondary endpoints were baseline characteristics associated with PEP noncompletion, the identification of factors associated with noncompletion, proportion of subjects who maintained subsequent follow-up visits, AE, PEP adherence, and rate of HIV-1 seroconversion.

Patient Consent Statement

This study was conducted according to the protocol and ethical principles stated in the Declaration of Helsinki, the applicable

guidelines on good clinical practices, and all applicable local laws, rules, and regulations. The hospital research committee and appropriate Spanish authorities authorized this study (approval number HCB/2019/1125). The patients signed a written consent form. Information regarding patients' identities was codified. The study was registered at ClinicalTrials.gov (identifier NCT04233372).

Statistical Analysis

Considering that a population of approximately 1400 individuals attends our center for PEP yearly, a sample of 400 individuals produces a 2-sided 95% confidence interval (CI) with a precision of 0.04 when the actual proportion of noncompletion (our primary outcome) is near 40%. We performed the sample size calculation using PASS 15 software (NCSS, LLC, Kaysville, Utah; ncss.com/software/pass).

We performed summary statistics using absolute frequency and percentages for qualitative variables and mean (standard deviation) or median (interquartile range [IQR]) for quantitative variables. Wilcoxon rank-sum test was used to analyze differences between groups for quantitative variables. The χ^2 test was used to analyze differences between groups for qualitative variables. In case of low frequency for some category of a variable, Fisher exact test was used instead. We reported the primary outcome as absolute frequency and percentage along with the 95% CI in the intention-to-treat (ITT) population, which included all participants who received at least 1 dose of PEP, and in the modified ITT (mITT) population, which meant a selection of those who had at least 1 follow-up measurement. We defined noncompletion as participants who did not attend at least 1 follow-up visit. For the secondary objectives, we evaluated baseline characteristics associated with PEP noncompletion using a logistic regression model, selecting variables using clinical judgment and a stepwise process. We reported the incidence rate of AE as the number of AEs per 100/person-months and its 95% CI, differentiating those leading to discontinuation and those caused by laboratory abnormalities (grade 1–2 and 3–4) during study treatment and also until week 12 of follow-up. Furthermore, we estimated incidence rate ratios using a negative binomial regression model and obtained the significance level with a likelihood ratio test. Changes over time in laboratory parameters were assessed using a mixed-effects regression model. All tests were 2-tailed, and the significance level was set at <.05. We conducted the statistical analysis using Stata version 17 (StataCorp, College Station, Texas).

For missing data, the primary outcome includes the missing value in the noncompleter category. Completeness and plausibility checks ensured the collection of high-quality data. For data collection and monitoring, an electronic case report form was designed, implemented, and validated in the REDcap system hosted at Hospital Clinic.

RESULTS

Baseline Characteristics of the Study Population

Demographics

A total of 1535 subjects received PEP prescriptions between September 2019 and February 2022. Of these, 399 individuals who met PEP criteria and visited the emergency department with possible exposure to HIV were included in the study (Supplementary Figure 1). The median age was 30 years (interquartile range [IQR], 27–36 years), and 91% (n = 364) were male. HIV acquisition risk was men who have sex with men (MSM) in 84% (n = 331) of cases; 60% (n = 231) were European and 35% (n = 135) were Latin American. Table 1 shows demographics of the study population.

Previous PEP Use and STIs

One hundred thirty-eight participants reported previous PEP use (198 episodes), with some having used PEP more than once (15% [n = 60]). Among these participants, prior PEP regimens frequently included a combination of elvitegravir (EVG) boosted with cobicistat (EVG/c) and TDF/FTC (80% [n = 158]), or raltegravir (RAL) and TDF/FTC (15% [n = 30]). It is worth noting that 6% (21 of 373) of the participants had initiated preexposure prophylaxis (PrEP) prior to the study.

Additionally, 32% (126 of 390) reported a history of STIs, with a total of 182 episodes described in some cases more than once. Specifically, 64 (35%) reported *Neisseria gonorrhoeae* infection, 58 (32%) syphilis, and 44 (24%) *Chlamydia trachomatis* infection. Of the patients with basal-reported STIs, 26% (n = 33) reported 2 episodes and 8% (n = 10) 3 episodes. Throughout the follow-up period, there were a total of 4 asymptomatic syphilis diagnoses; 4 cases of *N gonorrhoeae* infection; and 2 cases of *C trachomatis* infection. Supplementary Figure 2 shows previous STIs.

Seroprevalence of Hepatitis and Syphilis

At baseline, among the 345 participants, 85% (n = 291) were HAV IgG positive, 69% (n = 239) were HBVs surface antibody positive, 7% (n = 24) were IgG HBVc core antibody positive, and 1% (n = 3) were HBVs surface antigen positive; 1% (n = 3) were HCV antibody positive. IgG anti–*T pallidum* antibodies were present in 13% (43 of 338) of participants. One individual tested positive for HIV-1 at baseline. Of the 384 patients, 177 reported prior vaccination for hepatitis B.

Characteristics of the Exposure

The median time from exposure until PEP initiation was 24 hours (IQR, 13–40 hours). HIV status of the source of exposure was unknown in 86% (n = 343) of cases; 11% (n = 45) cases had a known HIV-positive status of the source of exposure. Condomless sex occurred in more than half of the population (66% [n = 258]) and condom breakage occurred in 33% (n = 128) of the participants. Most cases (n = 361 [92%]) had a risk of transmission via anal

Table 1. Characteristics of Individuals With HIV Exposure From the Entire Cohort (n = 399) and Individuals Coming to at Least 1 Follow-up Consultation (n = 356)

	Whole Cohort (ITT Population)				Coming at Least to 1 Follow-up Consultation (mITT Population)			
Characteristic	Cohort	Completion	Noncompletion	*P* Value	Cohort	Completion	Noncompletion	*P* Value
No.	399	285	114	<.001[a]	356	284	72	.004[a]
Age, y, median (IQR)	30 (27–36) [399]	31 (27–37) [285]	29 (24–33) [114]	.017[b]	31 (27–36) [356]	31 (27–37) [284]	29.5 (25–32.5) [72]	.291[c]
Male sex	367 (92) [399]	268 (94) [285]	99 (87) [114]	.523[b]	330 (93) [356]	265 (93) [284]	65 (90) [72]	.913[b]
European origin	231 (60) [382]	175 (61) [285]	56 (58) [97]	.758[a]	217 (61) [355]	174 (61) [284]	43 (61) [71]	.760[a]
Time from exposure, median (IQR)	24 (13–40) [388]	24 (14–40) [285]	24 (12–36) [103]	.972[b]	24 (13–40) [355]	24 (13.5–40) [284]	24 (12–36) [71]	.420[b]
Type of exposure: MSM[d]	331 (84) [395]	246 (87) [284]	96 (86) [111]	1.000[c]	309 (87) [354]	245 (87) [283]	64 (90) [71]	.693[c]
Evaluable risk of infection[e]	385 (97) [397]	275 (97) [284]	110 (97) [113]	.809[b]	345 (97) [355]	274 (97) [283]	71 (99) [72]	.878[b]
Previous PEP, yes	138 (35) [392]	101 (36) [284]	37 (34) [108]	.948[b]	126 (35) [355]	101 (36) [283]	25 (35) [72]	.664[b]
Previous STI	125 (33) [383]	91 (33) [278]	34 (32) [105]	.200[b]	115 (33) [348]	90 (32) [277]	25 (35) [71]	.092[b]
Source known to be HIV infected	45 (11) [399]	36 (13) [285]	9 (8) [114]	<.001[a]	43 (12) [356]	36 (13) [284]	7 (10) [72]	.004[a]

Data are presented as No. (%) unless otherwise indicated. Values in brackets indicate the number of individuals for each study variable.

Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range; ITT, intention-to-treat; mITT, modified intention-to-treat; MSM, men who have sex with men; PEP, postexposure prophylaxis; STI, sexually transmitted infection.

[a]Wilcoxon rank-sum test.

[b]χ^2 test.

[c]Fisher exact test.

[d]Men who have sex with other men.

[e]Defined as any sexual exposure excluding those with low-to-intermediate risk.

sex, either insertive or receptive. Unprotected oral sex was reported in 91% of cases (n = 343), and unprotected vaginal sex in 13% of cases (n = 53). Semen and blood exchange were reported in 60% (n = 202) and 23% (n = 69) of cases, respectively. Table 1 shows the characteristics of the exposures.

Previous Drug Use and Comedications

PEP users reported self-referred use of recreational drugs in 30% (111 of 370) of cases; cannabinoids were the most commonly referred substance (50% [n = 56]), followed by cocaine (33% [n = 37]), gamma-hydroxybutyrate/gamma-butyrolactone(GHB/GLB) (32% [n = 36]), methamphetamine (19% [n = 21]), nitrites (19% [n = 21]), ketamine (16% [n = 18]), MDMA (16% [n = 18]), mephedrone (15% [n = 17]), ecstasy (15% [n = 17]), and amphetamines (11% [n = 12]) (Supplementary Figure 3). Concomitant treatment during the study period was present in 26% (101 of 393) of the participants; 45% (45 of 101) of the concomitant treatments were psychiatric medications.

Primary Endpoint: PEP Noncompletion

The percentage of individuals who prematurely discontinued PEP at day 28 was 29% (n = 114) (95% CI, 24%–33%). The median time reported for PEP duration until discontinuation was 8 days (IQR, 0–14 days). Reasons for noncompletion were loss to follow-up in most cases (n = 104 [91%]), intolerance and AEs (n = 8 [7%]), and patient decision/withdrawal of informed consent (n = 2 [2%]). In mITT, the PEP noncompletion percentage at day 28 was 20% (95% CI, 16%–25%) (n = 72). The percentage of individuals who maintained follow-up was 89% (n = 354) on day 7, 72% (n = 286) at week 4, and 63% (n = 243) at week 12. Follow-up HIV testing was achieved in 273 (68%) and 203 (51%) individuals at weeks 4 and 12, respectively.

Factors Associated With PEP Noncompletion

In the multivariable logistic regression model including all enrolled patients, the unique independent factor associated with PEP noncompletion was younger age (odds ratio [OR], 0.94 [95% CI, .91–.97]; $P < .001$). Restricting the sample only to those patients who came at least 1 visit after enrollment, the independent factors associated with PEP noncompletion in the multivariable logistic regression were younger age (OR, 0.94 [95% CI, .91–.98]; $P < .001$) and the emergence of any AE during PEP (OR, 1.96 [95% CI, 1.13–3.38]; $P = .016$). Table 2 shows factors associated with PEP noncompletion in both samples and unadjusted and adjusted logistic models.

Adverse Events

A total of 123 (31%) patients reported AEs, with 183 AE episodes overall. The incidence rate was 60.09 cases per 100 person-months (95% CI, 51.98–69.45). AEs were mild in 150 (82%) participants, moderate in 28 (15%), and severe in 5 (3%). Employing the Primary System Organ Class classification, the most common AE types were gastrointestinal (35% [n = 63]), neurological (21% [n = 37]), and musculoskeletal

Table 2. Factors Associated With Postexposure Prophylaxis Noncompletion at Day 28 due to Any Cause or Adverse Event

	PEP Discontinuation due to Any Cause in the Entire Cohort (n = 399), OR (95% CI)		PEP Discontinuation due to Any Cause in Patients Who Attended Least 1 Follow-up Visit (n = 356), OR (95% CI)[a]	
Characteristic	Univariable	Multivariable	Univariable	Multivariable
Age: 1-y increase	0.94 (.91–.97), ***P* = .0003**	0.94 (.91–.97), ***P* = .0002**	0.94 (.90–.97), ***P* = .0012**	0.94 (.91–.98), ***P* = .003**
Type of exposure: homosexual, yes vs no	0.99 (.52–1.88), *P* = .972	…	1.42 (.60–3.33), *P* = .422	…
Risk assessment: high vs intermediate/low	1.2 (.32–4.52), *P* = .787	…	2.33 (.29–18.77), *P* = .426	…
Sex: male vs female	0.42 (.20–.87), ***P* = .019**	…	…	…
AE during PEP treatment: yes vs no	1.04 (.63–1.70), *P* = .885	…	2.06 (1.20–3.54), ***P* = .008**	1.96 (1.13–3.38), ***P* = .02**
Adherence to PEP[b]: high vs low	0.23 (.08–.67), ***P* = .007**	…	0.23 (.08–.67), ***P* = .007**	0.21 (.07–.67), ***P* = .008**

Factors associated with PEP noncompletion at day 28 in the unadjusted model. Baseline characteristics associated with treatment noncompletion are identified using a logistic regression model. The dependent variable is "Have discontinued the 28-day treatment." Bold formatting represents significant *P* values.

Abbreviations: AE, adverse event; CI, confidence interval; OR, odds ratio; PEP, postexposure prophylaxis.

[a]Attending individuals with a human immunodeficiency virus (HIV)–positive test at baseline or with an HIV-negative partner were excluded from the analysis.

[b]Not measured in patients who did not attend the day 1 visit.

(9% [n = 16]) (Supplementary Figure 4). The most common specific symptom in AE episodes (n = 80) was abdominal pain, nausea, and vomiting (n = 26 [36%]), followed by diarrhea (n = 12 [14,9%]), asthenia (n = 9 [12.2%]), and headache (n = 9 [12.2%]).

There were no potentially life-threatening (grade 4) AEs related to the medication and no serious AEs. Discontinuation due to AEs accounted for 8 (7%) cases among all types of PEP noncompletion. There was an established causal relationship in 55 (14%) individuals with 78 AE episodes overall (Supplementary Table 2).

There were no clinically significant differences among laboratory values during the follow-up period with administration or cessation of the study medication. Laboratory abnormalities were not the reason for PEP noncompletion in any patient (Supplementary Table 3).

Adherence

Adherence was evaluated on day 7 for 88% (n = 350) of participants and reassessed on day 28 for 71% (n = 285) of participants. The median time from PEP start to adherence loss was 2 (IQR, 1–6) days. Self-reported adherence to PEP in the assessed users was 96% (336 of 350) and 99% (281 of 285) at day 7 and week 4, respectively, with corresponding pill count data. The number of nonadherent patients was 18 during the study period.

Seroconversion

No cases of seroconversion were found during the study period. At weeks 4 and 12, respectively, 54% (n = 218) and 38.8% (n = 155) of participants tested negative for HIV.

DISCUSSION

This study evaluated the combination of DOR/3TC/TDF as STR for nonoccupational PEP. DOR/3TC/TDF seems appealing as a PEP regimen for several reasons: the coformulation of their components, the low drug–drug interaction potential, the higher genetic barrier of DOR compared to other NNRTIs, and the good tolerance reported in pivotal naive and switch randomized controlled trials (RCTs) exploring this regimen [25, 26]. The DORAVIPEP trial aimed to investigate noncompletion rates of PEP for HIV.

Results of DORAVIPEP trial can be compared to 3 RCTs conducted at our center: MARAVIPEP, RALPEP, and STRIBPEP [27–29]. While these studies are 2-arm trials, in contrast with DORAVIPEP, a single-arm trial, they are methodologically similar in an equivalent population with consistent PEP noncompletion rates. An examination of the results from these studies indicates that combination therapy of DOR/3TC/TDF has lower PEP noncompletion rates than those of regimens belonging to the ritonavir-boosted lopinavir (LPV/r), maraviroc, and RAL arms. The exception is the EVG arm in the STRIBPEP trial study, in which DOR/3TC/TDF had the theoretical advantage of lower potential for drug–drug interactions.

The TDF/FTC + dolutegravir (DTG) regimen, a popular choice for HIV PEP in numerous US institutions, was evaluated in an Australian study involving MSM and bisexual men, demonstrating high adherence (98%) and completion rates (90%). It should be noted, however, that the study's conclusions are constrained by a small participant pool, a single-arm design using a multi-pill regimen, and limited external validity due to its singular geographic focus [30].

Further extending this comparative analysis, recent single-arm studies using bictegravir offer additional insight. One of these studies involved 52 individuals and compared the outcomes to historical treatments [31], while another study included 102 participants but lacked a comparison group [32]. Although both studies yielded important results, their relatively limited sample sizes might have prevented the detection of subtle variances or infrequent adverse effects. Nevertheless,

pharmacokinetic/pharmacodynamic studies noted reduced levels in cervical and vaginal tissues for tenofovir alafenamide compared to TDF [33]. This limitation could influence the treatment's prophylactic effectiveness, emphasizing the need for additional exploration. Younger age has consistently been identified as a significant factor in multiple studies examining PEP noncompletion. Furthermore, AEs contribute to noncompletion in the ITT analysis of these studies [27–29].

Previous studies have identified female sex as a factor for PEP noncompletion, perhaps due to a higher risk perception among males. However, in our studies, being female was not associated with noncompletion. This discrepancy may be attributable to the smaller proportion of females in our sample, which did not have enough power for us to detect a statistically significant difference.

In our study cohort, 30% of PEP users reported engaging in chemsex; an additional third had comorbidities, with half of these individuals receiving psychiatric medications. The DOR/3TC/TDF regimen is associated with a lower risk of drug–drug interactions than many other PEP regimens [34]. This is relevant because of the potential for drug–drug interactions among different PEP regimens recommended in current guidelines, including pharmacokinetic enhancers such as protease inhibitors or EVG-based regimens.

This clinical trial has shown improved retention and follow-up testing rates compared to previous PEP studies. This may be due in part to shorter follow-up periods [35]. The sensitivity of HIV serologic tests has also risen with the emergence of newer kits that allow for faster seroconversion detection; however, this does not impact the external validity of the primary endpoint—PEP noncompletion at day 28. The end of the follow-up testing in the current standard of care is 120 days, whereas older studies had follow-up testing of up to 180 days [36]. In old PEP studies, the recommendation was to wait until 6 months for discharge, making it more feasible for higher dropout rates to be present. With the introduction of fourth-generation HIV tests in 2010 (with a shorter detection window of up to 4 weeks), recent guidelines recommended shorter follow-up periods until 4 months as a measure of precaution because of a potential delay in seroconversion due to PEP use [37].

PEP efficacy can be jeopardized due to early discontinuation and low adherence. AEs and PEP discontinuation are often described when using ritonavir-boosted protease inhibitors such as LPV, atazanavir, or darunavir [38–40]. With the appearance of very well-tolerated, new antiretroviral agents for HIV treatment, such as integrase strand transfer inhibitors (INSTIs), current guidelines recommend RAL as the third drug in PEP regimens; protease inhibitors as an alternative; and, to a lesser extent, some other INSTIs [8, 41, 42]. The incidence of AEs in this study during treatment was 32% and treatment discontinuation was 2%; lower and similar rates are observed among INSTI-based STR in PEP studies, respectively [27, 43].

An adherence meta-analysis including 3 RCTs, 9 prospective studies, and 5 retrospective studies [44] showed an overall pooled adherence—evaluated by self-reporting—of 77%. In our study, overall self-reported adherence was 97%. This discrepancy might be explainable by lower adherence and the use of multiple tablet regimens. Other studies using STR with EVG/c, RPV, or DTG as a third agent support this theory based on their adherence results [43, 45, 46].

A significant portion of PEP users in the DORAVIPEP cohort met criteria for PrEP as outlined by Spanish guidelines. In a study conducted in the United Kingdom, 12% of PEP users had prior PrEP use, while in the DORAVIPEP cohort, 6% had previously taken PrEP. One possible explanation for our lower percentage is the fact that PrEP availability in Spain was limited at the start of our study. The UK study also found that 44% of PEP users who had not started PrEP returned a year later to initiate it [43]. These findings suggest that PEP can continue to play a crucial role in preventing HIV infection in individuals who have stopped using PrEP and in providing protection to those who have experienced sexual assault or healthcare-related occupational exposure.

Our study has some limitations to consider. First, this is an open-label study with no comparator arm. Second, PrEP was initiated in Spain in November 2019, which might have had a mitigation effect on the event of seroconversion compared with historical PEP studies. Although it is a relatively new intervention, in the course of DORAVIPEP trial initiation, implementing PrEP in Spain may have contributed to a decrease in overall HIV prevalence. This means it could have lowered the incidence of seroconversion among participants within the 2-year study period. This makes it challenging to compare the results of this trial to previous PEP studies conducted before the introduction of PrEP. The incomplete data and potential bias introduced by the lower follow-up rates emphasize the need for caution when drawing definitive conclusions about the efficacy and effectiveness of PEP based on our results. Although limitations in longer-term follow-up testing exist in PEP studies, it is essential to consider the primary focus on safety evaluations rather than efficacy. Third, the coronavirus disease 2019 pandemic may have contributed to less follow-up, fewer testing opportunities, and underreporting of AEs during the follow-up period. To take advantage of its relatively quick and cost-effective nature when contrasted with comparative studies, and based on our center's previous experience with a similar population and PEP framework in conducting clinical trials, this study was conducted as a single-arm study. Without a control group, it is still difficult to determine whether the observed effects are due to the intervention being studied. Fourth, our study sheds light on PEP use in MSM populations, predominantly observed in larger cities within affluent nations. However, the universality of our findings is limited, particularly in contexts where PEP users are predominantly non-MSM, such

as females, a demographic not extensively covered in our research. Last, due to the constraints in our study, it was not feasible to utilize any drug-based strategies for monitoring adherence, such as drug level testing or electronic bottle monitoring. Instead, we used the SMAQ as our primary tool for assessing adherence. The constraints in the available objective methods for monitoring adherence suggest that our findings based on self-report should be interpreted with caution.

In conclusion, DOR/3TC/TDF as STR was a well-tolerated option for once-a-day PEP, with high adherence, low rates of AEs, and treatment discontinuation. An RCT may reinforce the results of this single-arm trial.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. E. F., E. S., B. T., A. I., D. A., I. C., S. H., N. G.-P., A. R., M. H.-M., P. P., V. R., P. M., A. U., J. A., L. D. M., M. M., A. G., M. L., I. C., and V. R. performed clinical assessments. A. I. and E D. L. designed the study. A. I., E. D. L., and L. B. contributed to data analysis and wrote the first draft of the manuscript. A. I., E. S., E. F., L. B., and P. C. were responsible for data entry. A. I., J. A., J. M., E. M., and J. L. B. critically reviewed the manuscript. All authors approved and agreed on the final version.

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Data sharing. Extra data are available and can be requested by emailing ajinciar@clinic.cat.

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