J Antimicrob Chemother
doi:10.1093/jac/dky547

Journal of Antimicrobial Chemotherapy

Tenofovir DF/emtricitabine/rilpivirine as HIV post-exposure prophylaxis: results from a multicentre prospective study

Marie Chauveau[1]*, Eric Billaud[1,2], Bénédicte Bonnet[1], Dominique Merrien[3], Hikombo Hitoto[4], Sabelline Bouchez[1], Christophe Michau[5], Nolwenn Hall[1], Lucia Perez[4], Solène Sécher[2], François Raffi[1,6] and Clotilde Allavena[1,6] on behalf of the COREVIH Pays de la Loire Study Group†

[1]Department of Infectious Disease, CHU Hôtel-Dieu, Nantes, France; [2]COREVIH Pays de la Loire, CHU Hôtel-Dieu, Nantes, France; [3]Internal Medicine Department, CHD Vendée, La Roche-sur-Yon, France; [4]Internal Medicine Department, CH Le Mans, France; [5]Internal Medicine Department, CH St Nazaire, France; [6]CIC UIC 1413 INSERM, CHU Nantes, France

*Corresponding author. Tel: +33 2 40 08 30 99; Fax: +33 2 40 08 31 81; E-mail: marie.chauveau@chu-nantes.fr
†Members are listed in the Acknowledgements section.

Received 30 August 2018; returned 13 October 2018; revised 19 November 2018; accepted 28 November 2018

Objectives: Since 2016, French guidelines have recommended the single-tablet regimen of tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC)/rilpivirine (RPV) as HIV post-exposure prophylaxis (PEP), but few data support this usage. We evaluated the tolerability, treatment completion and occurrence of HIV seroconversion associated with this combination in occupational and non-occupational PEP.

Patients and methods: We conducted an observational, prospective, multicentre, open-label, non-randomized study in five French HIV centres. Adults requiring PEP according to national French guidelines were prescribed TDF/FTC/RPV one pill once a day for 28 days. Clinical and biological tolerability was assessed at week 4; occurrence of HIV seroconversion was evaluated after week 16.

Results: From March 2016 to March 2017, 163 courses of PEP were prescribed for 150 sexual exposures (44% heterosexual and 56% MSM) and 13 non-sexual exposures. Five participants stopped PEP after a few days because the source person was HIV uninfected. Of the remaining 158 individuals, 15 (9.5%) were lost to follow-up at week 4, 7 (4.4%) prematurely discontinued PEP [patient's decision/non-adherence ($n = 3$) or adverse events (gastrointestinal intolerance $n = 3$, fatigue $n = 1$)] and 136 (86.1%) completed the 28 day treatment. Overall, 69.6% of participants declared at least one adverse event, mostly of mild to moderate intensity and no serious adverse events or hepatic or renal toxicity occurred. No HIV seroconversion occurred at week 16.

Conclusions: The low rate of premature treatment interruption, the good tolerability and the absence of documented HIV seroconversion support the current French guidelines of a 28 day course of TDF/FTC/RPV for sexual and non-sexual PEP.

Introduction

Post-exposure prophylaxis (PEP) is commonly recommended to prevent HIV infection after blood, sexual or percutaneous exposure.[1–3] Efficacy data supporting PEP are mainly extrapolated from animal studies[4–6] and from human studies demonstrating the efficacy of ART in preventing maternal–infant and perinatal transmission of HIV.[7,8] Even though some PEP failures have been reported,[9–12] seroconversions have been very rare since the advent of three-drug combinations as PEP, and confounding factors explaining the failure of PEP are frequent.[12,13] Recommendations concerning the indications and modalities of PEP vary from one country to another, and have evolved considerably in the past few years.[14–17] Most guidelines recommend using a three-drug combination, by analogy with HIV treatment,[18–21] but very few studies have comparatively evaluated the different therapeutic options.[22,23] The most important factors associated with PEP completion are tolerability, and a regimen that facilitates adherence.

In many countries,[18,20,21] regimens consisting of multiple pills, with tenofovir disoproxil fumarate/emtricitabine plus raltegravir twice daily or dolutegravir or a boosted PI, are still recommended.

Since October 2016 the French national guidelines have recommended the single-tablet regimen of tenofovir disoproxil fumarate, emtricitabine and rilpivirine (TDF/FTC/RPV) for both occupational and non-occupational PEP.[17] Only one open-label Australian study has evaluated this combination as non-occupational PEP[24] in an MSM cohort and showed an excellent adherence with a high completion rate and no seroconversion.

The aim of our study was to evaluate premature treatment discontinuation, safety and occurrence of HIV seroconversion after

using single-tablet TDF/FTC/RPV in an unselected population referred for occupational or non-occupational PEP.

Patients and methods

This observational, prospective, multicentre, open-label, non-randomized study was conducted in five French HIV centres in the Pays de la Loire (Nantes, La Roche-sur-Yon, Le Mans, Saint-Nazaire and Laval) from March 2016 to March 2017. Adult individuals who required PEP according to French guidelines[16] were offered the option of participating in the study. PEP had to be started within 48 h after exposure. Pregnant or breast-feeding women, subjects under legal guardianship, and subjects with a previous positive HIV test or treated with proton-pump inhibitors, which are contraindicated with rilpivirine, were not eligible.

Subjects were prescribed single-tablet TDF/FTC/RPV, taken once daily with food for 28 days. They attended a single visit at their inclusion (first day of PEP or within 4 days after PEP initiation if it had been started at the emergency room); at the end of the 4 week treatment, patients were called by telephone to evaluate completion of study treatment, reasons for premature discontinuation, if applicable, and tolerability. Clinical tests were planned at weeks 2, 4, 8 and 16.

At baseline we recorded sociodemographic and medical data, and information concerning the source person (when this was known) and the circumstances of the exposure. These data were collected according to the participant's declarations. Participants were provided with single-tablet TDF/FTC/RPV for 28 days, and given education and counselling according to the standard of care regarding PEP adherence and HIV risk. They were told to take TDF/FTC/RPV with food, and with no proton-pump inhibitor co-medications. A telephone call to assess tolerability was made between days 28 and 35 by a physician taking part in the study. Biological assessment was performed at baseline according to French guidelines, and included HIV, HBV and HCV antibody tests, screening for sexually transmitted infections if the exposure was sexual (syphilis serology, chlamydia PCR in urine), pregnancy test for women, and biochemistry (creatininaemia, AST and ALT). The biological follow-up included assessment of renal and hepatic functions at weeks 2 and 4, and HIV, HBV and HCV serological testing at week 16, as recommended by the French guidelines at the time of the study.[16] The biological follow-up was prescribed to the patient during the first visit, and could be done in a nearby laboratory.

The primary endpoint was the proportion of participants who discontinued PEP prematurely, i.e. before day 28, unless they stopped because the source person was found to be HIV uninfected or with an undetectable HIV viral load.

Secondary endpoints evaluated safety and occurrence of HIV seroconversion, including proportion of participants with clinical adverse events, proportion of participants with laboratory abnormalities, proportion of participants discontinuing PEP due to adverse events, and proportion of participants with a negative HIV serology at week 16.

All the subjects who agreed to participate in the study were included in the baseline data analysis and the tolerability analysis; for efficacy analysis, the population included all participants except those who had stopped prematurely because the source person was HIV uninfected. SAS® 9.4 was used to analyse the data. To identify significant differences between quantitative variables, the Wilcoxon–Mann–Whitney test was used. $P < 0.05$ was considered statistically significant.

Ethics

The ethics committee of the CHU de Nantes approved this research (approval reference 15.1022) and each participant gave informed consent.

Results

Between March 2016 and March 2017, 163 single-tablet TDF/FTC/RPV PEP treatments were prescribed to 162 individuals for 150 (92%) sexual exposures, and 13 (8%) non-sexual exposures. Almost half (49.7%) of the participants were started on PEP in the emergency room. Participants' characteristics are presented in Table 1.

Amongst non-sexual exposures, 8 (61.5%) were occupational [clinical ward nurses ($n = 3$), operating room nurse ($n = 1$), biologist ($n = 1$), physician ($n = 1$), midwife ($n = 1$), dentist ($n = 1$)], and 5 (38.5%) were non-occupational [penetrating wound with an intravenous drug user's needle ($n = 2$); wound with a blood-stained razor blade belonging to an HIV-positive subject who had ceased treatment 3 years earlier ($n = 1$); puncture with a needle through a glove ($n = 1$); penetrating wound with an unknown sharp object in a waste dump ($n = 1$)].

More than half (56.7%) of the sexual exposures occurred in MSM. Exposures comprised receptive anal intercourse (56.5%), insertive anal intercourse (48.2%), receptive fellatio (43.5%) and insertive fellatio (34.1%). The main heterosexual exposures were receptive vaginal intercourse (47.7%), insertive vaginal intercourse (46.2%), receptive or insertive fellatio (26.2%), and insertive or receptive anal intercourse (7.7%). Amongst the sexual exposures, 17 (11.3%) were sexual assaults (14 females, 3 males). No condom was used in 80 (53.3%) sexual exposures, and a disruption (break, slip over, or other) occurred in the other cases. Details about the HIV status of the source persons are reported in Table 2. Three source persons were HIV infected with detectable viral load, at 22 500, 1400 and 5570 copies/mL, respectively; the first two had no HIV follow-up, were untreated, and no genotype of their HIV strain was available; the third had started antiretroviral therapy (TDF/FTC/RPV) 2 weeks before the exposure; the genotype of his HIV strain showed no resistance mutations for tenofovir, emtricitabine and rilpivirine. In most of the 150 sexual exposures (85.3%), the source person belonged to the 'high HIV-prevalence group': MSM or bisexual (56.9%), multipartner heterosexual (22.2%) or heterosexual coming from a high-HIV-prevalence region (9.7%); in 4 cases the source person had no identified risk, and in 18 cases, the risk was unknown. One hundred and six participants (66 MSM, 40 heterosexual) mentioned having different partner(s) in the previous 6 months, of whom 58 (54.7%) admitted unprotected sexual intercourse (55.2% MSM).

The flow chart of the study is presented in Figure 1. No participant was found to be HIV positive at enrolment. Amongst the 163 participants, 5 (3.1%) discontinued PEP prematurely because the source person was found to be HIV uninfected, and were excluded from the week 16 documentation of HIV seroconversion analysis. The clinical follow-up (telephone contact and evaluation) was completed for 143 of the 158 participants with confirmed indication for PEP (90.5%); 98 participants (62.0%) completed the biological follow-up until week 16. No HIV, HBV, HCV or syphilis seroconversion was observed at week 16 in these 98 individuals. The 60 participants with confirmed indication for PEP who did not perform HIV testing after completing PEP represented 40% of the non-sexual exposures (4/10), 50.8% of the heterosexual exposures (33/65) and 27.7% of the MSM exposures (23/83).

Of the 148 individuals assessed at the end of week 4, 5 discontinued PEP prematurely for non-confirmed indication, and 7 discontinued PEP prematurely in spite of a confirmed indication for PEP: 2 for non-adherence (discontinued at day 19 and day 23), 1 for subject's decision (discontinued at day 1), and 4 because of adverse events: 3 participants for gastrointestinal intolerance at day 3, day 15 and day 17, respectively, and 1 participant for fatigue at day 25.

Table 1. Baseline sociodemographic and medical characteristics of the 162 participants

	Total	Non-sexual exposure ($N = 13$)	Sexual exposure	
			heterosexual ($N = 65$)	MSM ($N = 84$)
Male	120 (74.1)	4 (30.7)	32 (49.2)	84 (100)
Age (years, mean ± SD)	32.9 ± 11.1	36.9 ± 11.8	30.9 ± 8.7	34.1 ± 12.4
Geographic origin				
born in France	137 (84.6)	11 (84.6)	49 (75.4)	77 (91.7)
born outside France	25 (15.4)	2 (15.4)	15 (24.6)	7 (8.3)
European Union[a]	6 (3.7)	0	3 (4.6)	3 (3.6)
Africa[b]	18 (11.1)	2 (15.4)	13 (20.0)	3 (3.6)
other[c]	1 (0.6)	0	0	1 (1.2)
Study level ($n = 129$)				
primary school	3 (2.3)	0	3 (5.8)	0
school-leaving diploma	42 (32.6)	3 (30)	17 (32.7)	22 (32.8)
university	84 (65.1)	7 (70)	32 (61.5)	45 (67.2)
Professional activity ($n = 133$)				
worker	84 (63.2)	9 (69.2)	32 (61.5)	43 (63.2)
student	24 (18.0)	1 (7.7)	9 (17.3)	14 (20.6)
inactive[d]	25 (18.8)	3 (23.1)	11 (21.2)	11 (16.2)
History of consulting for PEP ($n = 154$)	33 (21.4)	3 (25)	4 (6.5)	26 (32.5)
HBV status ($n = 122$)[e]				
unprotected	44 (36.1)	2 (25.0)	21 (39.6)	21 (34.4)
protected by vaccination	71 (58.2)	5 (62.5)	30 (56.6)	36 (59.0)
previous recovered infection	7 (5.7)	1 (12.5)	2 (3.8)	4 (6.6)
History of syphilis (TPHA+) ($n = 133$)	20 (14.9)	0	2 (3.5)	18 (24.0)
HCV-positive serology ($n = 140$)	0	0	0	0

Values shown are *n* (%), unless otherwise indicated.
[a]European Union: Germany ($n = 2$), Belgium ($n = 1$), Spain ($n = 1$), Portugal ($n = 2$).
[b]Africa: Algeria ($n = 1$), Morocco ($n = 1$), Tunisia ($n = 2$), Angola ($n = 1$), Cameroon ($n = 2$), DR Congo ($n = 1$), Republic of the Congo ($n = 1$), Côte d'Ivoire ($n = 3$), Gabon ($n = 2$), Niger ($n = 1$), Nigeria ($n = 3$).
[c]Other: Haiti.
[d]Unemployed ($n = 15$), disabled ($n = 2$), retired ($n = 4$), other non-active ($n = 4$).
[e]HBV serological status interpretation—unprotected: negative anti-HBs Ab and negative anti-HBc Ab; protected by vaccination: positive anti-HBs Ab and negative anti-HBc Ab; previous recovered infection: positive anti-HBs Ab and positive anti-HBc Ab or positive anti-HBs Ab and equivocal anti-HBc Ab.

One hundred and three participants (69.6%) declared at least one adverse event during PEP: the most frequent were fatigue, gastrointestinal intolerance, headache and sleeping disorders. No participant presented a severe clinical adverse event. Clinical adverse events and time of occurrence are reported in Table 3.

At baseline, mean AST and ALT were 27.17±11.69 and 26.2±17.08 IU/L, respectively, with no significant variation at weeks 2 and 4. Mean creatininaemia increased very slightly between baseline and week 2 to 79.8±12.7 and 87.1±13.2 μmol/L, respectively ($P < 0.0001$), and remained stable at week 4. No other biological adverse event occurred. No participant stopped PEP due to a biological adverse event.

Discussion

This study confirms that the TDF/FTC/RPV single-tablet regimen for 28 days is well tolerated as occupational and non-occupational PEP. Even though almost 70% of the participants experienced at least one adverse event, mostly of mild severity, no serious adverse event occurred, and only four participants (2.8%) stopped PEP prematurely due to an adverse event. This study corroborates the observations made in 100 MSM treated with TDF/FTC/RPV 1 pill/day for 28 days as PEP in Australia, where 88% participants experienced at least one adverse event, but none of these was serious.[24] The high frequency of adverse events could be exacerbated by the anxiety experienced by these subjects, which can engender or worsen non-specific symptoms such as those mainly observed during PEP treatment: gastrointestinal and sleeping disorders amongst others.

Even though this study was not designed for this objective, treatment adherence was assessed by participants' self-evaluation. We found that <5% of subjects stopped their treatment prematurely with no medical reason to do so, and >85% of participants completed the 4 week treatment as planned. Almost 10% of participants were lost to follow-up before the telephone contact at week 4, leading to missing data concerning adherence and tolerability. Complete clinical follow-up (until week 4) is slightly higher in most of the recent studies evaluating PEP; however, these studies usually set a shorter follow-up, with more visits and more counselling than our study in close to real-life conditions.[23–25] Only

Table 2. HIV status of the source person

			Sexual exposure ($N = 150$)	
	Total ($N = 163$)	Non-sexual exposure ($N = 13$)	heterosexual ($N = 65$)	MSM ($N = 85$)
Unknown	134 (82.2)	7 (53.8)	61 (93.9)	66 (77.7)
HIV negative	2 (1.2)	0 (0)	1 (1.5)	1 (1.2)
HIV positive	27 (16.6)	6 (46.2)	3 (4.6)	18 (21.2)
viral load ($n = 27$)				
<50 copies/mL	7 (25.9)	0 (0)	0 (0)	7 (38.9)
≥50 copies/mL	3 (11.1)	2 (33.3)	1 (33.3)	0 (0)
unknown	17 (63.0)	4 (66.7)	2 (66.7)	11 (61.1)
HIV follow-up ($n = 27$)				
none	6 (22.2)	3 (50)	1 (33.3)	2 (11.1)
unknown	2 (7.4)	0 (0)	0 (0)	2 (11.1)
regular follow-up	19 (70.4)	3 (50)	2 (66.7)	14 (77.8)
ART				
none	1 (5.3)	0 (0)	1 (50)	0 (0)
unknown	5 (26.3)	1 (33.3)	0 (0)	4 (28.6)
ART[a]	13 (68.4)	2 (66.7)	1 (50)	10 (71.4)

All values shown are *n* (%); ART, antiretroviral therapy.
[a]Viral load ≥50 copies/mL $n = 1$ (heterosexual exposure); viral load <50 copies/mL $n = 7$ (MSM); viral load unknown $n = 5$ (two non-sexual exposures, three MSM).

38% of participants did not complete their HIV serology at week 16. This is better than the rates reported in real-life situations: in a meta-analysis including 97 studies, only 31% of the individuals treated by PEP completed the serological follow-up,[26] and in a retrospective French study, serological follow-up was completed by 30% of the patients consulting for PEP, whether a treatment was prescribed or not.[27] The reasons why a third of persons who had high-risk exposure and were prescribed PEP and counselling did not consider having an HIV test after completing post-exposure treatment might be diverse: high confidence in prophylaxis and/or a decrease in risk perception 4 months after the index event and/or omission and/or denial, etc. Sociopsychological determinants around this issue could help to evaluate this behaviour and propose solutions such as text reminders for the 4 month clinic visit. A second clinic visit, 3 months after end of PEP, could also be used to reinforce prevention messages and counselling around safer practices.

Amongst the important criteria to consider when formulating national or local guidelines concerning the choice of a specific medication for PEP are its cost and the probability of transmission of a drug-resistant HIV strain. The cost was obviously an important consideration when we designed this study, and when the experts later wrote new French guidelines. In fact, single-tablet TDF/FTC/RPV was at that time up to 33% cheaper than other alternatives, such as tenofovir/emtricitabine+raltegravir, tenofovir/emtricitabine+darunavir/ritonavir or TDF/FTC/elvitegravir/cobicistat. Concerning the risk of transmission of a drug-resistant HIV strain, since the rate of primary resistance to rilpivirine is <5% in antiretroviral-naive HIV-1-infected patients in France,[28] guidelines recommend not taking into account the risk of primary resistance to rilpivirine when prescribing PEP unless the source person is known to be infected with a rilpivirine-resistant HIV strain. The fact that no HIV seroconversion was reported after TDF/TFC/RPV PEP supports this attitude.

Compared with the study conducted in Australia,[24] in an exclusively MSM population, our study enrolled a very diverse population. Apart from the MSM group, aged ∼35 years, born in France, with a high sociocultural level, 44% of PEP for sexual exposures were in heterosexual men and women in their early thirties, a quarter of whom were born outside France, and 4.9% of our cohort were healthcare workers with occupational exposure, a quarter of whom had already received PEP in the past.

The population of our study differs from the HIV-positive population in France: in 2015, 43% of the newly diagnosed HIV-infected persons were MSM who were mostly born in France (82%), and 38% were heterosexual men or women who were born elsewhere.[29] Furthermore, the same year, another study estimated that between 35% and 49% of the HIV-infected migrants living in France and coming from sub-Saharan Africa had contracted HIV in France and not in their country of origin.[30] Oddly, this population only represents ∼10% of the individuals consulting for PEP in our region. Therefore, it seems on the one hand that the French MSM population is correctly represented in our study, and consults for PEP, but on the other hand that the heterosexual migrants (who are at high risk of acquiring HIV) do not consult for PEP after an unprotected sexual exposure. One hypothesis is the low risk perception of HIV transmission during unprotected sex, and ignorance of PEP itself and how simple it is to access PEP for free in French hospitals. A recent study in New York in HIV-negative individuals at high risk of acquiring HIV showed that more than half of the MSM knew about PEP, compared with <20% of heterosexuals, and that knowledge about PEP was better in white individuals (53%) than in African Americans (30%) and Hispanics (36%), even though apart from MSM, African American and Hispanic

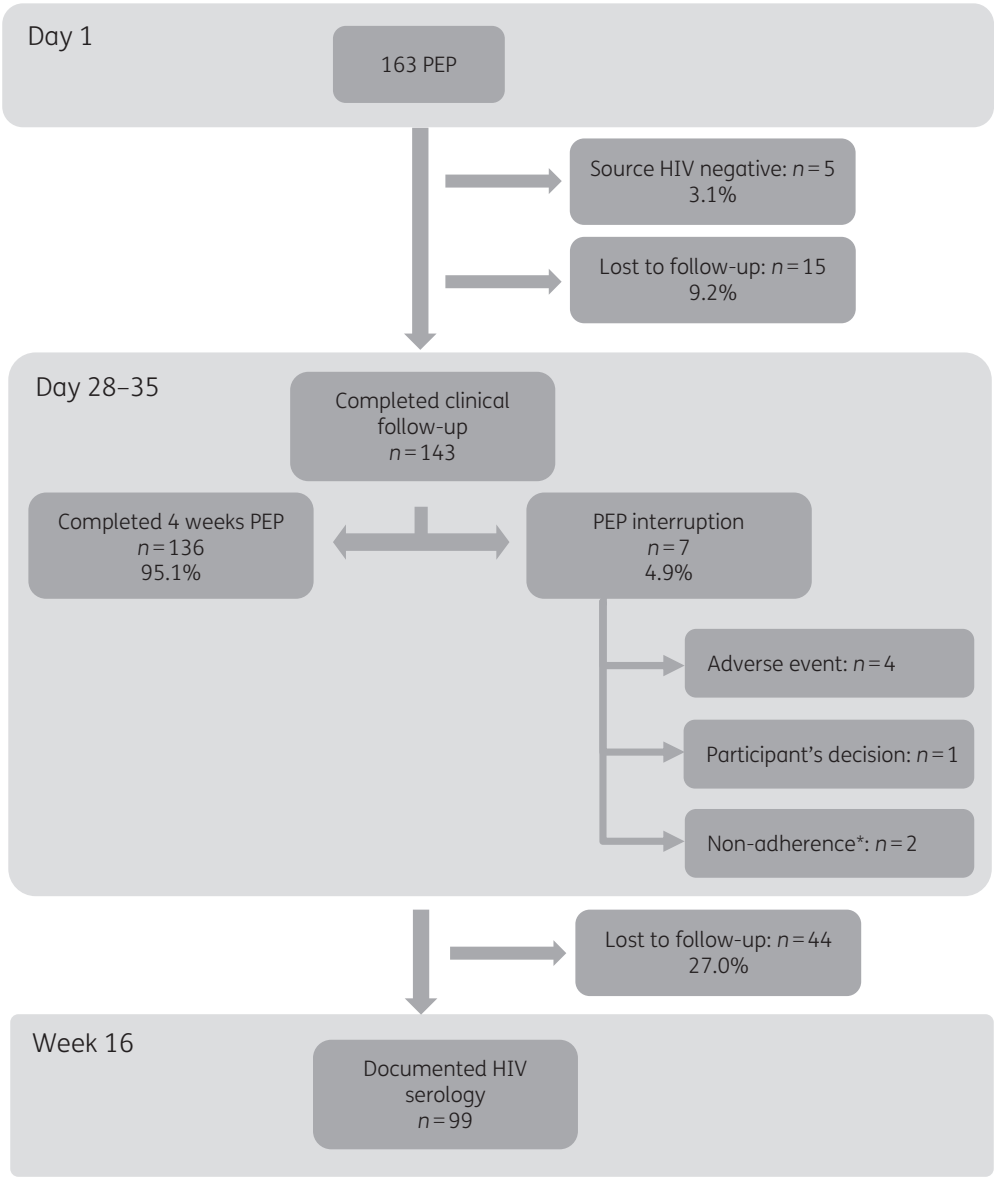

Figure 1. Flow chart of the 163 PEP. The asterisk indicates that non-adherence was self-reported at the week 4 telephone call.

heterosexuals are now the groups most exposed to HIV.[31,32] Another hypothesis that could explain insufficient seeking of PEP by some individuals is having bad previous experiences, such as excessive anxiety, blaming and sanctimonious speeches from hospital staff, long waits, difficulty finding the hospital pharmacy, and bad tolerability of the PEP regimen eventually administered, leading these highly exposed subjects to reject PEP following a subsequent risky exposure, as previously described in a study amongst HIV-positive subjects who had previously consulted for PEP.[33] Therefore there is both an urgent need for information about HIV transmission and the means of prevention in specific, highly exposed populations, and a necessity to improve the overall medical care of subjects consulting for PEP. There is also a need to adapt PEP clinics to the changing population attending for high-risk exposure. With large-scale implementation of pre-exposure prophylaxis in MSM at high risk of acquiring HIV, such as those having a history of syphilis (24% of our population) or previous PEP use (one-third of our population), the relative proportion of heterosexuals, including migrants, presenting for PEP is going to increase soon.

Our study has some limitations. The main limitation is its open-label design and the missing data, particularly regarding HIV serology test post-PEP. However, our results do not differ from those of previous studies. Evaluation of tolerability was based on self-reporting and on a telephone call at the end of the 4 week PEP course. Even if the evaluation was subjective and not standardized, we could assess the severity of the claimed symptoms, and whether or not these led to premature PEP discontinuation. It would have been interesting to collect data on subjects who consulted for sexual or non-sexual exposure risk who were not prescribed TDF/FTC/RPV.

Table 3. Most frequent adverse events (>5%) in the population that completed the clinical follow-up (143 participants)

	Frequency			Severity		
Adverse event	*N*[a]	%[b]	Mean time of occurrence (days ± SD)	grade	*N*	%
Gastrointestinal disorders						
nausea	31	21.7	12.6 ± 10.9	1–2	30	96.8
				3	1	3.2
diarrhoea	28	19.6	12.8 ± 10.1	1–2	25	89.3
				3	3	10.7
abdominal pain	23	16.1	13.2 ± 9.7	1–2	22	95.7
				3	1	4.3
vomiting	9	6.3	4.8 ± 5.2	1–2	9	100
				3	0	0
General signs						
fatigue	50	35.0	16 ± 12.2	1–2	47	94
				3	3	6
muscle and joint pain	10	7.0	11.8 ± 5.8	1–2	8	80
				3	2	20
Sleep disorders						
insomnia	14	9.8	17.6 ± 18.9	1–2	13	92.9
				3	1	7.1
CNS disorders						
dizziness	13	9.1	6.9 ± 4.8	1–2	12	92.3
				3	1	7.7
headache	16	11.2	13.5 ± 10.7	1–2	15	93.8
				3	1	6.2

[a]Number of participants with an event (participants can have multiple events).
[b]Percentage of total population with event.

Finally, even though no PEP failure occurred in our study, this result can only be extrapolated to settings where prevalence of primary rilpivirine resistance is low, and further studies are required to evaluate rilpivirine-based PEP in other epidemiological settings. The main strength is the unselected population of the study as very few studies have evaluated TDF/FTC/RPV in a large population both in sexual and occupational settings.

In conclusion, the one pill a day regimen of TDF/FTC/RPV for 28 days is a well-tolerated therapeutic option after sexual and non-sexual events causing exposure to HIV. This excellent tolerability and the simplicity of intake lead to low premature discontinuation of treatment, which is a strong asset of this PEP regimen. This study validates the choice made in French guidelines in 2016, and recently reasserted in the new 2017 guidelines, to make single-tablet TDF/FTC/RPV the first-line PEP apart from particular cases. The low number of subjects born outside France in comparison to the frequency of newly HIV diagnosed infections in this population highlights a lack of knowledge regarding the existence and accessibility of PEP, and should lead to specific prevention campaigns to avoid missed opportunities for PEP in this population.

Acknowledgements

An abstract of these data was presented at 9th AIDS Conference in Paris, France, 23–25 July 2017 (poster WEPECO918) and EACS European AIDS Clinical Society, 25–27 October 2017, Milan, Italy (PE9/29).

Members of the COREVIH Pays de la Loire Study Group

François Raffi, Clotilde Allavena, Camille Bernaud, Éric Billaud, Bénédicte Bonnet, Sabelline Bouchez, Cécile Brunet, Nolwenn Hall, Pascale Morineau-Le Houssine, Véronique Reliquet, Florian Vivrel, Hervé Hue, Morane Cavellec, Albane Soria (Nantes); Sophie Blanchi, Nicolas Crochette, Hikombo Hitoto, Lucia Perez, Naoual Qatib (Le Mans); Olivier Bollengier Stragier, Jean-Luc Esnault, Thomas Guimard, Dominique Merrien, Marine Morrier, Philippe Perré, Laetitia Laine (La Roche-sur-Yon); Christophe Michau, Carole Grand-Courault (Saint Nazaire); Thomas Jovelin, Solène Sécher.

Funding

This study was supported by internal funding.

Transparency declarations

F. R. received research funding or honoraria or consulted for AbbVie, Bristol-Myers Squibb, Gilead, Janssen and MSD. C. A. and E. B. received travel grants or honoraria from Gilead, ViiV, MSD and Janssen. All other authors: none to declare.

Author contributions

All authors met the criteria for authorship including study conception and design; data acquisition (E. B., B. B., D. M., H. H., S. B., C. M., N. H., L. P., C. A.), analysis (S. S., C. A., M. C.) and interpretation (F. R., E. B., C. A., S. S., M. C.);

and drafting and critical revision of the work for important intellectual content (F. R., M. C., C. A.). All authors approved the final version for publication and agree to be accountable for all aspects of the work.

References

1 World Health Organization. Guidelines on Post-Exposure Prophylaxis for HIV and the Use of Co-Trimoxazole Prophylaxis for HIV-Related Infections among Adults, Adolescent and Children: Recommendations for a Public Health Approach. *Supplement to the 2013 WHO Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection*. 2014. http://www.who.int/hiv/pub/guidelines/arv2013/December2014-ARVsupplement-chap5.pdf?ua=1.

2 Ford N, Mayer KH, World Health Organization Postexposure Prophylaxis Guideline Development Group. World Health Organization guidelines on post-exposure prophylaxis for HIV: recommendations for a public health approach. *Clin Infect Dis* 2015; **60** Suppl 3: S161–4.

3 Günthard HF, Saag MS, Benson CA *et al*. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2016 recommendations of the international antiviral society-USA Panel. *JAMA* 2016; **316**: 191–210.

4 Martin LN, Murphey-Corb M, Soike KF *et al*. Effects of initiation of 3′-azido, 3′-deoxythymidine (zidovudine) treatment at different times after infection of rhesus monkeys with simian immunodeficiency virus. *J Infect Dis* 1993; **168**: 825–35.

5 Tsai CC, Emau P, Follis KE *et al*. Effectiveness of postinoculation (R)-9-(2-phosphonylmethoxypropyl) adenine treatment for prevention of persistent simian immunodeficiency virus SIVmne infection depends critically on timing of initiation and duration of treatment. *J Virol* 1998; **72**: 4265–73.

6 Otten RA, Smith DK, Adams DR *et al*. Efficacy of postexposure prophylaxis after intravaginal exposure of pig-tailed macaques to a human-derived retrovirus (human immunodeficiency virus type 2). *J Virol* 2000; **74**: 9771–5.

7 Connor EM, Sperling RS, Gelber R *et al*. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. *N Engl J Med* 1994; **331**: 1173–80.

8 Wade NA, Birkhead GS, Warren BL *et al*. Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. *N Engl J Med* 1998; **339**: 1409–14.

9 Camacho-Ortiz A. Failure of HIV postexposure prophylaxis after a work-related needlestick injury. *Infect Control Hosp Epidemiol* 2012; **33**: 646–7.

10 Borba Brum MC, Dantas Filho FF, Yates ZB *et al*. HIV seroconversion in a health care worker who underwent postexposure prophylaxis following needlestick injury. *Am J Infect Control* 2013; **41**: 471–2.

11 Roland ME, Neilands TB, Krone MR *et al*. Seroconversion following nonoccupational postexposure prophylaxis against HIV. *Clin Infect Dis* 2005; **41**: 1507–13.

12 Jochimsen EM, Luo CC, Beltrami JF *et al*. Investigations of possible failures of postexposure prophylaxis following occupational exposures to human immunodeficiency virus. *Arch Intern Med* 1999; **159**: 2361–3.

13 Hawkins DA, Asboe D, Barlow K *et al*. Seroconversion to HIV-1 following a needlestick injury despite combination post-exposure prophylaxis. *J Infect* 2001; **43**: 12–5.

14 Yeni P. *Prise en charge médicale des personnes infectées par le VIH*. Rapport d'expert. 2006. https://solidarites-sante.gouv.fr/IMG/pdf/rapport_experts_2006.pdf.

15 Yeni P. *Rapport sur la prise en charge médicale des personnes infectées par le VIH, sous la direction du professeur Patrick Yeni. Recommandations du groupe d'experts*. 2010. https://solidarites-sante.gouv.fr/IMG/pdf/Rapport_2010_sur_la_prise_en_charge_medicale_des_personnes_infectees_par_le_VIH_sous_la_direction_du_Pr-_Patrick_Yeni.pdf.

16 Morlat P. *Prise en charge médicale des personnes vivant avec le VIH. Recommandations du groupe d'experts. Sous l'égide du CNS et de l'ANRS. La documentation française*. 2013. http://solidarites-sante.gouv.fr/IMG/pdf/Rapport_Morlat_2013_Mise_en_ligne.pdf.

17 Morlat P. *Prise en charge médicale des personnes vivant avec le VIH. Recommandations du groupe d'experts. Sous l'égide du CNS et de l'ANRS. Prise en charge des accidents d'exposition sexuelle et au sang (AES) chez l'adulte et l'enfant*. 2017. https://cns.sante.fr/wp-content/uploads/2017/10/experts-vih_aes.pdf.

18 Cresswell F, Waters L, Briggs E *et al*. UK guideline for the use of HIV post-exposure prophylaxis following sexual exposure, 2015. *Int J STD AIDS* 2016; **27**: 713–38.

19 Irvine C, Egan KJ, Shubber Z *et al*. Efficacy of HIV postexposure prophylaxis: systematic review and meta-analysis of nonhuman primate studies. *Clin Infect Dis* 2015; **60** Suppl 3: S165–9.

20 EACS Guidelines. Version 9.0. 2017. http://www.eacsociety.org/files/guidelines_9.0-english.pdf.

21 Centers for Disease Control and Prevention, US Department of Health and Human Services. *Updated Guidelines for Antiretroviral Postexposure Prophylaxis after Sexual, Injection Drug Use, or other Nonoccupational Exposure to HIV*. 2016. https://www.cdc.gov/hiv/pdf/programresources/cdc-hiv-npep-guidelines.pdf.

22 Diaz-Brito V, León A, Knobel H *et al*. Post-exposure prophylaxis for HIV infection: a clinical trial comparing lopinavir/ritonavir versus atazanavir each with zidovudine/lamivudine. *Antivir Ther* 2012; **17**: 337–46.

23 Fätkenheuer G, Jessen H, Stoehr A *et al*. PEPDar: a randomized prospective noninferiority study of ritonavir-boosted darunavir for HIV post-exposure prophylaxis. *HIV Med* 2016; **17**: 453–9.

24 Foster R, McAllister J, Read TR *et al*. Single-tablet emtricitabine-rilpivirine-tenofovir as HIV postexposure prophylaxis in men who have sex with men. *Clin Infect Dis* 2015; **61**: 1336–41.

25 Valin N, Fonquernie L, Daguenel A *et al*. Evaluation of tolerability with the co-formulation elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate for post-HIV exposure prophylaxis. *BMC Infect Dis* 2016; **16**: 718.

26 Ford N, Irvine C, Shubber Z *et al*. Adherence to HIV postexposure prophylaxis: a systematic review and meta-analysis. *AIDS* 2014; **28**: 2721–7.

27 Gantner P, Treger M, De Miscault C *et al*. Predictors of standard follow-up completion after sexual exposure to HIV: five-year retrospective analysis in a French HIV-infection care center. *PLoS One* 2015; **10**: e0145440.

28 Lambert-Niclot S, Charpentier C, Storto A *et al*. Prevalence of pre-existing resistance-associated mutations to rilpivirine, emtricitabine and tenofovir in antiretroviral-naive patients infected with B and non-B subtype HIV-1 viruses. *J Antimicrob Chemother* 2013; **68**: 1237–42.

29 Santé Publique France. *Découvertes de séropositivité VIH et de sida. Point épidémiologique*. 2017. http://invs.santepubliquefrance.fr/Dossiers-thematiques/Maladies-infectieuses/VIH-sida-IST/Infection-a-VIH-et-sida/Actualites/Decouvertes-de-seropositivite-VIH-et-de-sida.-Point-epidemiologique-du-23-mars-2017.

30 Desgrées du Loû A, Pannetier J, Ravalihasy A *et al*. Migrants subsahariens suivis pour le VIH en France: combien ont été infectés après la migration? Estimation dans l'Étude Parcours (ANRS). *Bull Epidémiol Hebd* 2015; 40–41: 752–8. http://www.invs.sante.fr/beh/2015/40-41/2015_40-41_2.html.

31 Misra K, Udeagu C-C. Disparities in awareness of HIV postexposure and preexposure prophylaxis among notified partners of HIV-positive individuals, New York City 2015-2017. *J Acquir Immune Defic Syndr* 2017; **76**: 132–40.

32 Centers for Disease Control and Prevention. *HIV Surveillance Report, 2015*. 2016. https://www.cdc.gov/hiv/library/reports/hiv-surveillance.html.

33 Palich R, Martin-Blondel G, Cuzin L *et al*. Experiences of HIV postexposure prophylaxis (PEP) among highly exposed men who have sex with men (MSM). *Sex Transm Infect* 2017; **93**: 493–8.