UNIVERSITAT DE BARCELONA

Assessment of different post-exposure prophylaxis regimens for prevention of HIV infection in exposed individuals

Alexy Inciarte Portillo

Assessment of different post-exposure prophylaxis regimens for prevention of HIV infection in exposed individuals

Doctoral thesis dissertation presented by

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to apply for the degree of doctor at the University of Barcelona.

Directed by Dr. Esteban José Martinez Chamorro and Dr. Felipe Garcia Alcaide associated professors of University of Barcelona.

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Dr. Felipe García Alcaide holds the title of associated professor of the Department of Medicine of the Faculty of Medicine of the University of Barcelona and Senior Consultant of the Infectious Diseases Service of the Hospital Clínic de Barcelona.

CERTIFIES:

The dissertation entitled:

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Authored by Alexy Inciarte Portillo and directed by myself, is ready to be presented before the appropriate tribunal as part of the requirements for the attainment of a Doctorate degree.

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STATEMENT OF THE DOCTORAL CANDIDATE AND DIRECTOR/S OF ORIGINALITY AND GOODPRACTICES OF THE THESIS

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DECLARE THAT

The doctoral thesis entitled "**"Assessment of different post-exposure prophylaxis regimens for prevention of HIV infection in exposed individuals"**", is original, containing own results and information, without plagiarism from other thesis, publicationsor research from other authors. They also confirm that ethical codes and good practices havebeen followed for its preparation. They declare that they consent that the thesis may be submitted to procedures to verify itsoriginality.

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Director

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Candidate

"Though the back door may be humble, the front door opens to a palace. Appearances deceive, for those who enter through the humble door may leave through the grand entrance."

Own thoughts

“Let no science cease to amaze you, and never lose the spark that ignites your curiosity and passion for discovery. Always strive to expand your horizons and deepen your understanding of the world around you. Don't stop learning, for knowledge is the key that unlocks the doors to new possibilities and more extraordinary achievements. Embrace every opportunity to challenge yourself and grow, for the journey of self-discovery is a never-ending one filled with wonder and excitement”

Own thoughts

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y las ambiciones que, juntas, forman una potencia colectiva insuperable, una fuerza que se materializa en acciones y realidades concretas. A todos y cada uno de los que conforman este hospital caras sin nombres y con nombres, muchas gracias en cada noche y cada día, de incertidumbres, alegrías derrotas y victorias.

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TABLE OF CONTENTS

GLOSSARY

3TC: lamivudine

ABA: abacavir

ABT: albuvirtide

AE: Adverse event.

ARV, Antiretroviral

ARV: antiretroviral.

ATV: atazanavir.

AUC: Area under the curve

BB, Backbone;

BIC, bictegravir.

CAB: cabotegravir

CDC: Center of disease control.

CT: Chlamydia Trachomatis.

DC: dentritic cells.

DOR: doravirine

DRV: darunavir

DTG: dolutegravir

EFV: efavirenz.

ETV: etravirine

EVG: Elvitegravir

FDA: Food drug administration.

FTC, emtricitabine.

GALT: gut associated lymphoid tissues

HSV2: herpes simplex 2.

IAS: International AIDS society.

IDV, indinavir.

II, integrase inhibitors;

ISL, islatravir.

ITIAN

LPV/r: Lopinavir boosted ritonavir

LPV: Lopinavir

MMC: Mucosal mononuclear cells.

MSM, men who have sex with men;

MTR: Multiple tablet regimen.

MVC: maraviroc

NG: Neisseria gonorrhoeae

nPEP: Nonoccupational post exposure prophylaxis:

NNTRI: non-nucleoside reverse transcriptase inhibitor

NVP: nevirapine

OR: Odd ratio.

PD: pharmacodynamics.

PBMC: Peripheral blood mononuclear cells.

PEP, post-exposure prophylaxis;

PI, protease inhibitors;

PID, people who inject drugs;

PK: pharmacokinetics.

PLWH: People living with HIV.

PMPA: (phosphonomethoxy)propyl]adenine

Post exposure prophylaxis: PEP

PrEP: Pre.exposure prophylaxis.

RAL; raltegravir

RPV: rilpivirine

RTV: ritonavir

RT: Rectal tissue.

RF: Rectal fluid.

BP: Blood plasma.

SAE Serious adverse event

SA: Sexual Assault

SMAQ: Simplified Medication Adherence Questionnaire.

SIV: Simian immunodeficiency virus.

SOC, standard of care;

SOC: Standard of care.

STIs: Sexually transmitted diseases.

STR: Single tablet regimen.

TAF: tenofovir/alanine

TasP: Treament as prevention.

TDF: Tenfovir

TDR, trasmitted drug resistance;

WHO: World health organization

ZDV: Zidovudine.

Thesis in the form of collection of published articles

1.- . **Inciarte A**, Leal L, Masfarre L, et al. Post-exposure prophylaxis for HIV infection in sexual assault victims. *HIV Med*. 2020;21(1):43-52. doi:10.1111/hiv.12797

HIV Medicine achieved an impact factor of 3.180 in the ISI Journal Citation Reports, Q1, SUBJECT AREA AND CATEGORY: Infectious disease, Pharmacology and health policies.

2.- **Inciarte A**, Leal L, González E, et al. Tenofovir disoproxil fumarate/emtricitabine plus ritonavir-boosted lopinavir or cobicistat-boosted elvitegravir as a single-tablet regimen for HIV post-exposure prophylaxis. *J Antimicrob Chemother*. 2017;72(10):2857-2861. doi:10.1093/jac/dkx246

J Antimicrob Chemother achieved an impact factor of 5.758 in the ISI Journal Citation Reports 1Q, SUBJECT AREA AND CATEGORY: Infectious disease, Pharmacology and microbiology.

3.- Inciarte A, Lorna L, Alberto C. et al. PK and effect on HIV ex-vivo infectivity of elvitegravir in postexposure prophylaxis. On revision Infect Dis Ther achieved an impact factor of *5.673* in the ISI Journal Citation Reports.

4.- Inciarte et al. Evaluation of (Doravirine / Lamivudine / Tenofovir Disoproxil Fumarate) (Delstrigo®) as a New Strategy for Non-occupational Post Exposure Prophylaxis, a Prospective Open Label Study (DORAVIPEP) https://clinicaltrials.gov/ct2/show/NCT04233372. *Clinical infectious disease* achieved an impact factor of 20.9 in the ISI Journal Citation Reports. On revision Clinical infectious disease, Q1. SUBJECT AREA AND CATEGORY: Infectious disease.

5.- Fernández I, de Lazzari E, **Inciarte A**, et al. Network meta-analysis of post-exposure prophylaxis randomized clinical trials. *HIV Med*. 2021;22(3):218-224. doi:10.1111/hiv.12964 *HIV Medicine* achieved an impact factor of 3.180 in the ISI Journal Citation Reports, Q1.
SUBJECT AREA AND CATEGORY: Infectious disease, Pharmacology and health policies.

Thesis Summary

Introducción: La profilaxis post-exposición (PEP) es una medida para prevenir el VIH utilizada en el contexto posterior a una potencial exposición al mismo. No existen estudios en humanos que puedan valorar su eficacia, por lo que los datos se han extrapolado de modelos animales en donde se consiguió experimentalmente evitar la infección. A partir de los datos de estos estudios, se concluyen dos supuestos para que la PEP sea efectiva:

1. La PEP se debe iniciar en un período inferior a las 72 horas desde el inicio de la exposición.

2. La PEP se debe mantener por un período de 28 días.

A finales de 1980 obtienen los primeros resultados en un estudio de casos y controles en humanos en donde se vio una reducción significativa de la infección del 88%. Posteriormente se realizaron muchos estudios descriptivos y observacionales con una calidad de evidencia baja, y escasos ensayos clínicos que vienen a valorar la tolerabilidad de los distintos regímenes de PPE mas no su eficacia por las limitaciones éticas y metodológicas de los mismos, por lo que los datos clínicos son incompletos, heterogéneos y de calidad científico metodológica baja.

A su vez y de igual importancia son las consideraciones farmacocinéticas y farmacodinámicas del uso de la PEP, como se ha demostrado en los estudios de PrEP en hombres y mujeres donde los resultados han sido muy discordantes y que además de atribuirse a la mala adherencia, el comportamiento farmacocinético y farmacodinámico

(Pk/PD) de los mismos varían según el tipo de tejido y fármaco. Existen pocos estudios que valoren los PK/PD para las distintas pautas de PEP en los distintos compartimentos.

Materiales y Métodos: La presente tesis doctoral tiene un desarrollo metodológico descriptivo-retrospectivo entre el 2006 y el 2016, prospectivo en el contexto de ensayos clínicos y experimentales entre 2015 y 2022. Su ámbito de desarrollo es el Hospital Clínic de Barcelona en la parte Clínica y en la parte experimental involucrando también el Hospital Carlos III, Laboratorio CEK del IDIBAPs y el departamento de Biología Molecular de Chapell Hill, USA.

Se inició un proceso de recolección de datos descriptivos de una cohorte histórica de forma retrospectiva de agresiones sexuales, y por tanto con potencial exposición al VIH (n=1600). Se realizaron dos ensayos clínicos abiertos. El primero donde se comparan dos ramas de tratamiento Tenofovir/Emtricitabine + Eviltegravir/cobicistat (TDF/FTC +EVG/c) vs TDF/FTC+ Lopinavir/Ritonavir (LPV/r) y un ensayo clínico posterior con una única rama consistente en Tenofovir/Lamivudine/Doravirine (TDF/3TC/DOR). Se evaluó la tolerabilidad, la seguridad, el grado de no cumplimento de la PEP y las seroconversiones. En el desarrollo experimental se valoró el comportamiento de farmacodinámico y farmacocinético, la inmunidad de mucosas y la infectividad en modelos de explantes ex vivo para las pautas de tratamiento TDF+FTC +EVG/c vs TDF+FTC+LPV/r. Finalmente se realizó un metaanálisis de distintas pautas de PPE correspondientes a 5 ensayos clínicos.

Resultados: Se detallan los resultados de los 5 estudios realizados.

Trabajo 1:

Profilaxis post-exposición para el VIH en víctimas de agresión sexual (SA): 883 personas que recibieron PEP durante el periodo de 2005 al 2016, de las cuales 631 vivían en Cataluña. En este grupo, la tasa de finalización de la PEP al día 28 fue del 29% (n = 183). La tasa de seguimiento fue del 63% (n = 400) y del 38% (n = 241) en los días 7 y 28, respectivamente. La interrupción del tratamiento estuvo presente en 58 (15%) de 400 pacientes que asistieron al menos a la visita del día 1, siendo el motivo principal los efectos adversos (EA) (n = 35; 60%). Se notificaron EA en 226 (56%) pacientes y fueron principalmente gastrointestinales (n = 196; 49%). Sólo 211 (33%) pacientes regresaron para la prueba del VIH el día 90. Se observó una sola seroconversión en un paciente de hombres que tienen sexo con hombres (HSH) el día 120 adherente al tratamiento, pero con múltiples exposiciones sexuales fuera de la agresión.

Trabajo 2:

Lopinavir/ritonavir vs. Elvitegravir/cobicistat ambos combinados con Tenofovir Fumarato/emtricitabina como regímenes para PPE: El no cumplimiento de profilaxis hasta el día 28 fue de 34% (n=54) sin diferencias significativas entre las ramas [LPV/r 42% (n=16) vs. EVG/c 32% (n=38), p=0.25]. La proporción de pacientes con adherencia subóptima fue significativamente mayor en la rama de LPV/r que EVG/c ((47% vs 9% p 0,0001). Los efectos adversos fueron significativamente más comunes en la rama de LPV/r. Se observó seroconversión en 1 paciente de la rama de EVG/c.

Trabajo 3:

Farmacocinética, farmacodinamia, homeostasis inmunológica e infectividad del Elvitegravir/cobiscistat y Lopinavir/ritonavir con Tenofovir/emtricittabina en profilaxis post exposición: EVG como el RTV alcanzan concentraciones elevadas en la mucosa rectal con proporciones de área bajo la curva (AUC) superiores a 1 con respecto al plasma en ambos fármacos, en contraste, la proporción de LPV es inferior a 1. Se encontró una correlación significativa en los niveles de EVG, LPV, RTV entre diferentes compartimentos ($r = 0.4$, $p = 0.028$). Sin embargo, tanto EVG como LPV no previnieron la infección ex vivo en explantes rectales humanos después de 28 días de PEP. En cuanto la inmunidad la infectividad estuvo inversamente correlacionada con la activación de las células T CD8 en el tejido mucoso rectal [CD38+DR+ ($r= -0,87$, $p< 0,005$), HLA-DR+ ($r= -0,85$ $p< 0,007$) y CCR5+ ($r= -0,9$ $p< 0,002$)].

Trabajo 4:

Evaluación de la combinación de Doravirina/Lamivudina/Tenofovir como pastilla única para PEP no ocupacional: Entre septiembre de 2019 y marzo de 2022, el estudio incluyó a 399 personas. La mediana de edad fue de 30 (27-36) años y el 91% (n = 364) eran hombres. La forma de exposición fue sexo entre hombres en el 84% (n = 331) de los casos; la evaluación del riesgo de transmisión del VIH-1 se consideró "alta" en el 97% (n = 385) de los participantes. El tiempo mediano desde la exposición a la consulta fue de 24 (13-40) horas. La no finalización de la profilaxis postexposición (PEP) fue del 29% (n = 114) (IC del 95%: 24-33) y del 20% (n = 72) (IC del 95%: 16-25) por ITT modificado. Las principales razones de la no finalización fueron la pérdida en el seguimiento (n = 104, 91%) y la intolerancia (n = 8, 7%). La edad avanzada se asoció con un menor riesgo de interrupción prematura (OR = 0,94, $p <0,001$). Ciento veintitrés (31%) participantes

informaron eventos adversos, en su mayoría leves y autolimitados (82%); se produjo la interrupción en ocho casos (2%). La adherencia a la PEP fue del 96% (337/351) y del 99% (285/289) en el día diez y en la semana 4, respectivamente. No hubo casos de transmisión del VIH.

Trabajo 5:

Metaanálisis de redes de profilaxis post-exposición en ensayos clínicos: Los participantes fueron HSH (n = 832, 75%) con exposición no ocupacional al VIH (89,86%). Cuatrocientos cincuenta y cuatro (41%) participantes no completaron su curso de PEP. El Odds Ratio (OR) para la no finalización de PEP en el día 28 en cada antirretroviral en comparación con LPV/r fue: Atazanavir (ATV) 0,95 (IC 95% 0,58-1,56; EVG/c: OR 0,65 IC 95% 0,30-1,37; Raltegravir (RAL): OR 0,68 IC 95% 0,41-1,13 y Maraviroc (MVC): OR 0,69 IC 95% 0,47-1,01 en un análisis de rangos se mostró que EVG/c tenía la mayor probabilidad de ser el mejor tratamiento para las tasas más bajas de incumplimiento de PEP al día. 28, cambio, pérdida de seguimiento o eventos adversos y MVC para discontinuaciones de PEP debido a eventos adversos.

Conclusiones:

1.- Las tasas de seguimiento y cumplimiento en las víctimas de SA fueron pobres. Además, el 50% de los pacientes experimentaron EA, que fueron la razón principal de la interrupción de la PEP.

2.- Se observó una mayor no finalización de la PEP, una adherencia deficiente y eventos adversos en los pacientes asignados al brazo de LPV/r comparado con EVG/c.

3.- Los niveles de PK de EVG y LPV respectivamente en diferentes compartimentos estaban correlacionados entre sí. Sin embargo, ni EVG, ni LPV previnieron la infección ex vivo en explantes rectales humanos después de 28 días de PEP. Por otro lado, la activación de las células T CD8 en la mucosa obstaculiza la infectividad en nuestro modelo. Se necesitan estudios adicionales para validar estos resultados.

4.- Doravirina/Lamivudina/Tenofovir es una opción de comprimido único bien tolerada para la PPE una vez al día.

5.- Existen ventajas de los inhibidores de la integrasa cuando se usan como PEP, particularmente EVG como un régimen de tableta única.

I.- INTRODUCTION

"First impressions are the most lasting." – Proverb

"The important thing is not to stop questioning. Curiosity has its own reason for existing." – Albert Einstein

CHAPTER I: Prevention strategies for HIV

The HIV pandemic has escalated globally to all levels of society since its beginnings, with an unprecedented social, educational, economic, and religious impact. High-income and low-income countries face different challenges, inequalities might have worsened the pandemic, and isolated interventions are not enough to stop new infections. A multidisciplinary approach, with large-scale intervention involving government, implementation of jurisdictional policies, and aid from non-governmental entities, associations, and philanthropic individuals, might help to stop the pandemic.

Behavioral health disparities, including mental health and substance use concerns, HIV stigma, puberty, race inequalities, lack of health education, war, and corruption, worsen HIV disparities among HIV individuals and communities. Evidence-based HIV prevention and behavioral health services are insufficiently scaled to target the population, perpetuating health disparities, thwarting efforts to control the HIV epidemic, and highlighting the need for culturally relevant evidence-based implementation strategies that address these disparities. Biomedical and non-biomedical interventions are needed to work in conjunction to solve challenges.

Figure 1.1.-Effective HIV prevention program require a combination of behavioral, biomedical and structural interventions.

Source: Global information and education on HIV and AIDS, available at: avert.org/professionals/hiv-programming/prevention/overview#footnote56_e7yuzgs

The introduction of this doctoral thesis focuses solely on biomedical strategies that work to avoid the transmission of HIV Infection. The main strategies for preventing HIV infection include: vaccines, barrier methods, microbicides, circumcision, and the use of ART as a treatment for infected people to prevent transmission (TasP), Pre-exposure prophylaxis (PrEP), and post-exposure prophylaxis (PEP). These strategies complement each other, having added value when working altogether. The reasons for using Antiretroviral treatment (ART) for prevention are based on several factors. First, the correlation between the viral load level and the likelihood of HIV transmission. Second, the pathogenesis of viral infection in the host, and lastly, the pharmacokinetics and pharmacodynamics of ART.

The success of transmission is based on the equilibrium between host susceptibility and the virulence of the virus. In the early stages of HIV infection, the virus is less prone to invade when replication is limited to a small number of infected cells (1,2). So, this moment represents an opportunity for interventions such as PrEP and PEP to block the establishment of founder populations of infected cells by inhibiting the steps of viral replication such as integration or reverse transcription. A critical determining factor would be the concentrations of active agents in the infected cells (3). Intrinsic factors of both the virus and the host might play a role in a successful infection(4,5). Also, the initial inoculum might play a role in infection(6). Numerous pharmacological studies have shown that some ART successfully penetrates the genital tract and reaches higher concentrations in genital secretions than in blood, which could play a role in preventing HIV transmission and acquisition (7,8). In addition, the efficacy of some ARVs for prophylaxis has been studied extensively in animal models and has provided proof of concept, and later in human clinical trials.

Biomedical prevention strategies for HIV play a crucial role in the overall efforts to reduce the spread of the virus. These strategies focus on utilizing scientific and medical interventions to prevent HIV transmission. These strategies should be integrated with other approaches, such as behavioral and structural interventions, to provide a comprehensive and holistic response to the HIV epidemic, as previously stated, the discussion in this doctoral thesis is limited to the medical approach. Still, Collaboration between researchers, healthcare providers, policymakers, and affected communities is crucial to ensure the development and implementation of effective prevention strategies.

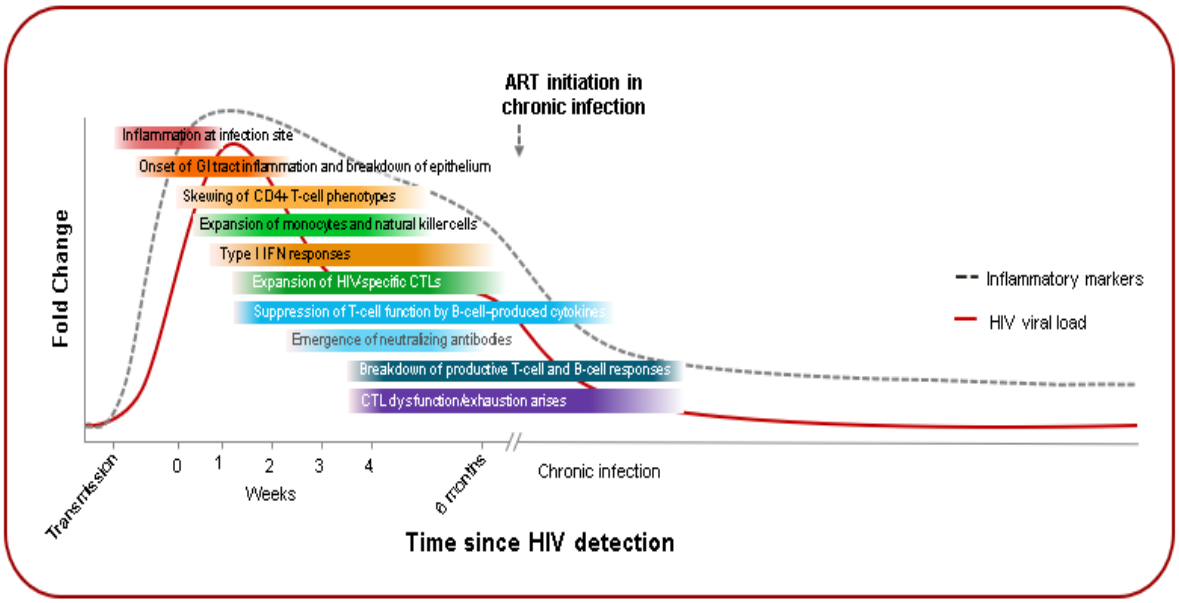
CHAPTER II: HIV transmission

For the most part, defining risk as a critical decision to determine preventive measures for HIV prevention depends on the population's overall prevalence, acquisition mode, and several intrinsic factors in the individual acquiring infection, the source, and the virus itself. This is a general mantra in epidemiology, but among infectious diseases, HIV infection has unique characteristics determining its transmission (9).

HIV infections start mostly in vaginal and rectal mucosae, HIV is transmitted through contact with infected body fluids, such as blood, semen, vaginal fluids, rectal fluids, and breast milk. Those membranes are rich in dendritic cells; the most critical role of DC is as professional antigen-presenting cells. Once inside the host cell, the virus's genetic material (single-stranded RNA) is reverse transcribed into double-stranded DNA by the viral enzyme reverse transcriptase.

It is speculated that dendritic cells migrate to lymph nodes and reticuloendothelial organs, where T cells infected with HIV play an essential role in primary infection. In the primary phase of the infection, massive depletion of CD4 t cells of gut associated lymphoid tissue (GALT) is accomplished by the virus, leading to a persistent microbial translocation with the latter immune activation (10,11). In the chronic stage of the infection memory, cells play an essential role in the latent reservoir (12,13). Multiple arms of the immune system are activated during acute HIV transmission and throughout initial infection (14) (figure 2.1)

Figure 2.1.- Immune responses during the HIV transmission and acute infection.



Modified: Kazer SW, et al. *Immunity* 2020;53:908-924

2.1.- Factors associated with higher transmission rates of HIV

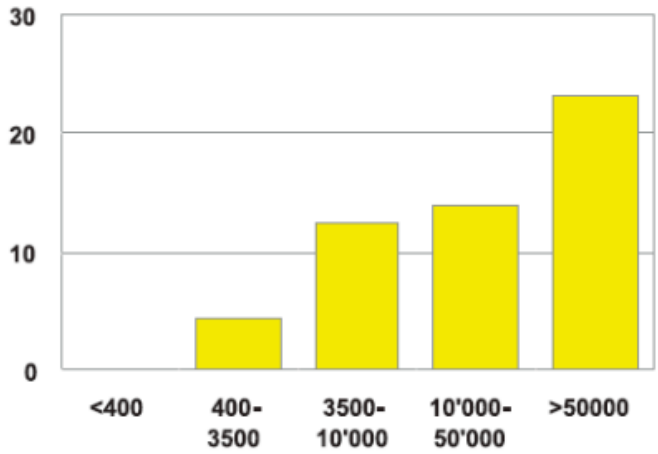
2. 1.2- Viral Subtype

HIV-1 transmission must depend on the appropriate HIV-1 variants; different subtypes may have diverse biological characteristics, which could influence transmission efficiency (15,16). The limited number of studies on the correlation between sexual transmission and the HIV-1 subtype has yielded unreliable results. Research performed in Brazil comparing subtypes B and C displayed an increased risk of heterosexual transmission associated with subtype C (17). Another study in Thailand found an association between subtype E and subtype B and increased risk for heterosexual transmission (18).

2.1.3 -Viral Load

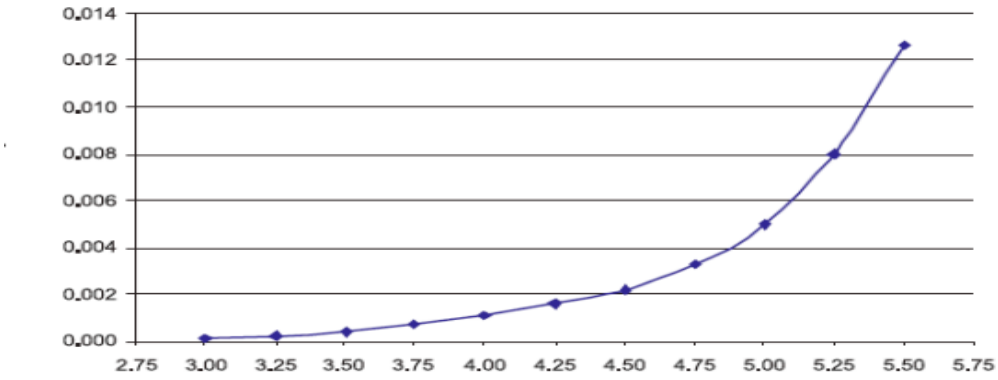
The viral load primarily determines the risk of HIV-1 transmission in the bloodstream. Individuals with a level of HIV-1 RNA of fewer than 1500 copies per milliliter have a low risk of transmission (as shown in Figure 2.2) (19). Additionally, the lower the concentration of HIV-1 RNA in genital secretions, the less likely transmission is to occur (20). This is particularly true for individuals receiving antiretroviral therapy. Conversely, a higher concentration of HIV-1 in genital secretions is associated with a higher likelihood of transmission (21) (Fig 2.2).

Figure 2.2.- Blood viral load and risk of HIV transmission.



The horizontal axis represents the viral concentration in blood (cop/ml), and the vertical axis represents the proportion of transmission. Source: Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *N Engl J Med*. 2000;342(13):921-929. doi:10.1056/NEJM200003303421303

Figure 2.3.- Correlation between seminal viral load and transmission rate.



Adapted from Chakraborty H, Sen PK, Helms RW, et al. AIDS. 2001;15(5):621-627.
The horizontal axis represents the viral concentration in semen (log10 cop/ml), and the vertical axis represents the transmission rate per sexual contact.
in genital secretions determines male-to-female sexual transmission of HIV-1: a probabilistic empiric model.

2.1.4 Sexually transmitted diseases

The concurrent existence of other sexually transmitted infections (STIs) can enhance HIV exposure by breaching the epithelial barrier, recruiting HIV target cells to the genital tract, or generating a pro-inflammatory local stimulus that facilitates transmission. HIV-infected co-infection can increase levels of HIV RNA; This group includes cytomegalovirus (CMV), herpes simplex 2 (HSV2), Neisseria gonorrhoeae (NG), chlamydia trachomatis (CT), and some others (22).

Having an STI more than doubles the risk of an HIV-negative heterosexual person acquiring HIV during sex with an HIV-positive heterosexual partner; no empirical data provides a direct estimate for MSM (see table 2.1) (23). A meta-analysis of 39 studies found that

urethritis, cervicitis, genital ulcerative disease, gonorrhea, and chlamydia increased HIV shedding 2- to 3-fold (24).

Table 2.1. Relative Risks in Per-Act Probability of HIV-1 Transmission

	Final Multivariate Model		
	RR	**95% CI**	***P* value**
Characteristics of the HIV-1–infected partner[a]			
Plasma HIV-1 RNA during follow-up, per $\log_{10}$ copies/mL	2.89	2.19–3.82	<.001
Reported condom use during follow-up	0.22	.11–.42	<.001
Characteristics of the HIV-1–uninfected partner			
Age, per 5 y	0.82	.71–.94	.006
HSV-2 seropositive at enrollment	2.14	1.18–3.88	.012
GUD, by exam or self-report, during follow-up	2.65	1.35–5.19	.004
Trichomonas vaginalis at enrollment, female	2.57	1.42–4.65	.002
Cervicitis or vaginitis during follow-up, female	3.63	1.47–8.92	.005
Circumcision, male	0.53	.29–.96	.037

Adapted from: Hughes JP *et al. Infect Dis*. 2012;205(3):358-365. Abbreviations: CI, confidence interval; GUD, genital ulcer disease; HIV-1, human immunodeficiency virus type 1; HSV-2, herpes simplex virus type 2; RR, relative risk; y, years.

a Gender is included in the model to ensure interpretability of the sex-specific covariates.

HSV2 infection was associated with increases in genital mucosal target cell populations that would be expected to increase susceptibility to HIV infection. In HIV uninfected, HSV2 infection was associated with a ten-fold increase in cervical immature dendritic cells (DC) expressing DC-SIGN receptors and a three-fold increase in cervical CD4+ T cells expressing CCR5 (25). Several studies have also linked the existence of human papillomavirus with HIV acquisition among women, heterosexual men, and MSM (26). Bacterial vaginosis, disruption of the normal vaginal flora, has been associated with a 60% increased risk of HIV-1 acquisition in women and a higher concentration of HIV-1 RNA in the genital tract of HIV-1-infected women. Also, bacterial vaginosis is associated with an increased risk of female-to-male HIV-1 transmission: a prospective cohort analysis among African couples (27).

2.1.5.- Cellular tropism

A critical factor in determining the institution of HIV infection in the mucosa is the availability of susceptible target cells, the CD4+ T cells, and the memory type CD4+ T cells. In mucosa, many CD4+ T cells express the receptor CCR5, for which founder viruses have the tropism; consequently, the presence of CD4+ T cells in mucosa increases susceptibility to infection (28).

2.1.6. -Epithelial Structure at Mucosal Level

The rectal epithelium exhibits the highest probability of HIV transmission (0.3–5%) in comparison to the female (0.05–0.5%) and male genital epithelium (0.04–0.14%), followed by the oral mucosa (0.01%), that is, the least susceptible epithelium (29).

2.2.- Global prevalence and key populations

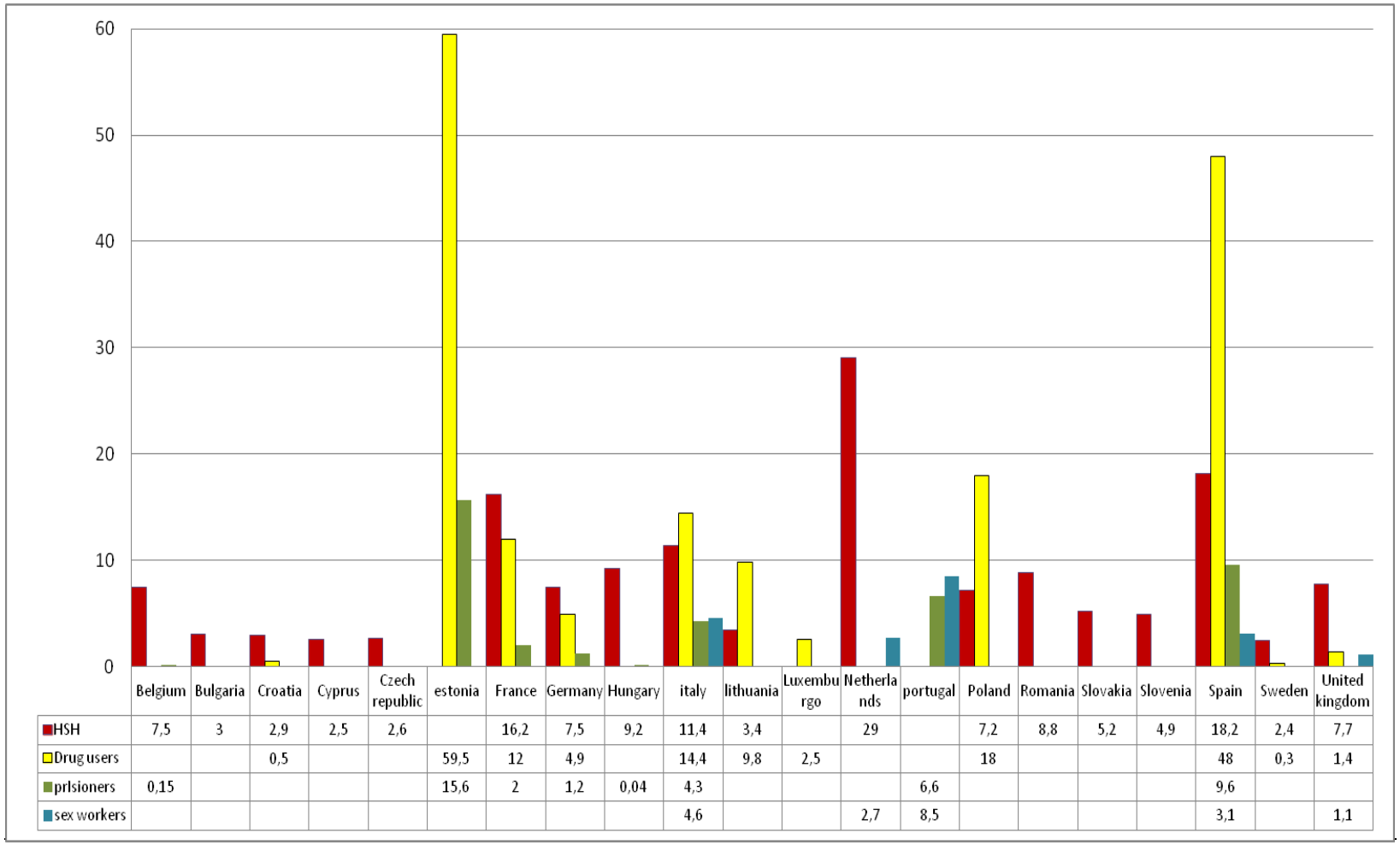
According to the UNAIDS database, 37.7 million people were living with HIV in 2020; of all people living with HIV, 84% knew their status, 73% were accessing treatment 66% were virally suppressed in 2020. About 6.1 million [4.9 million–7.3 million] people did not know they were living with HIV in 2020 (30). Most HIV currently lives in Africa, with 23 million people, representing 61% of the people infected worldwide.

The HIV key populations (sex workers, their clients, HSH, people who injects drugs (PID) and transgender) and their sexual partners accounted for 65% of HIV infections globally. In 2020 there were 1.5 million newly infected cases; there has been a reduction of 52% since the peak in 1997 (30).

In Europe he prevalence of HIV varies greatly across different population groups and countries. Certain key populations, such as those belonging to multiple marginalized groups, are particularly vulnerable to HIV infection. However, there is a need for more studies to be conducted, especially with regards to sex workers, transgender individuals, and people with multiple risk factors due to the limited data (31). (See figure 2.4)

In Europe studies focusing on men who have sex with men (MSM) had the highest number and the widest range of HIV prevalence rates, with prevalence rates ranging from 2.4% to 29.0% across 19 countries. Similarly, studies on people who inject drugs (PWID) revealed a wide variation in HIV prevalence rates, ranging from 0.0% to 59.5% across 13 countries. The prevalence of HIV in prisoners ranged from 0.0% to 15.6% in nine countries, while for sex workers, it ranged from 1.1% to 8.5% in five countries. Transgender individuals had a prevalence rate of 10.9% in one country. The prevalence of HIV was higher in individuals belonging to multiple key population groups.

Figure 2.4. Estimated proportion of HIV seroprevalence in key populations around Europe.



	Belgium	Bulgaria	Croatia	Cyprus	Czech republic	estonia	France	Germany	Hungary	italy	lithuania	Luxembu rgo	Netherla nds	portugal	Poland	Romania	Slovakia	Slovenia	Spain	Sweden	United kingdom
HSH	7,5	3	2,9	2,5	2,6		16,2	7,5	9,2	11,4	3,4		29		7,2	8,8	5,2	4,9	18,2	2,4	7,7
Drug users			0,5			59,5	12	4,9		14,4	9,8	2,5			18				48	0,3	1,4
prisioners	0,15					15,6	2	1,2	0,04	4,3				6,6					9,6		
sex workers										4,6			2,7	8,5					3,1		1,1

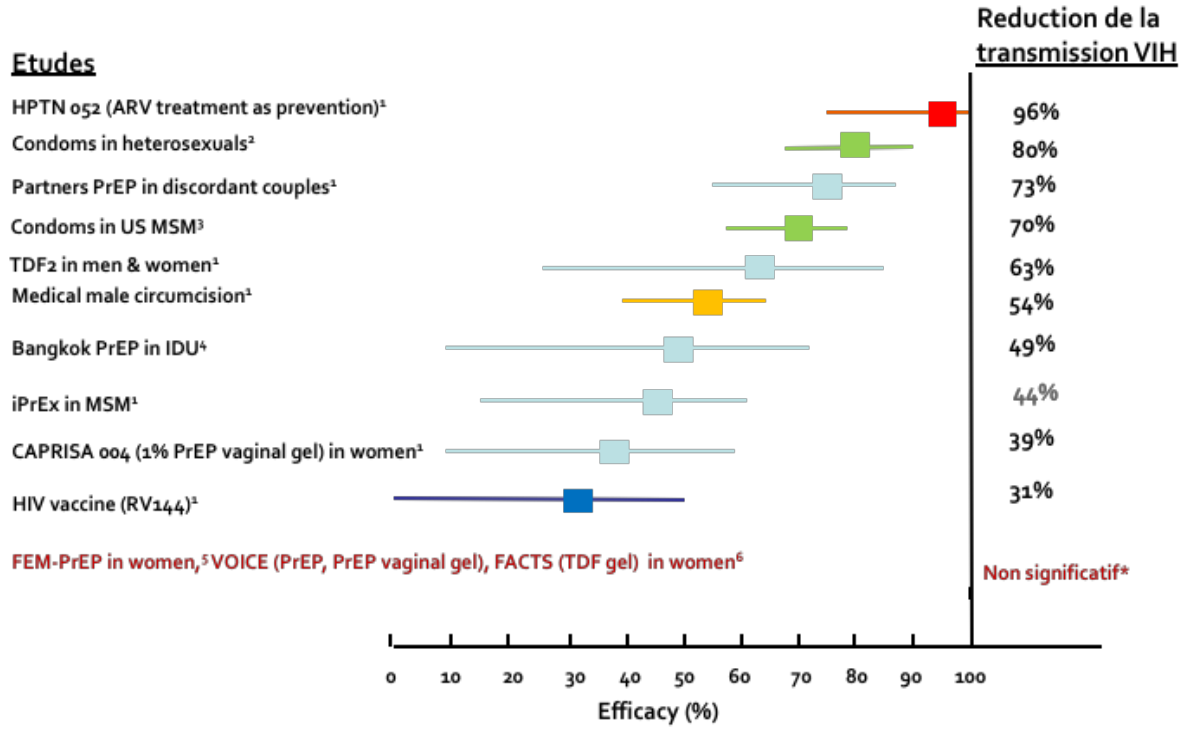
CHAPTER III: Medical prevention strategies on HIV.

Medical prevention strategies for HIV include:

1. Pre-exposure prophylaxis (PrEP): daily use of antiretroviral medication to prevent HIV transmission in individuals who are at high risk of contracting HIV.
2. Post-exposure prophylaxis (PEP): use of antiretroviral medication after a potential exposure to HIV to prevent infection.
3. Treatment as Prevention (TasP): providing antiretroviral medication to individuals who are HIV-positive, which not only improves their health but also reduces the amount of virus in their body and therefore their risk of transmitting HIV.
4. Male and female condoms: barrier methods that prevent the exchange of bodily fluids during sexual activity.
5. Voluntary medical male circumcision: the surgical removal of the foreskin of the penis, which has been shown to reduce the risk of HIV infection in men.

Relative efficacy of all the evaluable measures for preventing HIV are summarized, shown in figure 3.1.

Figure 3.1.- Relative efficacy of prevention strategies.



1. Adapted from Karim SS and Karim QA. Lancet 2011;378:e23–25; 2. Weller S and Davis K. Cochrane Database Syst Rev 2002:CD003255; 3. Smith DK et al. JAIDS 2015;68:337–344; 4. Martin M et al. AIDS 2015;29:819–24; 5. van Damme L et al. NEJM 2012;367:411–422; 6. Marrazzo JM et al. CROI 2013. Atlanta, GA. #26LB, Rees H, CROI 2015, Abs. 26LB

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1

3.1.- Male Circumcision.

Male circumcision is a surgical procedure involving removing the foreskin from the penis. The removal of the foreskin decreases the surface area of the penis that is susceptible to HIV infection and reduces the number of Langerhans cells, which are highly susceptible to HIV infection. Additionally, the foreskin may contain microabrasions that can increase the risk of HIV transmission during intercourse.

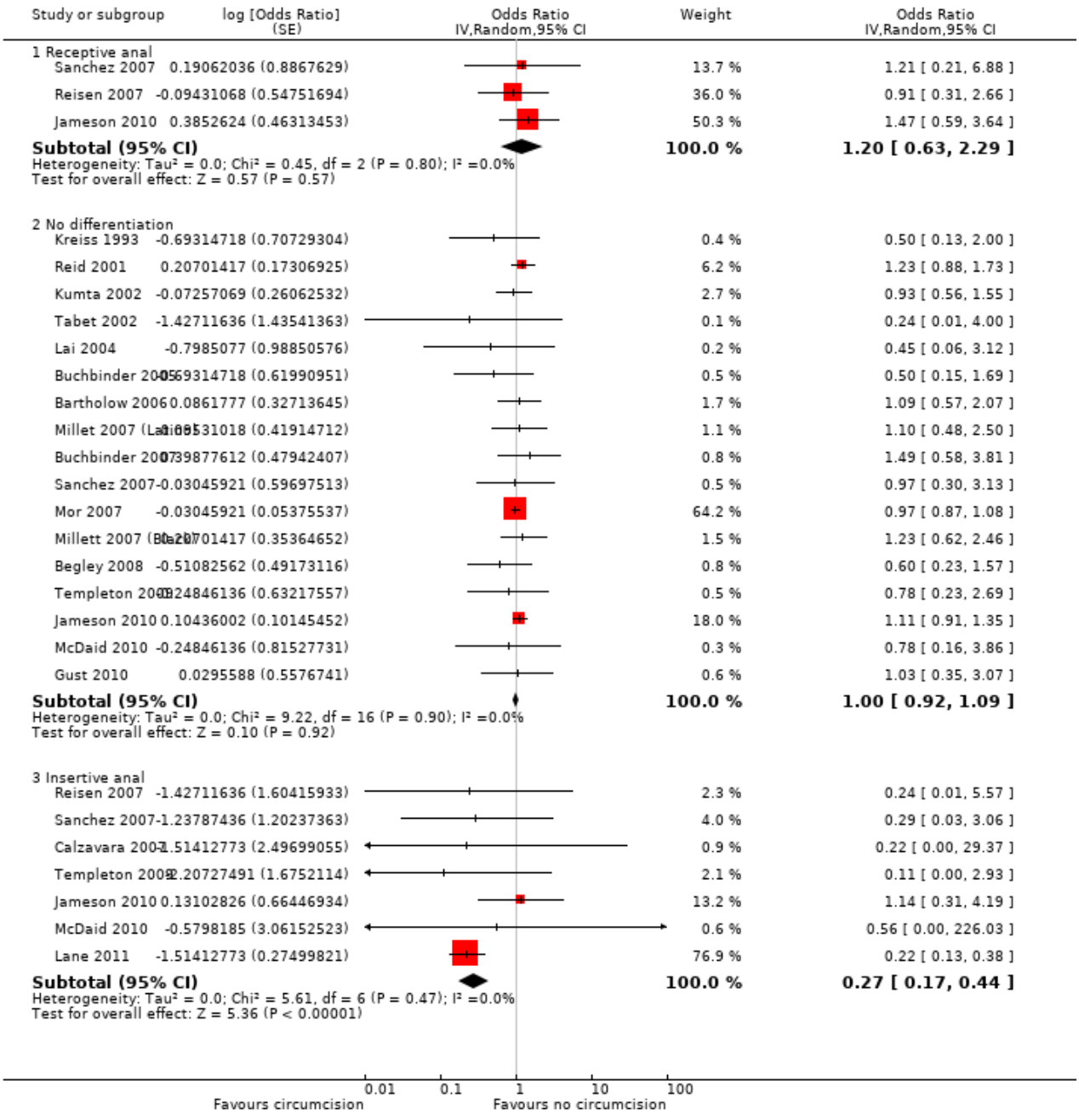
A large amount of evidence supports that male circumcision reduces the risk of HIV acquisition in males. It is biologically plausible that there is an increased susceptibility among uncircumcised men. During intercourse, the internal foreskin is exposed, which has

a more significant number of Langerhans cells and other HIV target cells (32). Also, the foreskin is more prone to epithelial disruption and mechanical abrasion (33). Data suggest that circumcision also reduces the risk of genital ulcerative disease such as syphilis and chancroid, which is a predisposing factor for HIV acquisition (34). Previous observational studies indicated a protective response to circumcision. Three clinical trials demonstrated a risk reduction of 60% of HIV acquisition (35-38).

One clinical trial evaluated the effect of male circumcision on female transmission. Due to futility, 18% of the women in the intervention group versus 12% in the control group after two years acquired HIV (39). Current information points out that male circumcision is not protective for HIV acquisition in female partners; this data is extrapolated from indirect epidemiological data of zero-discordant couples (40) According to mathematical models, at least theoretically, an indirect benefit of protection among women would be gained by a large-scale male circumcision due to decreasing prevalence of HIV in the potential partners (41)

A systematic review of 21 studies on the MSM population showed no significant differences in reducing HIV acquisition among MSM. However, a sub-analysis group of 7 studies on insertive penile sex found a significant effect of reduction in the pooled estimated of 73% in contrast with receptive penile sex (42).

Figure 3.2.- Male circumcision for prevention of homosexual acquisition of HIV in men, outcome by sexual position.



Source: Wiysonge CS et al. Cochrane Database Syst Rev . 2011 Jun 15;(6):CD007496. doi: 10.1002/14651858.CD007496.pub2., Outcome 2 HIV infection by sexual position.

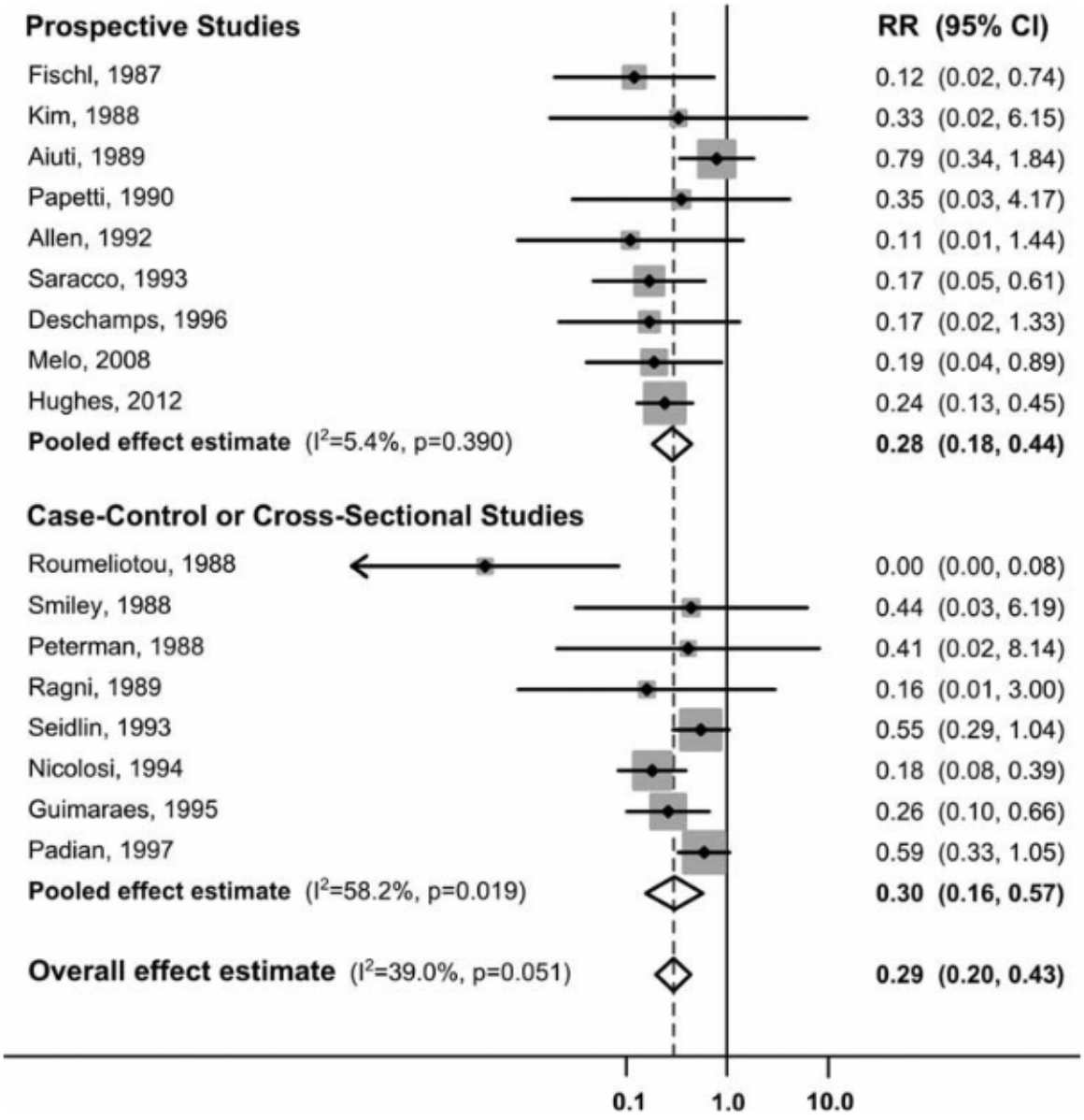
3.2.- Condom use.

Condom use is a highly effective measure for the prevention of HIV transmission during sexual intercourse. When used consistently and correctly, condoms act as a physical barrier that prevents the exchange of body fluids between sexual partners, including semen, vaginal fluids, and blood, all of which can contain HIV. Condoms are also effective in reducing the risk of other sexually transmitted infections (STIs) that can facilitate HIV transmission. However, the effectiveness of condoms is highly dependent on consistent and correct use, which can be influenced by a range of factors, including access, availability, acceptability, and individual preferences.

Scarve data has been available concerning condom effectiveness for MSM, the population at the most significant risk for infection in developed countries. Because of heterogeneous numbers of partners and acts, ostensible degrees of risk based on the relative frequency of condom use (always, sometimes, or never) do not consistently reflect increasing degrees of exposure. Memory bias makes it difficult to determine representative results regarding condom use in high-risk populations (33). A systematic review and meta-analysis aimed to reassess the effectiveness of condoms in reducing HIV transmission by more than 70% when used consistently by HIV serodiscordant heterosexual couples. (43). (Figure 3.3)

The effectiveness of condoms for MSM remains unclear due to inadequate information and unreliable data collection. This is due to varying numbers of partners and levels of risk that are not accurately reflected. However, in four significant cohorts, using condoms consistently during receptive anal intercourse reduced the odds of new HIV infection per HIV-positive partner by 91% (44).

Figure 3.3.- Transmission among HIV serodiscordant heterosexual couples who always used condoms compared to those who never used condoms:



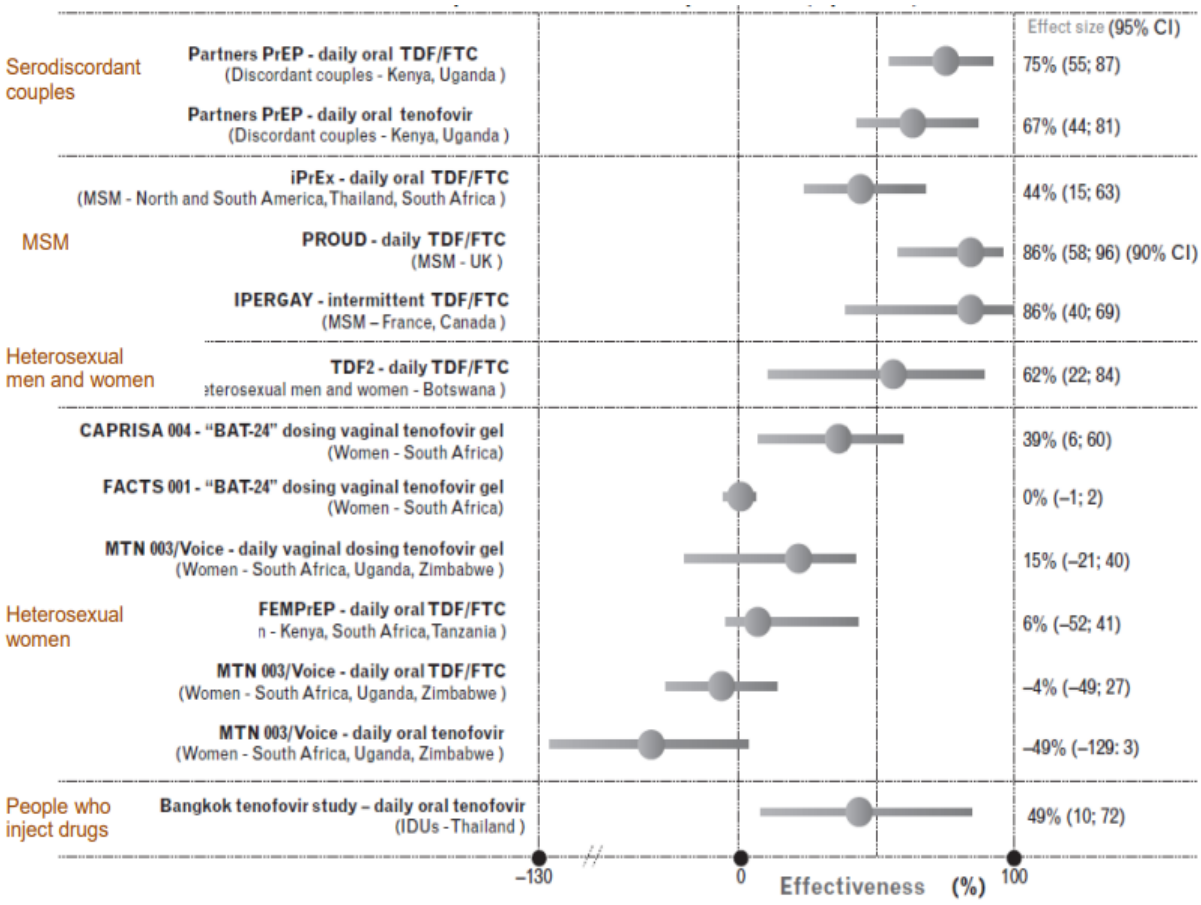
Source: Reisen CA et al, J LGBT Health Res. 2007;3(4):29-36. Forest plot for HIV transmission among HIV serodiscordant heterosexual couples who always used condoms compared to those who never used condoms: results from primary studies and meta-analyses. The RRs and 95% CIs are displayed on a logarithmic scale. Pooled effect estimates are from random-effects models. RR: relative risk; CI: confidence interval

3.3. - Pre-Exposure prophylaxis

The concept of using antimicrobials to prevent infectious diseases has been proposed previously. PrEP is the use of Antiretroviral (ARV) before potential exposure to HIV during risk periods. Clinicians widely use it to prevent numerous infectious diseases, including herpes simplex infection, rheumatic fever, recurrent meningitis, malaria, and pneumocystis infection (45). The ARV drugs recommended for oral PrEP are TDF alone or combined with FTC. These microbicides have been potent and have limited adverse effects, thus rendering them efficacious and safe for PrEP (46,47). PrEP has several advantages over other prevention strategies; it is used before exposure, the dose is not related to a particular sexual relationship, it does not require the individual to identify a specific high-risk situation, and it does not need to be initiated during a critical period after exposure (48).

Eleven clinical trials on PrEP with placebo among different risk groups were conducted from 2005 to 2015 (See Figure 3.4). Results from the literature on PrEP studies are not essentially homogeneous and substantially differ among the different risk groups. The efficacy ranges from absence of protection-to-protection levels as high as 96%, and the risk is reduced by more than 70% among people who inject drugs. Several studies in southern Africa did not find oral or topical PrEP to effectively prevent HIV transmission to women. They are attesting to the complex nature of PrEP implementation (49). While PrEP is highly effective when taken consistently, and studies have shown that it can reduce the risk of HIV transmission by up to 99% (47). It is important to note that PrEP is not a substitute for other prevention methods, such as condoms, and it does not protect against other sexually transmitted infections (STIs).

Figure 3.4.- Clinical trial evidence for oral and topical tenofovir-base prevention



Source : Mayer, KH, et al. Curr Opin HIV AIDS. 2015; 10:226-232. Modified from AVAC Report. 2013.

In 2012 the FDA announced the approval of Truvada® [tenofovir disproxil 245mg/emtricitabine 200mg (TDF-FTC)] as PrEP (50); since then, entities such as the WHO, the Center for Disease Control (CDC), the International AIDS Society (IAS) and the European AIDS Society have recommended PrEP as a prevention strategy and have developed guidelines for the use of TDF-FTC in HIV prevention (51-53).

PrEP was approved in Spain in 2017, and it was officially integrated into the public health system in November 2019. The implementation process has been challenging in various

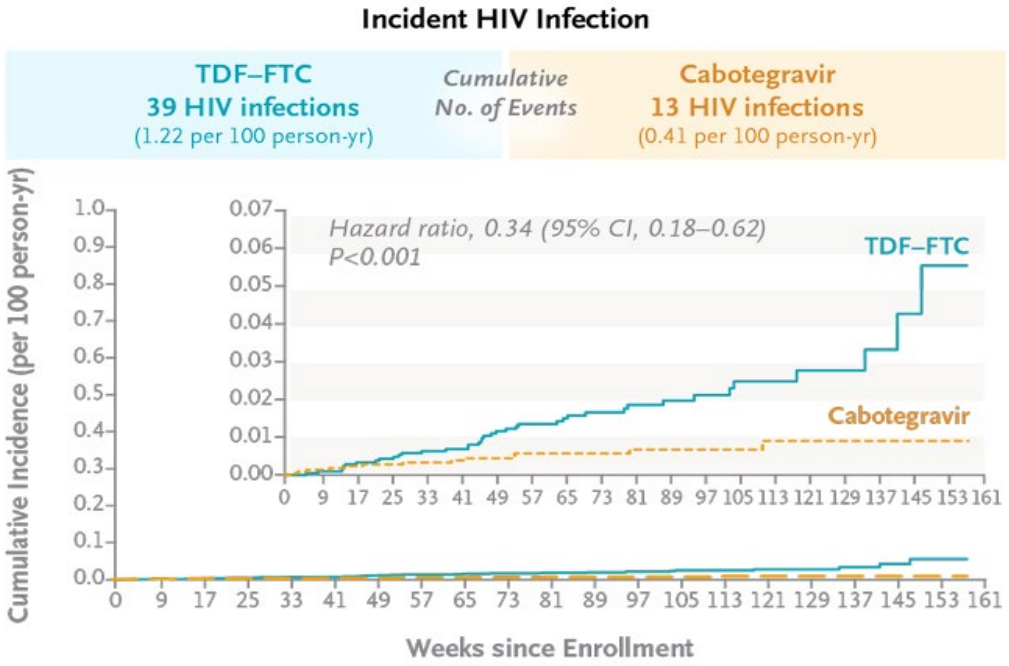
European countries since the FDA's initial approval. In December 2021, the FDA approved Apretude®, an extended-release formulation of cabotegravir, as the first long-acting injectable option for HIV, which reduces the risk of HIV acquisition more than the standard of care (SOC) (54).

A RCT with cabotegravir long acting (CAB-LA) vs. TDF-FTC for PrEP found that CAB was significantly more effective in preventing new cases of HIV infections in MSM and transgender women compared to daily oral TDF-FTC. The cabotegravir group had a lower incidence rate of new HIV infections, and the hazard ratio showed a significantly lower risk of infection in this group (55) (figure 3.5).

Another long-acting form of PrEP is under development; which is Islatravir indicated for cisgender women, however; several clinical trials of the drug were put on hold in 2021 due to safety concerns (56). PrEP implementation poses challenges due to lack of awareness of PrEP; perception of HIV risk, social stigma; provider bias, and distrust of healthcare providers and systems.

Although there have been exciting developments and advancements in HIV prevention, hurdles still need to be addressed to enhance HIV prevention efforts. Some of these challenges include reducing the stigma and discrimination associated with HIV and key populations, increasing the affordability and accessibility of PrEP, and finding ways to integrate PrEP with other healthcare services effectively. Furthermore, efforts are needed to identify and implement targeted approaches for HIV prevention that address the unique needs of specific populations.

Figure. .3,5. Kaplan–Meier estimates of incident HIV infection comparing cabotegravir vs TDF-FTC.



Adapted from Landovitz RJ, Donnell D, Clement ME, et al. Cabotegravir for HIV Prevention in Cisgender Men and Transgender Women. *N Engl J Med*. 2021;385(7):595-608. doi:10.1056/NEJMoa2101016

3.4.- Treatment of HIV seropositive individuals as prevention.

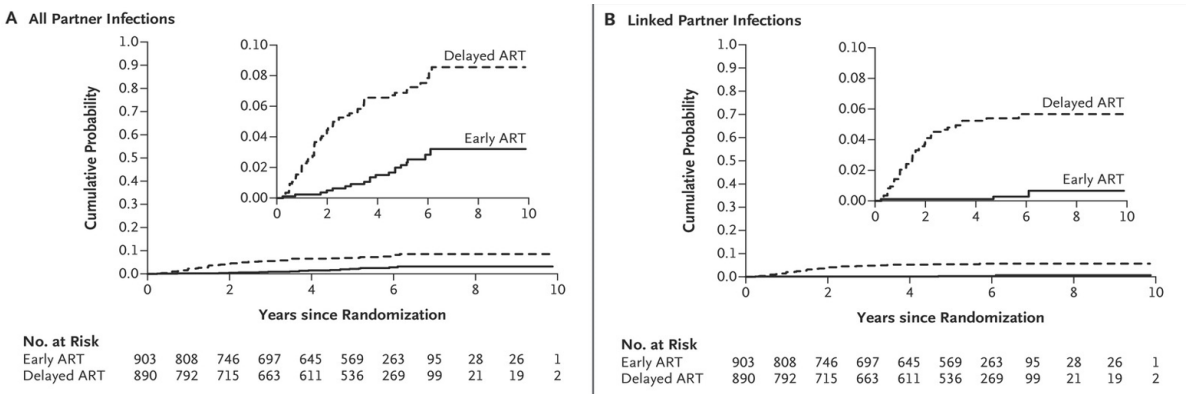
TasP is a definition employed to portray HIV prevention strategies that use ARV in people living with HIV (PLWH) to diminish the likelihood of HIV transmission independent of CD4 cell count. Scientific evidence increasingly supports the alternative of using ART earlier than severe immunocompromise at ≤350 cells/mm3 to exploit health and prevention benefits.

Several facts support the use of ARV for the prevention of HIV transmission, such as:

1. Transmission is only possible from persons with HIV.
2. Viral load is a determining risk factor for transmission (57).
3. ARV lowers the plasma viral load to undetectable levels(58).

The odds of mother-to-child transmission of HIV are directly proportional to maternal viral load; ART is currently used worldwide to decrease the risk of mother-to-child transmission with impressive results (59). A meta-analysis conducted in 2009 found numerous studies on HIV transmission in serodiscordant heterosexual and non-heterosexual couples. The studies revealed that there were no episodes of HIV transmission if the infected member was on ART and had a viral load below 400 copies/mL (58). In 2011, the "HPTN 052 study," which involved over 1700 serodiscordant couples, showed a minimum of 96% reduction of HIV in heterosexual couples due to antiretroviral treatment (61) (figure 3.6). Early treatment of HIV also significantly reduced other infections in the HIV-infected subjects. (62). However, to be effective, TasP requires early HIV diagnosis, immediate initiation of ART, and medication adherence. Thus, efforts to scale up HIV testing and linkage to care are crucial to the success of TasP. Furthermore, stigma, discrimination, and inadequate access to healthcare services can impede TasP implementation, particularly in marginalized populations. it is essential to ensure that the benefits of TasP are accessible to all populations, particularly those most vulnerable to HIV infection. Numerous efforts have been made since the recognition of its usefulness, increasing HIV testing, improving access to ART, and addressing social and structural barriers to TasP implementation are the key factors for TaSP success.

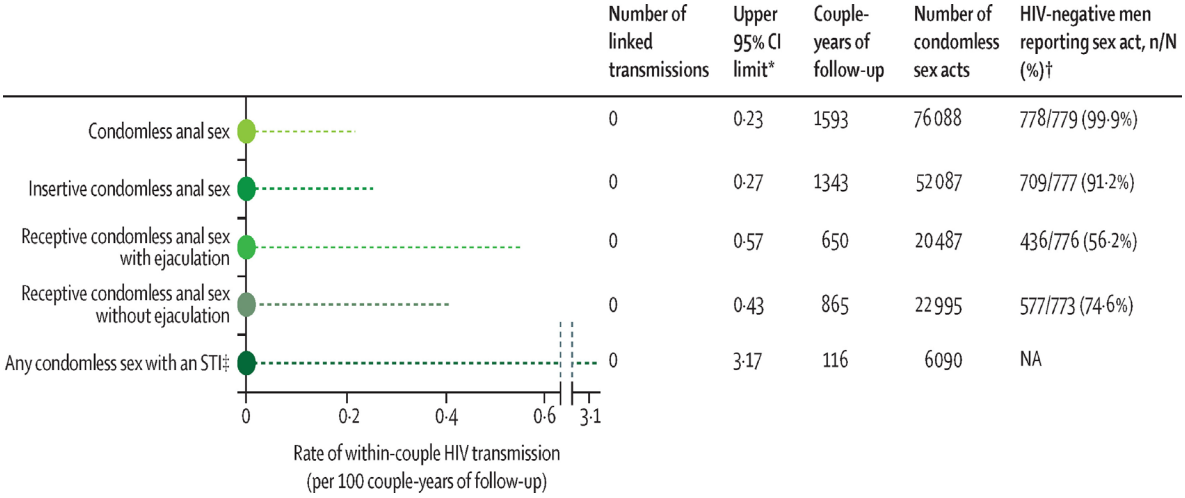
Figure 3.6. Kaplan–Meier Estimates of the Risk of HIV-1 Infection among Partners of Index Participants.



Adapted from: Myron S et at, N Engl J Med 2016; 375:830-839. Shown are the cumulative probabilities of all partner infections (Panel A) and genetically linked partner infections (Panel B) during study follow-up. The insets show the same data on an expanded y axis.

Subsequently, the PARTNER study consisted of serodiscordant couples who had unprotected sex (Data shown on figure 3.7). The seropositive partner was on ART with a viral load of ≤ 200 copies/ml to study the risk of transmission through anal and vaginal penetration. In this study no cases of HIV transmission among the couples. PARTNER II study on the MSM population provided similar evidence on viral suppression and HIV transmission risk for gay men to that previously generated for heterosexual couples (63).

Figure 3.7. Rate of within-couple HIV transmission through condomless sex according to sexual behavior reported by the HIV-negative partner



Adapted from: Rodger Aj, et al. The *Lancet* 2019 3932428-2438. STI=sexually transmitted infection. NA=not applicable. *Estimated using the exact Poisson method. †Numerator is the number of HIV-negative men within the eligible couples ever reporting that specific sexual act and denominator is the group-specific number of HIV-negative participants who contributed eligible couple-years of follow-up. ‡Refers to STIs (excluding HIV) self-reported by the HIV-negative partner.

CHAPTER IV: Post Exposure Prophylaxis in HIV prevention.

4.1. - Definitions and concepts.

Avoiding exposure to the virus is called primary prevention and is the most effective method of preventing HIV infection. However, accidental exposures to HIV sometimes occur. In these situations, ART has been proposed as secondary prevention to prevent infection. This is known as post-exposure prophylaxis (PEP) and is now routine clinical practice in developed countries. It may be used in two very different contexts: occupational and non-occupational.

- Occupational exposure is when a health professional comes into contact accidentally with blood and/or other biological fluids during work, even after taking preventive measures.
- Non-occupational exposure occurs accidentally outside the health setting via the sexual or parenteral routes even after taking preventive measures.

4.2. - Biological plausibility of PEP studies in animal models.

HIV exhibits rapid entry into cells within the colorectal and vaginal mucosa. Within 30 minutes of ejaculation, and certainly within an hour, the replication cycle is initiated and will be completed within 28 hours. However, during the initial stages, the signaling for viral spread is weak. Once amplification occurs, where every cell becomes infected, which may happen within the first few days of infection, a critical window emerges for preventing

infection. The dense packing of CD4 cells in local lymphoid tissues renders these tissues susceptible to the initial proliferation of the virus, which may lead to a rapid surge of the virus once the infection has become established. (64).

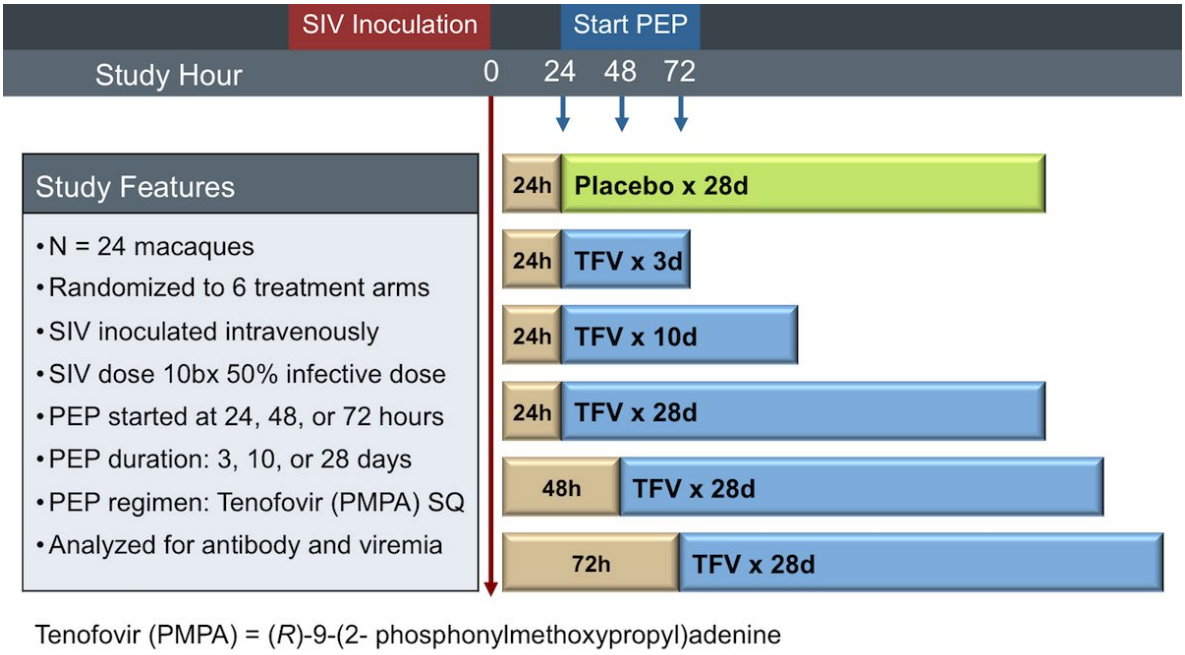
Studies on seroconversion in macaques provide evidence that irreversible infection is established within a range of four to ten days. After this time frame, preventing an infection is unlikely (65). Once multiple cells in the lymphoid tissue are infected, it becomes challenging to avoid infection. Systemic drug levels may play a role in prevention.

Zidovudine (ZDV) was used in retroviruses prevention with encouraging results in mice models. This was the first time it was tested that a live retrovirus cannot replicate due to pharmacological blockade, thus allowing the T-cell response to be still capable of protecting against a deadly retrovirus-induced disease. (66).

In the 90s Initial results using an simian immunodeficiency virus (SIV)-infected macaque model developed to evaluate the efficacy of (*R*)-9-(2-phosphonylmethoxypropyl)adenine (PMPA, tenofovir), demonstrated that (PMPA) treatment initiated 24 h after viral inoculation and continued for 28 days wholly avoided persistent SIV infection. PMPA did not begin until 48 or 72 h was less efficacious even though it was maintained for 28 days. Furthermore, limiting the duration of treatment to 10 days reduced protection to 25%, and diminishing the duration to 3 days further reduced the efficacy of PMPA against acute SIV infection (65) (see figure 4.1). Although this model was inadequate to closely mirror non-occupational exposures due to the nature of intravenous inoculation and cell-free virus,

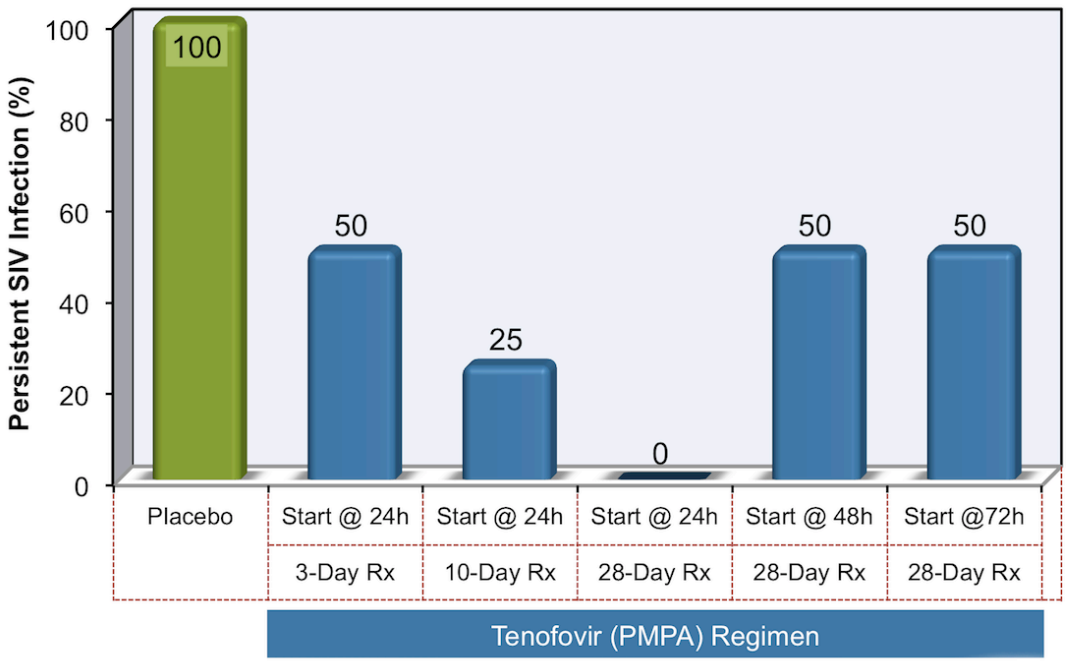
lacking a mucosae model mimicking the natural transmission modes, extrapolating these results to sexual exposures seemed inaccurate (figure 4.2).

Figure 4.1- Tenofovir for Postexposure Prophylaxis following SIV-1 Inoculation of Macaques



Source: 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.

Figure 4.2- SIV Transmission Based on Timing of Initiation and Duration of PEP



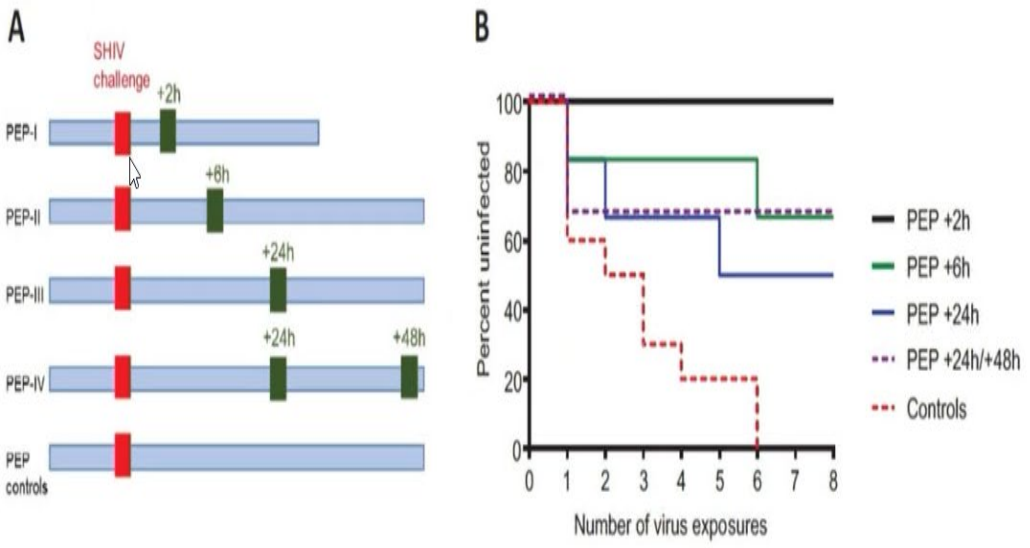
Source: Tsai CC, Emau P, Follis KE, et al. Effectiveness of postinoculation (R)-9-(2-phosphonylmethoxypropyl) adenine treatment for prevention of persistent simian immunodeficiency virus SIVmne infection depends critically on timing of initiation and duration of treatment. J Virol. 1998;72:4265-73.

Among animals that received placebo, all became infected with simian immunodeficiency virus (SIV). The most effective tenofovir prevention regimen consisted of early initiation of tenofovir (at 24 hours) and long duration of postexposure prophylaxis (28 days).

The viral challenge using the (HIV-2)/pig-tailed macaque transmission model demonstrated a preventive effect with daily tenofovir but failed if it was delayed until 72 hours (67). The rationale behind current recommendations comes from these studies (68).

Massud et al., provided an interesting study using Tenofovir alanine/emtricitabine (TAF/FTC) boosted with elvitegravir (EVG/c) assessing efficacy on macaques. Efficacy estimates for a single oral dose given to macaques two h after SHIV exposure was 100%, compared to 80% when single doses were given 6 and 24h post-challenge, respectively. A two-dose regimen at 24h and 48h after exposure was also protective at 77%. (See figure 4.2)

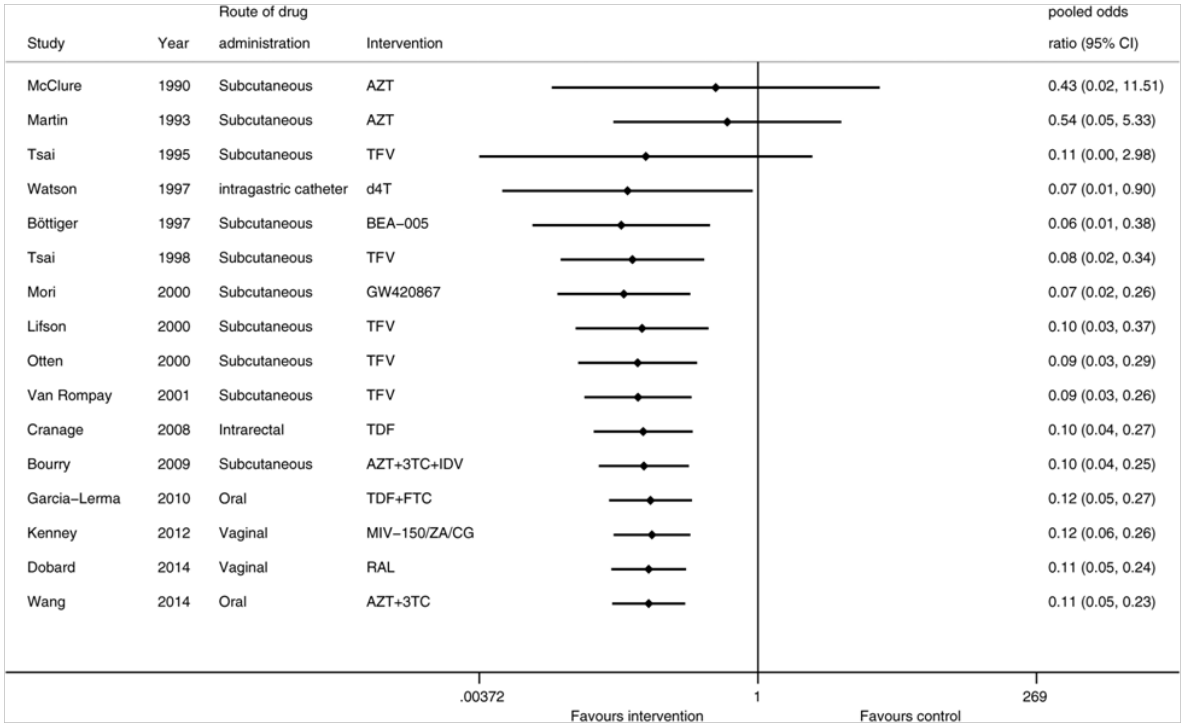
Figure 4.2.- Efficacy of single oral doses of FTC, TAF, and boosted EVG as PEP in macaques



Modified from Massud et al. A) Study design. B) Macaques received FTC, TAF , and boosted EVG orally by gavage at the indicated time points relative to the time of rectal SHIV exposure. The survival curve shows the cumulative percentage of uninfected macaques as a function of the number of rectal SHIV exposures. Time to infection was delayed in animals receiving single-dose PrEP 4h or 24h before exposure (p=0•005 and p=0•027, respectively).

A meta-analysis including 16 PEP efficacy studies in non-human primates reported that the risk of seroconversion among animals exposed was 89% lower among animals exposed to PEP (180 primates) compared with those that did not receive PEP (103 primates) (OR, 0.11 [95% CI, .05–.23]) lower than those not exposed. The sooner the PEP initiation the less likely the event of seroconversion, Tenofovir (TDF) treatment was associated with lower seroconversions(69). (Figure 4.3)

Figure 4.3.- Cumulative meta-analysis of the pooled odds of seroconversion in non-human primates.



Source: *Clin Infect Dis*, Volume 60, Issue suppl_3, June 2015, Pages S165–S169, https://doi.org/10.1093/cid/civ069. Abbreviations: 3TC, lamivudine; AZT, azidothymidine; BEA-005, 2',3'-dideoxy-3'-hydroxymethyl cytidine; CG, carregeenan gel; CI, confidence interval; d4T, stavudine; FTC, emtricitabine; IDV, indinavir; RAL, raltegravir; TDF, tenofovir disoproxyl fumarate; TFV, tenofovir; ZA, zinc acetate.

4.3.- Studies that support the use of PEP in humans.

One of the primary studies on PEP efficacy is a retrospective case-control of health care professionals from France, the United Kingdom (U.K.), and the United States (U.S.), where findings showed that using ZDV was associated with a 79% lower risk of HIV seroconversion in HCW (70). (Data shown table 4.1).

Table 4.1.- Postexposure Use of Zidovudine among Case Patients and Controls, according to the Number of Risk Factors Present.

No. of Risk Factors	Case Patients		Controls		Unadjusted Odds Ratio
	Total	Postexposure Zidovudine Use	Total	Postexposure Zidovudine Use	
	number (percent)				
0	0	—	128 (40)	40 (31)	—
1	3 (11)	0	124 (39)	51 (41)	0.20
2	11 (41)	2 (18)	55 (17)	33 (60)	0.15
3	8 (30)	1 (12)	12 (4)	7 (58)	0.10
4	5 (19)	5 (100)	1 (0.3)	0	33
Total	27 (100)	8 (30)	320 (100)	131 (41)	0.61

Source: Cardo et al, N Engl J Med 1997; 337:1485-1490.

In the early ’90s, ZDV was also tested for perinatal transmission. A randomized study comparing Partum and neonatal therapy with ZDV versus placebo demonstrated a substantial reduction in the rate of HIV transmission without severe toxicities. Another study using postpartum prophylaxis alone within 48hrs of birth showed reduced perinatal HIV transmission(see table 4.1)(71); although indirectly, results in this setting provide

evidence for reduced HIV transmission. These findings led the monitoring board to recommend prescribing ZDV to all patients (72). Other observational studies from different countries (U.S, Holland, Brazil, Italy) in occupational and non-occupational exposure cohorts where PEP is prescribed report no seroconversions, suggesting a preventive effect of this intervention (73-76).

PEP failure in preventing HIV acquisition has also been described, most likely related to delaying the start of treatment after 48hrs and not using enough active regimens (77,78)

Despite appreciable limitations, summarized studies offer proof that prompt PEP can protect against HIV infection.

Table 4.2- Timing of Zidovudine Prophylaxis and the Risk of a Positive PCR Test in the Validation Sample.

Time of Initiation of Zidovudine Prophylaxis	No. of Infants (%)	Positive PCR Test		Relative Risk (95% CI)
		no. (%)	95% CI	
Prenatal†	280 (61.7)	14 (5.0)	2.8–8.2	0.16 (0.09–0.27)‡
Intra partum§	19 (4.2)	1 (5.3)	0.1–26.0	0.17 (0.04–0.75)‡
Within 48 hr after birth	21 (4.6)	2 (9.5)	1.2–30.4	0.30 (0.10–0.96)‡
≥3 Days after birth (up to 42 days)	16 (3.5)	4 (25.0)	7.3–52.4	0.79 (0.33–1.89)
No zidovudine prophylaxis	95 (20.9)	30 (31.6)	22.4–41.9	1.00¶
Unknown	23 (5.1)	3 (13.0)	2.8–33.6	NA
Total	454 (100)	54 (11.9)	9.1–15.2	

Adapted from: Wade et at, N Engl J Med. 1998;339(29):1409–14. †A total of 253 of the 280 infants (90.4 percent) received prophylaxis during all three periods, 3 infants (1.1 percent)

§Seventeen of the 19 infants (89.5 percent) received zidovudine prophylaxis during both the intrapartum and newborn periods

‡P<0.05 for the comparison with the reference group (no zidovudine prophylaxis).

*During the prenatal period, 276 of 280 infants (98.6 percent) received zidovudine.

¶The group with no zidovudine prophylaxis served as the reference group.

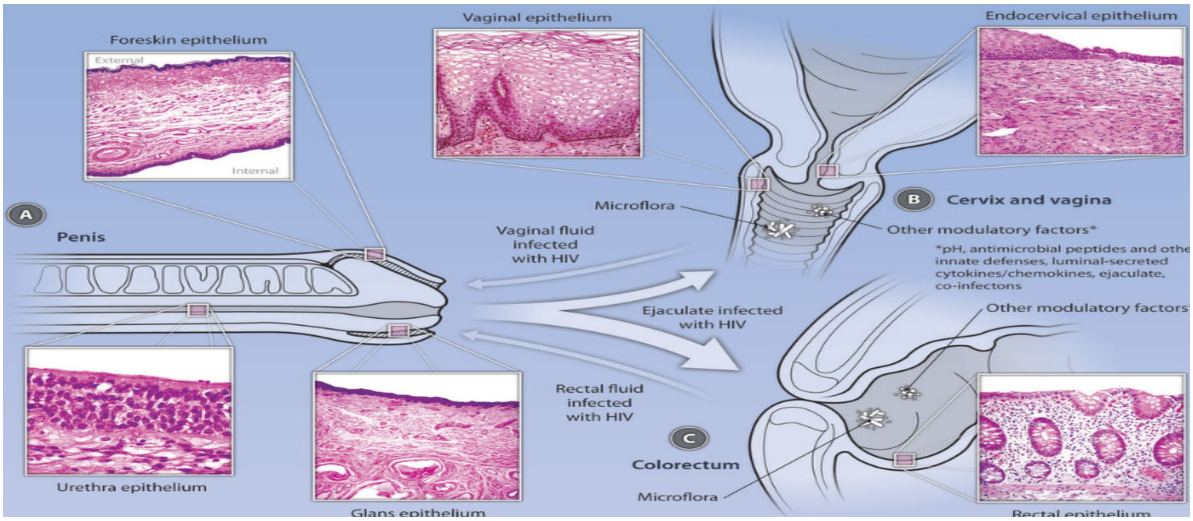
CHAPTER V: Basic Science in Post-Exposure Prophylaxis.

A combination of basic science approaches, including immunology, microbicides, PK/PD, and ex vivo models to prevent HIV from establishing a permanent infection. PK/PD studies are essential in understanding how drugs are absorbed, metabolized, and eliminated from the body to optimize dosing regimens. Ex vivo models are used to evaluate the efficacy of PEP strategies by testing drug efficacy, drug resistance, and host immune response in a controlled laboratory setting. Combining these basic science approaches is crucial in the development of effective PEP strategies for HIV prevention.

5.1.- Human mucosal immunology

Generally, the single-cell epithelia present in the colorectal and endocervical canal are more vulnerable, and the colorectum has a relatively increased area of exposure. The epidemic of sexually transmitted HIV-1 is primarily driven by three major anatomical compartments, each of which is shown with insets of local histology (Figure 5.1).

Figure 5.1. The relative vulnerability of HIV transmission is influenced by the features of the sexually exposed mucosal compartments



Source: Histology for Pathologists, Third Edition, S. E. Mills, Ed. (Lippincott Williams & Wilkins, Philadelphia, 2007), (A) the insertive penile area, which features urethral, glans, and foreskin histology; (B) the receptive lower female genital tract, which includes cervical and vaginal histology; and (C) the receptive colorectum.

Rectal tissue carries a much higher risk of transmission rates than other tissues. Histologically the rectal mucosa is constituted by a single layer of columnar epithelium that separates the intestinal lumen from the lamina propria. The lamina propria is a dense stroma containing a diverse population of HIV target cells such as: dendritic cells, macrophages, and CD4+ lymphocytes expressing CCR5 and CXCR4 receptors (79)

The immune composition of the rectal mucosa is likely at least partially responsible for the 10-20-fold increased risk of HIV transmission associated with anal infection compared to vaginal intercourse (80,81). Any molecule or compound that promotes local inflammation will likely increase the risk by activating or mobilizing immunological target cells. It is uncertain what may influence the risk of HIV acquisition by augmenting or reducing rectal transmission. The susceptibility of the rectal mucosa to trauma during sexual intercourse is due to the sub-epithelial layer that is easily exposed to luminal contents, with the subsequent risk of infection (82,83).

5.2.- Role of mucosal immunology and microbicides in HIV prevention.

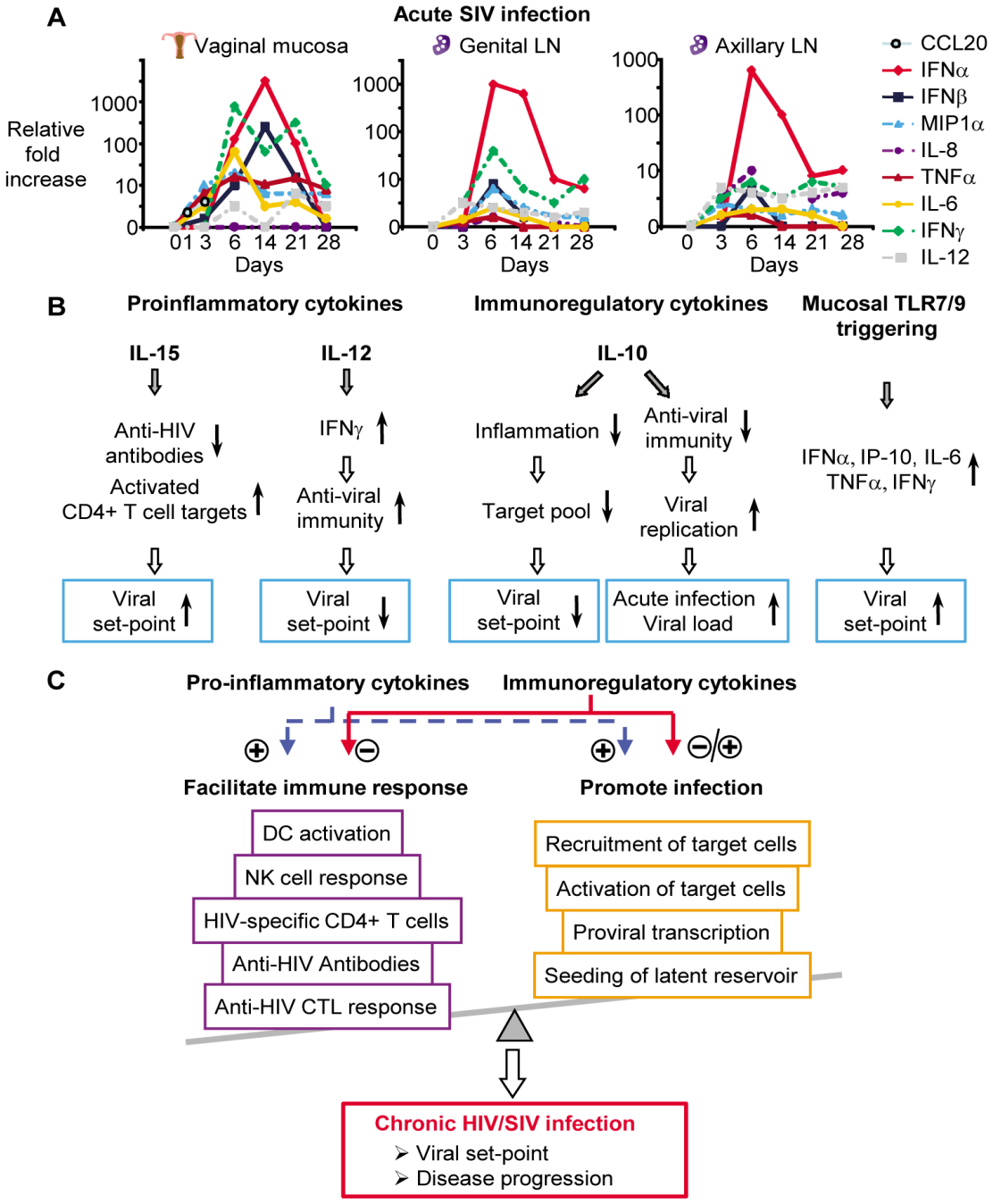
Co-receptor expression (CCR5, CXCR4) on exposed mucosal immunocytes is essential for HIV-1 entry. In healthy HIV-1 seronegative individuals, the expression level of CCR5 is increased seven-fold in mucosal mononuclear cells (MMC) compared to peripheral blood mononuclear cells (PBMC). CXCR4 is expressed on RMP-02/MTN-006, CD45RO+ T cells in similar levels in MMC and PBMC. Viral replication is easier in MMC than in PBMC. Several explanations for the high susceptibility to HIV-1 of MMC may include the increased

expression of HIV-1 co-receptors, especially CCR5, as well as the activation status of the MMC (84).

Condomless receptive anal intercourse may modify the mucosal immune conditions in HIV-negative MSM. A rectal mucosal analysis of the immune environment for the phenotype and production of pro-inflammatory cytokines, global transcriptomic estimations, and microbiota composition in HIV-negative MSM concludes that a distinct phenotype characterized by higher levels of Th17 cells, CD8+ T cell expansion, and pro-inflammatory cytokines, molecular marks associated with mucosal damage and repair mediated by innate immune cells, and a microbiota augmented for the *Prevotellaceae* family (85).

The expression of CCR5 is up-regulated by pro-inflammatory and T helper (Th)-1 cytokines. In contrast, Th-2 cytokines up-regulate CXCR4 (86,87), Suggesting that the Th1/Th2 type of cytokines controls the expression of CCR5 and CXCR4, which are up-regulated in rectal mucosa of HIV-infected patients. It will be essential to ascertain whether microbicidal agents trigger similar responses and associated increased vulnerability to HIV infection, halting its potential use for prevention (88). In animals models cytoquines are known to upregulate or accelerate the anti-viral immune response, which may aid in controlling the viral infection. Nonetheless, the same cytokines may have a counteractive effect by increasing the pool of target cells for HIV/SIV through the recruitment and activation of CD4+ T cells, which are the primary targets for HIV/SIV infection, similar model is prosed in humans (89). (See figure 5.2)

Figure 5.2.- Early cytokines determine pathogenesis of HIV/SIV infection.

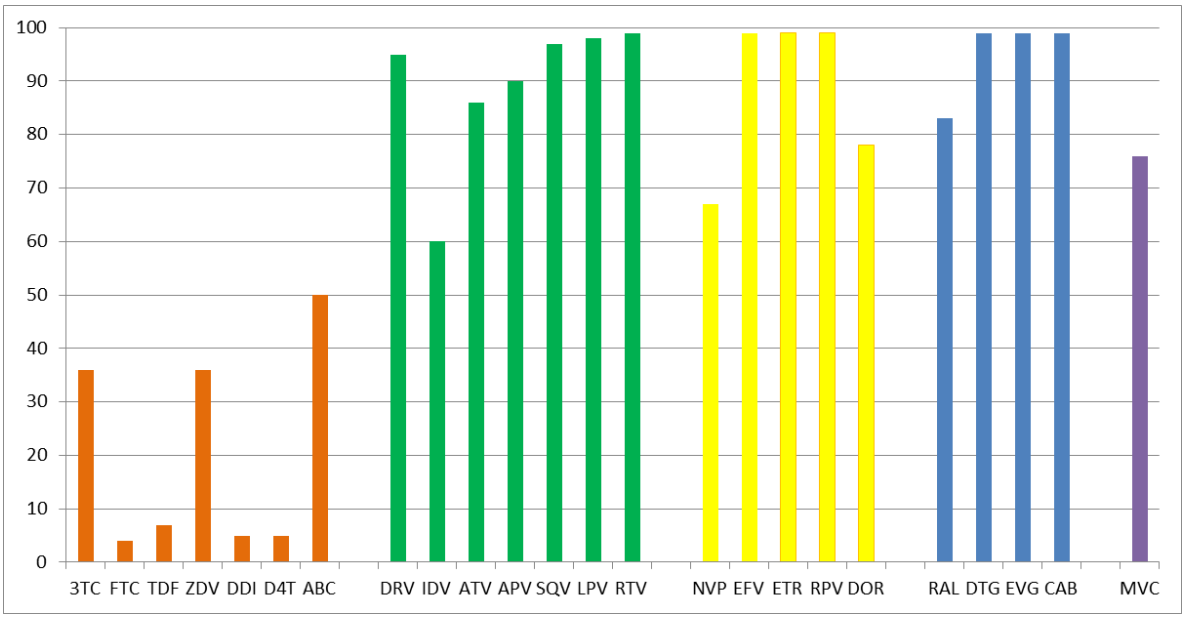


Adapted from: Katsikis P et al, 2011 (A) During acute SIV infection, various cytokines are produced at the site of initial viral exposure or in draining or distal lymphoid tissue (adapted from [18], [22]; the scale shows fold changes over time for each cytokine).(B) These cytokines can either increase (↑) or decrease (↓) immune parameters or target availability, which in turn directly affect viral replication and viral set-point (adapted from [8], [10], [23], [66], [70]). (C) Pro-inflammatory and immunoregulatory cytokines can negatively or positively modulate immune responses and viral replication, which ultimately determine viral set-points and disease progression during chronic HIV/SIV infection.

5.3.- Pharmacokinetics and pharmacodynamics of PEP.

A sum of factors can predispose the effectiveness of anti-infective prevention agents, including; tissue permeation in the compartments of HIV exposure, dose, and drug exposure, target cell bioavailability, in vivo half-life, protein binding, local immune responses, properties of organic fluids, and performances perturbing regular use of the product (90-92), (see figure 5.3 and 5.4).

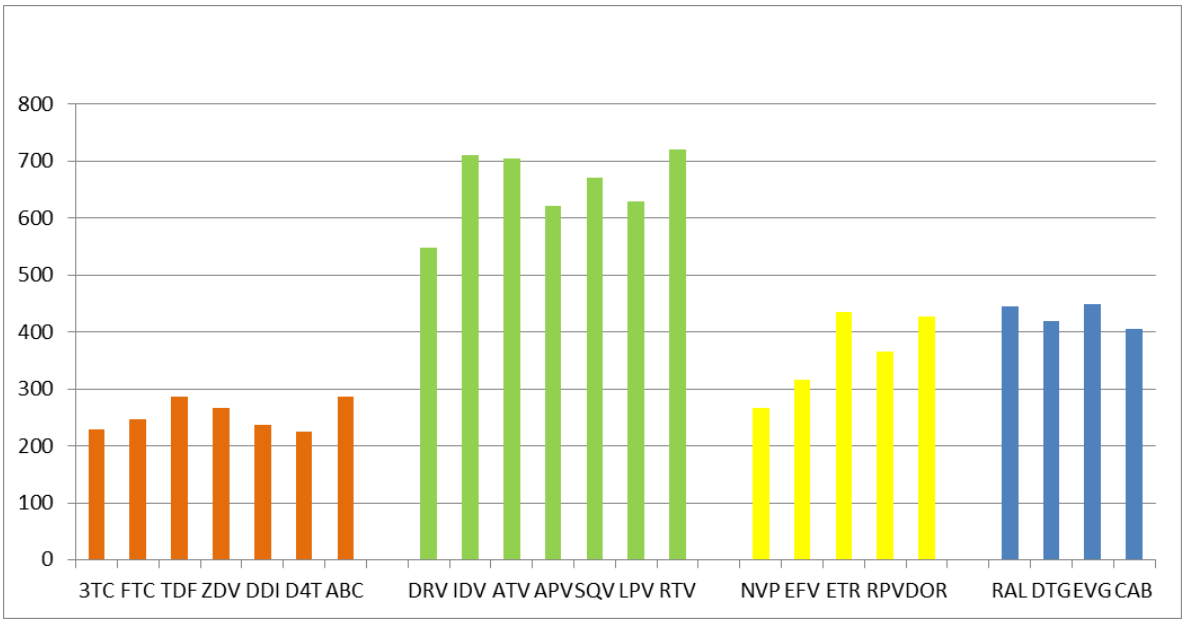
Figure 5.3.- Protein binding of different ART molecules expressed in percentages.



Source from: Guia Mensa Terapeutica Antimicrobiana, online version 2020.

ARTs with different physicochemical properties or mechanisms of action may show different efficacy outcomes. It is essential to address that it should not be presumed that the associations detected with one specific anti-HIV drug will be the same as another. Drug levels in plasma are not representative of mucosal concentration, and mucosal tissues differ from blood tissue in the immune response and its histological matrix. (93)

Figure 5.4. Molecular weight of different ART molecules expressed in grams/mol.



Source from: Guia Mensa Terapeutica Antimicrobiana, online version 2020.

Developing a phase II proof-of-concept study to find statistical significance in a prevention outcome might not be feasible given the extraordinarily high number of the minimal population needed. Therefore, the prevention field has relied on partial, alternative means of evaluating efficacy in the drug development pipeline, including animal and ex-vivo models (94).

Determining the free drug and the amount of total drug in the test system is pertinent to understanding the result. Methods for measuring drug concentrations that do not account for free versus total drug concentration in the tissues studied might lead to biased recommendations. A drug bound to another molecule in a model system is not available to wield a biological effect, at least not as effectively as a free drug. Variances in the protein-binding attraction of different ARTs have been well-reported in several studies (95)

The measured effect of a drug targeting a microbe in in-vivo could be confounded if the effects of the immune system on the biological outcomes are not understood. Innate and adaptive immune responses might play a role in diminishing infection; immune responses are not similar in all species (80). To compare results in animal models to humans is complicated and misleading. It is essential to recognize the complex variables that regulate drug distribution and metabolism at a tissue location and the physiological and biological differences between systems (96).

For a drug to be effective, it needs to achieve high concentrations with a rapid increase upon administration. Drugs that concentrate on the genital tract reduce the amount of HIV-RNA. PEP drugs increase the possibility of viral clearance before the host is irreversibly infected. However, the virus inhibition—and therefore PEP efficacy—fundamentally depends on the drug's tissue concentration at the target site (97,98).

Tissues are multicompartmental, and only very specific sub-compartments are susceptible to HIV infection, especially those with CD4+ and CCR5+ cell populations. Drug spreading may not be consistent over these diverse compartments and their cells. Therefore, the simple homogenization of tissue samples followed by drug concentration measurement may not demonstrate the potential for target cell defense against HIV (99).

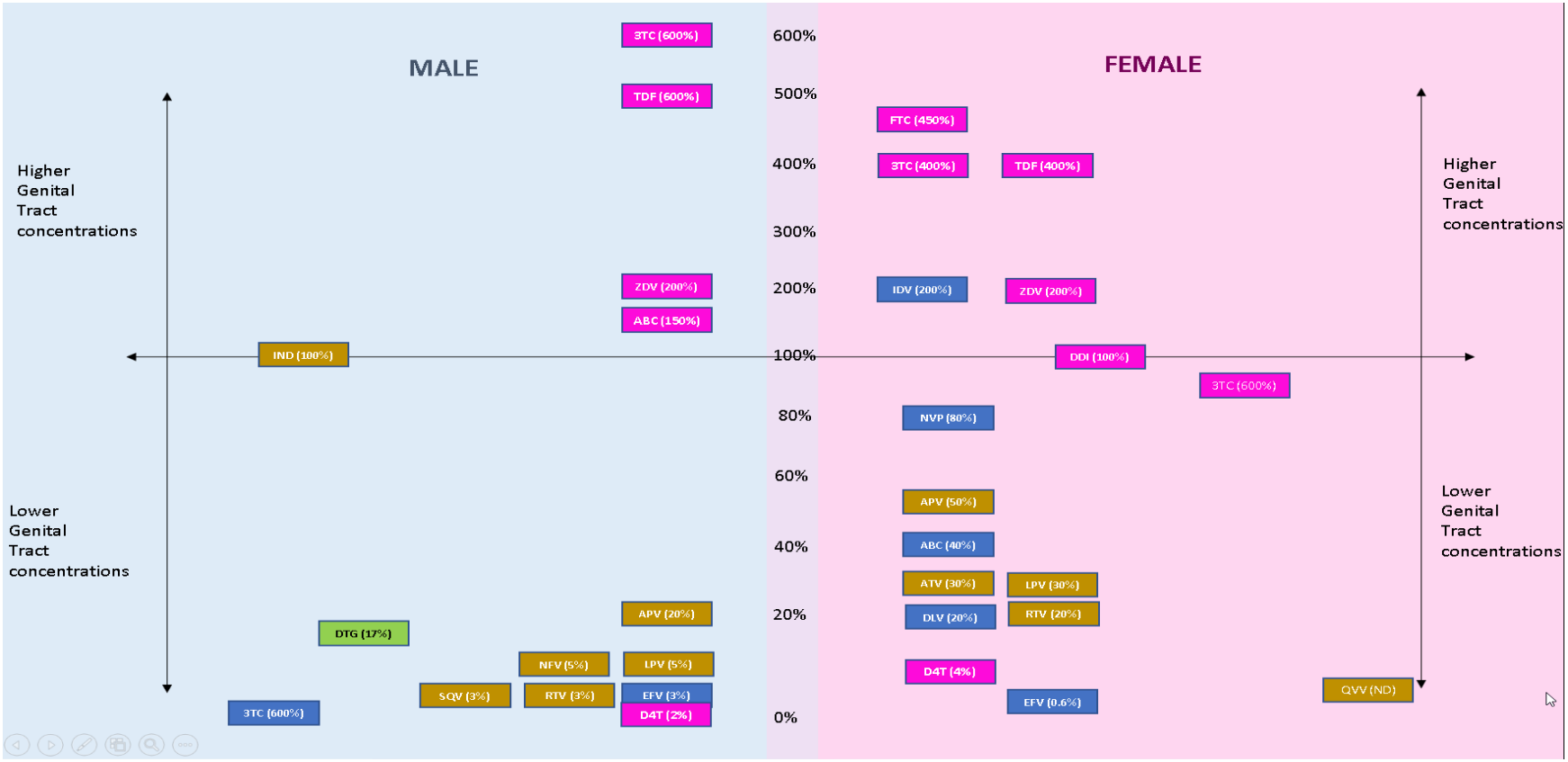
5.4.- Current studies assessing human mucosa models using PEP in HIV prevention.

Non-nucleoside transcriptase inhibitors have variable penetration rates and particular drug penetration. Penetration ratios differ depending on the colorectal tissue of the female genitourinary tract. These profiles are summarized in figure 5.5. Nucleoside transcriptase inhibitors achieve high concentration in the male and female gastrointestinal tract. For non-nucleoside reverse transcriptase inhibitor (NNTRI), the drugs that achieve higher tissue and plasma ratios are; etravirine

(ETR) and rilpivirine (RPV). The transcriptase reverse inhibitors NTRI are intracellular phosphorylated to be in their active forms, so determining the drugs intracellular is critical.

In contrast to Maraviroc, most protease inhibitors have poor penetration in the female genitourinary tract and acceptable colorectal tissue ratios. There is a moderate penetrative ability for RAL and dolutegravir (DTG). Concentration declines after repeated dosing in several drugs, such as TDF, lopinavir (LPV), and abacavir (ABA). Tissue penetration is irrespective of the doses administered for ATV, and efavirenz (EFV) (100,101). Our center conducted a study that found the ratio of rectal tissue (RT) to plasma for all three drugs examined to be: 16.8 for Maraviroc (MVC) , 4.8 for RAL, and 0.7 for LPV on MSM colorectal explants. (102)

FIGURE 5.5. Antiretroviral exposure in the male (Blue background) and female (pinkbackground) genital tracks compared to blood plasma.

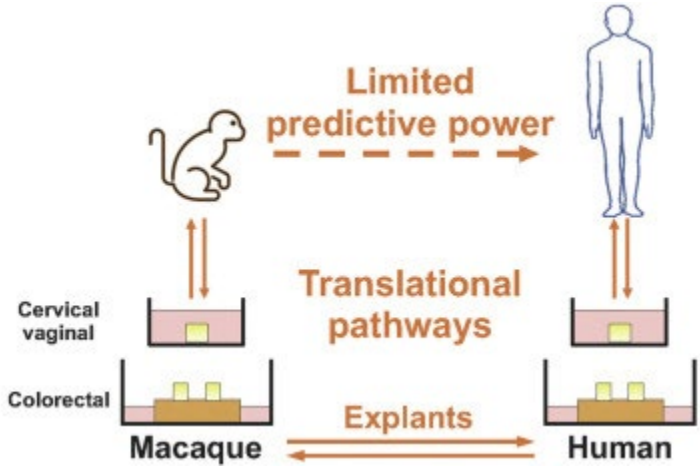


Male data pooled from: Pereira et al. 1999. Taylor et al, 2000. Vaan Praag et al, 2001. Chaudry et al, 2002. Reddy et al. 2003, Chosen et al, 2004. Vourvahis et al, 2006. Female pooled data from: Min et al, 2004. Dumond et al, 2006. Vourvahis et al 2006.The solid black line represents 100% or equivalent exposure in the genital tract and blood plasma. Antiretrovirals are abbreviated with percent exposure. Drugs abobelowve the lid black line (100%) have greater genital tract exposure than blood plasma. Drugs bellow the solid black line (100%) have lower genital tract exposure than blood plasma Drugs on the line have equivalent exposure. Exposure is the area under the time concentrations curve (AUC) over a dosing interval. To compare exposure, genital tract AUC was divided to blood plasma (BP) AUC to give CT exposure relative to BP. AUC to give exposure relative to BP

5.5.- Exvivo infectivity models

Ex-vivo infectivity models refer to the study of the infectivity of a pathogen outside of a living organism, usually in cell cultures or organoids, from either humans or monkey explants (see figure 5.6). Infectivity models using cultures with PBMCs and MNCs have been critical in evaluating the efficacy of ART for HIV prevention (103).

Figure 5.6. Ex-vivo explants on macaques and human models.



Modified from: Herrera C, Cottrell ML, Prybylski J, et al. The *ex vivo* pharmacology of HIV-1 antiretrovirals differs between macaques and humans. *iScience*. 2022;25(6):104409. Published 2022 May 16. doi:10.1016/j.isci.2022.104409

These models provide a laboratory environment that mimics the conditions in which the virus infects humans, allowing for testing of the effectiveness of different antiretroviral drugs and regimens without the ethical and logistic limitations associated with clinical trials. For HIV prevention, these models evaluate the efficacy of PEP strategies, which aim to reduce the risk of HIV transmission after exposure to the virus. They also provide valuable

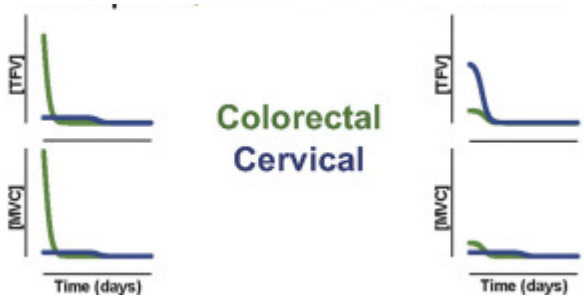
information about the optimal dosing regimens, the time window for starting therapy, and the duration of therapy needed for maximal efficacy. These models typically involve exposing HIV-susceptible cell lines to the virus in the presence of a PEP drug and measuring the viral replication or the number of infected cells, delivering a way to study the interactions between the virus and the host immune system, which is essential for understanding how ART can be used to prevent HIV infection.

Ex vivo infectivity models for HIV PEP have been established using various cell culture systems, including:

1. T-cell lines: T-cell lines, such as MT-2 or Jurkat, are commonly used to assess the efficacy of PEP drugs in reducing viral infectivity. T-cell lines are susceptible to HIV-1 infection and allow for the measurement of viral replication or the number of infected cells.
2. Monocyte-derived macrophages: Macrophages are important target cells for HIV-1 and are critical for virus dissemination in vivo. Monocyte-derived macrophages can be used to evaluate the efficacy of PEP drugs in limiting the spread of HIV-1 in these cells.
3. Primary peripheral blood mononuclear cells (PBMCs): Primary PBMCs, which include T-cells, macrophages, and dendritic cells, can be used to evaluate the efficacy of PEP regimens in a more complex and physiologically relevant cell culture system.

While these models can provide valuable insights into HIV transmission and PEP efficacy in developing and refining PEP regimens, their results may not accurately reflect the complex interplay between the virus, host immune response, and drug pharmacokinetics in vivo. The pharmacological response to HIV-1 antiretrovirals in ex vivo models using macaques and humans differs (104). Even in humans the level of infectivity within the same organ system may vary depending on the specific anatomical site (105). ARV efficacy in colorectal and cervicovaginal explants was studied in humans and macaques. High concentrations of TDF and MVC were effective in inhibiting viral replication. However, the combination of TFV and maraviroc showed higher potency in maquaces than in humans. In addition, TFV concentrations were higher in colorectal explants compared to cervicovaginal explants in macaques, while the opposite was observed in humans (figure 5.6).

Figure 5.6.- Differences between ex-vivo inhibition between macaques (left) and human (right) models.



Modified from: Herrera C, Cottrell ML, Prybylski J, et al. The *ex vivo* pharmacology of HIV-1 antiretrovirals differs between macaques and humans. *iScience*. 2022;25(6):104409. Published 2022 May 16. doi:10.1016/j.isci.2022.104409

Colorectal ex-vivo models have demonstrated that using multiple drugs in combination is more effective in reducing viral infectivity compared to using a single drug. For instance, combining tenofovir and emtricitabine, two NRTIs, has been found to significantly decrease

viral replication in T-cell lines and monocyte-derived macrophages, even against RTI-escape mutants. Quadruple combinations did not show much more benefit than double or triple combinations. (106)

In a study performed in our center, administering MVC twice daily in a steady state has been shown to decrease viral replication in ex-vivo RT explants. However, neither RAL nor LPV/r showed any effect on HIV ex-vivo RT infection. This lack of impact may be due to poor distribution at this level, although it is also possible that the explants challenge assay is not appropriate for characterizing these ARV profiles in rectal tissue (102). Further research and validation using in vivo animal models and human trials are necessary to understand the potential of PEP strategies in HIV prevention fully.

CHAPTER VI: Clinical research applied in HIV Post-exposure prophylaxis.

Clinical research plays a crucial role in the development of effective PEP strategies. This research involves studying the safety, efficacy, and adherence of different PEP regimens in non-occupational and occupational settings. Researchers focus non-occupational PEP studies on individuals potentially exposed to HIV through sexual activity or injection drug use. These studies evaluate the effectiveness of PEP regimens in reducing the risk of HIV transmission and investigate factors that influence adherence, such as patient education and counseling. Occupational PEP studies focus on healthcare workers and other individuals who may be at risk of exposure to HIV in their workplace. Clinical research in PEP guides clinical practice and optimizing HIV prevention strategies.

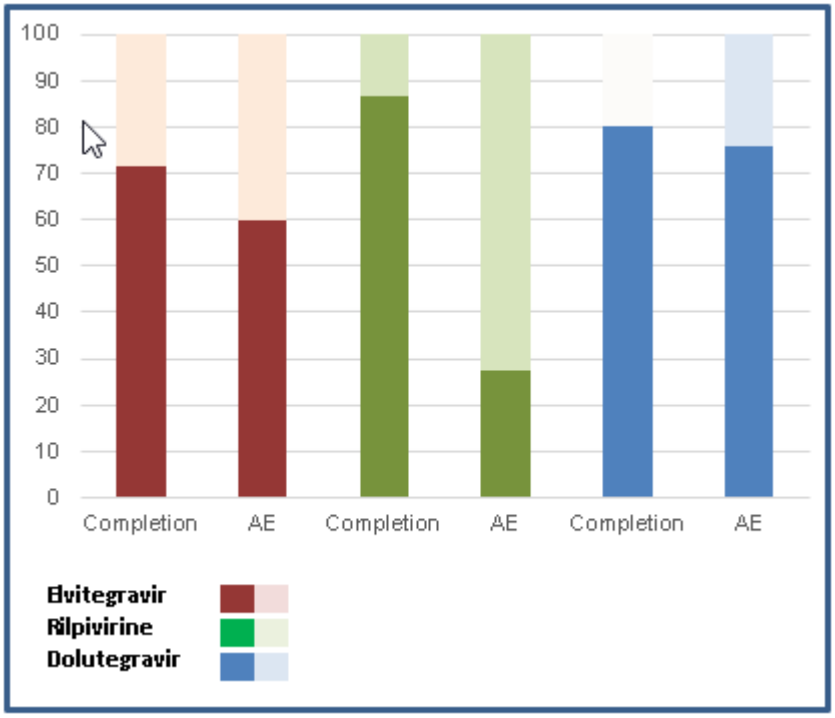
6.-1 Studies in occupational PEP.

The use of occupational PEP is founded on limited evidence of an effect. However, it is unlikely that a definitive placebo-controlled trial will ever be conducted (107). The initial information about occupational PEP divers from a case-control study (108). The outcomes from this study conclude that HIV transmission was significantly associated with deep injury (OR 15, 95% CI 6.0-41), visible blood on the device (OR 6.2, 95% CI 2.2-21), procedures involving a needle placed in the blood vessel from the source (OR 4.3, 95% CI 1.7-12), and terminal illness in the source patient (OR 5.6, 95% CI 2.0-16) (108). No randomized controlled trials for occupational PEP. In table 6.1 it is described compiled data about current studies in PEP.

6.-2 HIV non-occupational PEP studies.

In terms of the effectiveness of non-occupational post-exposure prophylaxis (nPEP), no randomized, large-scale, prospective, placebo-controlled clinical trial has been conducted due to ethical and methodological issues. The collected data comes from descriptive, prospective, and very few randomized clinical trials with primary endpoints related to overall tolerance and PEP non-completion between different regimens (109-112).

The collected data comes from descriptive, prospective, and very few randomized clinical trials with primary endpoints related to overall tolerance and PEP non-completion between different regimens (109-112). Regarding PEP efficacy in real world data, although nPEP failures were rare in the observational studies inadequate follow-up testing rates for HIV infection; might underestimate nPEP failures (113-119). There are also differences in characteristics of PEP completion rates and follow-up testing between different populations such as MSM, sexually assaulted victims, and pediatric populations. In studies involving pediatric populations, a large proportion of eligible children did not receive HIV-PEP, and follow-up rates were also found to be poor among them. (120). Very few studies assess safety, tolerability, and adherence of new single-tablet regimens (see figure 6.1) (121-123) and single dosing regimens (124-125). Figure 6.1. Studies assessing safety, tolerability, and adherence to new single-tablet regimens (STR).



Data from: Chauveau 2019; Foster R, 2015. Valin; 2019. McAllister 2017.

It is not feasible to assess the effectiveness of sexual exposure. Due to obvious ethical and methodological issues, no randomized, large-scale, prospective, placebo-controlled clinical trial of nPEP has been conducted. There is no information on clinical efficacy in non-occupational post-exposure prophylaxis. We included studies from nPEP in mixed populations in the following table 6.1, excluding sexual assault victim.

table 6.1.-. Studies of non-occupational post-exposure prophylaxis

Author, Year	Study	Location	Size	Drug regimen or arms	BIAS	Primary Endpoint	Outcome	HIV+	Conclusion
Schechter 2004	Prospective	Brazil	200	ZDV/3TC	Non-randomized 48h Inclusion criteria	Safety, Tolerability, Comparisons between PEP users and non-PEP users	PEP completion 89% AEs 82% TD 11% SC: PEP users 1/61 Non-PEP users 10/128	1	PEP was well tolerated 1 participant with a history of pancreatitis
Vives 2008	Multicenter prospective	Spain	569	AZT/3TC+NFV AZT /3TC+ATV+R	Selection Bias Non-randomized	Epidemiological characteristics	PEP completion 79% AEs: 52% TD: 4%	3	A national registry for monitoring non-occupational post-exposure prophylaxis to HIV is needed Considerable incidence of side effects, and lost to follow-up.
Sonder 2010	RP	Amsterdam	309	**ZDV+3TC+NFV** **ZDV/3TC+ATV**	Open Label No randomization	To compare 2 regimens	PEP completion 91% AE:**91%** vs 81% TD1:**11%** vs **8%**	5	ATV was much better tolerated than nelfinavir, but compliance with the 2 PEP regimens was equally high. The 5 seroconversions were most likely caused by ongoing HIV exposures
Diaz-Brito 2012	RCT	Spain	255	**ZDV/3TC+LPV/r** **ZDV/3TC+ATV**	Open Label	To compare 2 regimens	Overall 64% AE1: **43%** vs. **49%**	NR	Both arms showed similar rates of PEP discontinuations

							TD1: 16% vs. 17%		
MCallsitter 2014	Prospective	Sydney Australia	123	TDF/FTC RAL+TDF/FTC	Open Label No randomization	Completion Rate	Completion: 92% vs 91% TD: 2% vs 3%	NR	9% of the 3-drug arm experienced grade 4 creatinine kinase elevations
Li 2014	Cohort	Tapei Taiwan	255	AZT regimen TDF regimen LPV/r as 3d agent	No randomization	Discontinuation rate	AE: 62.5% vs 32.1% TD: 17.0% vs 8.2%	1	NPEP could be an effective prevention method in a part of HIV prevention strategy and TDF-based regimen had better tolerability
Foster 2015	Prospective	Melbourne, Australia	100	RPV+FTC+TDF	single arm Open Label	Pep Completion	Completion 92% AE: 88% TD: 2% AD: 86% (BP)	NR	STR regimen well tolerated with high levels of completion
Jain 2015	Retrospective	Boston, Massachusetts	788	ND	LTFP	Seroconversion	Seroconvertion: 4% Incidence: 2.2 PPY	39	Younger age, being Latino and/or being African American, but not repeated nPEP use, were associated with incident HIV infection
Fätkenheuer 2016	RCT	Cologne	324	TDF/FTC+DRV/r ZDV/3TC+LPV/r	open-label	Discontinuation rates	TD: 6% vs. 10% AE: 68 vs 75	NR	Noninferiority of DRV/r to SOC was demonstrated

		Germany							
Pierce 2016	Retrospective Descriptive	Melbourn Australia	1500	**Two drugs regimes** **Three drugs regimens**	LTFP Only RAIU included	PEP Failures	PEP failure **0.5%** vs **0.9%**	70 (5%)	two-drug NPEP regimens do not result in excess seroconversions compared with three-drug regimens when used following RAIU.
Leal 2016	Case-control 1:1	Spain	138	Non-converters Seroconverters	Lost to follow-up	Factors associated with seroconvertions	MSM OR 5.2 (1-20) previous STI OR 4.6 (2-11), PEP OR 4 (1-16)	69GT	Being MSM, a previous PEP, an HIV + sexual partner and previous STI were predictive factors for HIV seroconversion.
Leal 2016	RCT	Spain	243	**TDF/FTC+LPV/r** **TDF/FTC+RAL**	No blinding Lost to follow up	completion	Completion: **66%** vs **79%** AE: **73%** vs 60% AD: **51%** vs **69%**		poor adherence and adverse events were significantly higher in patients allocated to TDF/FTC+LPV/r
Leal 2016	RCT	Barcelona Spain	117	**TDF/FTC+LPV/r** **TDF/FTC+MVC**	No blinding Lost to follow up	PEP completion	Completion: **56%** vs **68%** AE: **72%** vs **51%** AD: **52%** vs **47%**	**1**	EP non-completion and AE were both higher in patients allocated to TDF/FTC+LPV/r
Milinkovic 2017	RCT	London	230	**TDF/FTC+LPV/r** **TDF/FTC+MVC**	Open Label	completion	Completion: **65%**vs**71%** AE: **91%** vs **71%**	NR	The completion rate in the absence of grade 3 or 4 AEs was similar with both

		UK					TD: 18% Both		regimens. Maraviroc-based PEP was better tolerated.
McAllister 2017	Prospective	Australia	101	TDF/FTC+DTG	Single Arm	completion	Completion: 90%, AE:26%, AD:98%, TD:1%	NR	DTG with TDF-FTC is a well-tolerated option for once-daily PEP
Beymer 2018	Descriptive	Angeles. USA	267	65% TDF/FTC+LPVr 25% TDF/FTC+RAL	Missing data Selection bias Open label	PEP implementation program	Completion 81% ADH:51% AE:29% Diarrhea, 16% nausea	7 2.5%	PEP program was feasible to care continuum on PEP users.
Chauvenau 2019	Prospective	France	150	TDF/FTC/RPV	Open Label Missing data	completion	completion 86% AE: 70% TD: 4.4%	0	The low rate of premature treatment interruption, the good tolerability and the absence of documented HIV seroconversion
Quah SP 2021	retrospective	UK	143	TDF/FTC+RAL	Missing data	Safety	AE: 11% TD: 1.4%	0	RAL 1200 mg with TDF+FTC is a well-tolerated daily option for PEP
Mayer 2022	Prospective	USA	52	BIC/FTC/TAF	LTUP Missing data	Safety	Completion: 90% AE 15%, TD: 2%	0	BIC/FTC/TAF coformulated as a single daily pill was found to be safe, well-tolerated, and highly acceptable when used for PEP.

Highlighted regimens correspond to colored bold numbers in each columns. TD: Treatment discontinuation, AE; adverse event, ND: No data, FOPD 7; follow up at day 7, FOPD 28; follow up at day 28, FOPD180; Follow-up at day 180, HIV seroconversion column; numerator (seroconversion o NR: not reported) denominator (total individual with HIV negative test).

6.3.- Studies in sexual assault victims.

There is no striking evidence that PEP after sexual assault prevents transmission or is cost-effective. Nevertheless, there may be certain sexual assault cases where PEP ought to be given or at least considered. Even though more definitive clinical studies are needed, PEP after sexual assault should be considered case-to-case basis. It is important to note that PEP is not a substitute for other forms of care and support for sexual assault survivors, such as counseling and medical care for other injuries or STIs. Sexual assault survivors should also receive testing for other STIs, and may benefit from additional medical care and follow-up.

While there may be uncertainties around the effectiveness and cost-effectiveness of PEP after sexual assault, it is a potential option that can help to reduce the risk of HIV transmission in some instances. Further research is needed to establish more definitive evidence around the use of PEP in this context and to identify strategies for improving access to care and support for sexual assault survivors. The present data (Table 6.2) summarizes the current information reported in the case series and descriptive studies.

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Table 6.2. Studies of non-occupational post-exposure prophylaxis related to sexual assault.

Author, Year	Study	Location	Sample Size	Drug regimen	Outcome	HIV+	Conclusion
Wiebe 2000	Retrospective	US	258/71	AZT+DDC AZT+3TC	Completion 8/71 FOPD28 29/71 DAE 9/29	NR	Patients at highest risk for HIV infection were more likely to accept prophylaxis and more likely to complete the treatment than those at lower risk. Compliance and follow-up were the main problems with implementing this service.
Kerr 2003	Retrospective	UK	673/34	AZT/3TC+NEL	Completion **NR**	NR	Thirty-four (5%) received a three-day starter pack of post-exposure prophylaxis against HIV (PEP), but 20(59%) of these did not return for repeat prescriptions
Tadayuki 2005	Retrospective 1999-2002	Brazil	166/149	AZT/3TC+NEL AZT/3TC+IND	FOPD7 80% FOPD28 50% FOPD180 29%	NR (28)	Emergency care for victims of sexual assault is effective in reducing unwanted pregnancies and infections.
Meel BL 2005	Retrospective	South Africa	225	AZT/3TC	Completion **NR** FOPD28 12%	1	Most of the sexual assault victims (84.5%) did not report for the second test; 80% of those who had the second test did not report for the third test. Only 1 victim one seroconverted
Linden 2005	Retrospective	US Boston	85/181	ZDV + 3TC (Combivir) (n=78)	Completion:18 of 85 (21%)	NR	PEP was offered to less than half of sexual assault patients, and few completed treatment.

Chu 2005	Retrospective 2001 -2004	Hong Kong	137 (50%)	ND	D10 (10/137) FOPD28 (%,90/137) FOPD90(%,70/137) FOPD180(40%, 55/137)	NR (55)	All tests for antibody to human immunodeficiency virus were negative.
Garcia 2005	Prospective 1997-2001	Brazil	347/278	AZT/3TC+NEL AZT/3TC	D28 122 (44%) D 34 (12%) Completion: 169 (61%) AE:2D 66% vs. 3D 92%	NR (180)	Triple therapy was associated with side effects, which suggested that drug regimens should be reviewed. The variables related to a high risk of HIV transmission were also significant for compliance.
Carrieri et al, 2006	Retrospective-Survey	France	94	2 and 3 drug regimens	Completion of nPEP: 25%	NR	Half of all participants were lost to follow-up after the first consultation.
Loutfy 2008	Prospective cohort study	Canada	798	Combivir + Kaletra	Completed nPEP (23.9%)	NR	The most common side effects were fatigue, nausea, and diarrhea.
Griffith 2010	Retrospective	US	151	Kaletra + Truvada or Combivir	Completion of nPEP: 62/151 (41%) 37 of the 62 (60%) took nPEP for ≥21 days	NR (36)	Full medication compliance and follow-up counseling remain challenges for sexual assault survivors
Sheridan, 2011	Systematic review	Sub-Saharan Africa		NR	Completion of nPEP: 0%–65%	NR	Anywhere from 5%–100% of eligible patients received nPEP

Chacko, 2012	Systematic review	U.S	24 studies	Various 2- and 3-drug regimens	Completion of nPEP: 40%	NR	Overall adherence was poor but was higher in developing countries compared to developed countries. Common side effects were: nausea and vomiting, diarrhea, and fatigue.
Akinlusi 2014	Retrospective 2008-2012	Nigeria	59/201	ND	ND	NR	Adolescents remain the most vulnerable requiring life skills training for protection. Survivors delay in presenting for care.
Krause et al, 2014	Retrospective	U.S	176 36/139	FTC/TDF and LPV/r) (n=85, 59.4%) or FTC/TDF alone (n=32, 22.4%)	Completion of nPEP: 34 of 124 (27.4%) 1 FOP 63.7% 72/124 Discontinuation 5/124	NR (36)	Of patients who accepted nPEP, a minority are documented to have completed a course of treatment. Systems to improve post assault follow-up care should be considered.
Morgan 2014	Retrospective	UK	51/275	ND	Completion 12 33% FOP 54%	0	Completion rate of the full course of HIV PEP was low.
Muriuki 2017	Crossectional	Zimbawe	207/385	ZDV /3TC+LPV/r	nPEP completion 70/207 (34%) Follow up 148	NR (22)	PEP was only initiated in 54% of sexual assault cases. late presentation and poor adherence were the greatest gaps in PEP provision.
Kumar 2017	Retrospective	Canada	429	FTC/TDF+DTG FTC/TDF+RAL Vs. FTC/TDF+DRV/r	nPEP completion 66% vs. 42% AEs 17% vs 56%	NR	Two and three-drug HIV post-exposure prophylaxis regimens are better tolerated by patients and associated with greater compliance than four-drug therapy.

Eber 2018	Retrospective	Germany	1218/223	NR	Completion N=36 16% FOP 112 50% AEs 9 21%	NR (10)	patient compliance and completion rates are low.
Nisida 2019	Retrospective 2001-2013	Brazil	505/199	AZT/3TC+NEL AZT/3TC+LPV/r	Completion 104/166 (65%) AE 127 (79%) DR 25/166 (15%) FOPD28 FOPD180 89/199	NR (89)	Provision of psychology was associated with higher adherence of PEP and retention to follow-up.

TD: Treatment discontinuation, AE; adverse event, ND: No data, FOPD 7; follow up at day 7, FOPD 28; follow up at day 28, FOPD180; Follow-up at day 180, HIV seroconversion column; numerator (seroconversion o NR: not reported) denominator (total individual with HIV negative test). Sample size: number of individuals who received PEP/number of individuals eligible for PEP.

6.4.- Guidelines of PEP use for HIV prevention.

Optimal treatment has to balance side effects, efficacy, and costs. Recommendations on PEP regimens are based on experience in HIV treatment, although uninfected individuals may have different outcomes with ART than HIV-infected.

Since 2013, the main PEP guidelines have been updated. In the same document, some recommendations have changed several prescribed drugs, preferred regimens, a complete 28-day prescription instead 7-day starter pack, and occupational and non-occupational recommendations (126). Preferred regimens contain 2 nucleoside reverse transcriptase inhibitors (NRTI) as the backbone (BB) and the third drug from another antiretroviral family: protease inhibitors (PI), non-NRTI (NNRTI), or integrase inhibitors (II). (127-128)

WHO and U.S previous guidelines had recommended a 2-drug regimen for PEP because of concerns about adherence and side effects; if there was a risk of ART resistance, adding a third drug was recommended (129-130). Nowadays, to simplify prescription and presumably increase efficacy, a 3-drug regimen is recommended for all exposures (130); although toxicity could increase with more drugs and worsen adherence, no significant differences in PEP completion rates between 2 and 3 drug regimens have been observed ((73).

Previously ZDV plus Lamivudine (3TC) was the preferred 2 NRTI backbone regimen; considering evidence of better tolerability of TDF+FTC in the HIV treatment (131-132) and lower proportion of PEP discontinuation due to side effects (133), current guidelines recommend this regimen.

As a third drug, the historically most recommended and still widely used in low-income countries are ritonavir-boosted protease inhibitors such as ritonavir-boosted lopinavir (LPV/r), atazanavir (ATZ/r), or darunavir (DRV/r). Adverse events and PEP discontinuation are often described with no significant difference when using these drugs.(133-136). PEP efficacy can be jeopardized because of early discontinuation and low adherence.

As for NNRTI, Nevirapine (NVP) is not recommended for PEP due to the severe toxicity observed (137-138). EFV is recommended as a third alternative drug, although there is limited data in this field and concerns about possible early neurological/psychiatric side effects. A recent retrospective study in Thailand with HCW found this drug as the only factor associated with treatment discontinuation (139).

Guidelines suggest RPV as an option to be studied, given that very well tolerated in the HIV treatment and available with TDF/FTC backbone as a STR; both features could have a role in PEP adherence and completion rates improvement as shown in two studies conducted in MSM in Australia and France (121-122).

With the appearance of very well-tolerated new antiretroviral agents for HIV treatment, like II, current guidelines recommend RAL as the third drug in PEP regimens and PI as an alternative (140-142). Observational PEP studies using RAL with TDF/FTC backbone found this regimen well-tolerated and had better completion rates than previous studies (143-145). A study, comparing LPV/r versus RAL with TDF/FTC backbone observed an improvement in tolerance and adherence with RAL (145); this evidence supports this current recommendation.

No randomized trials compared boosted PI versus II when major guidelines were reviewed; because of limited data, lower cost, and higher availability in low-middle income countries, WHO still recommends boosted PI as a preferable third drug (146).

Other newer II, such as DTG and EVG, with high tolerability and potency in HIV treatment, are being considered for prevention; a recent pharmacokinetic study in non-human primates showed high and sustained concentrations of DTG and EVG in mucosal secretions, suggesting them as good candidates for HIV prevention (147).

There has been a recent update in the UK and WHO guidelines recommending RAL and DTG as third agents. EVG is recommended as an alternative regimen in the most updated guides. As for Bictegravir (BIC), no recommendations for PEP can be made now because of its limited evidence. However, EACS guidelines in its last update include BIC as an alternative agent (see table 6.3).

MVC, a CCR5 inhibitor that prevents virus entry into the host cell, with a high tolerability profile and rarely described resistances (148), could be considered an option for PEP after sexual contact. MVC absorbs rapidly and penetrates very efficiently into cervicovaginal and rectal tissue achieving high and sustained concentrations (149-150); these are valuable characteristics in the prevention field. Although there are several ongoing studies, data about MVC for prevention is limited. One case report is about an HCW who received PEP, including MVC, after a needlestick percutaneous injury to an HIV-infected individual harboring a multi-drug resistance virus, where the regimen was well-tolerated and completed (151). A randomized study comparing LPV/r versus MVC with TDF/FTC backbone

found that the MVC-containing regimen was better tolerated and had higher completion rates (111).

- The CDC guidelines for non-occupational PEP recommend initial regimens containing RAL + TDF/FTC, or DTG + TDF/FTC, or ATV/r + TDF/FTC. Alternative regimens are also suggested, depending on factors such as comorbidities and potential drug interactions.
- The WHO guidelines for PEP recommend a combination of three antiretroviral drugs, including two NRTIs and a third drug from another class, such as an II (RAL or DTG), a boosted protease inhibitor (DRV/r), or an NNRTI (EFV). Specific regimens are suggested for adults, pregnant women, and children, depending on factors such as age, weight, and comorbidities.
- The EACS guidelines for PEP recommend initial regimens containing RAL plus TDF/FTC or DTG plus TDF/FTC, or alternative regimens containing other drugs such as DRV or RPV. Specific regimens are suggested for different populations, including adults, pregnant women, and children, depending on factors such as renal function and potential drug interactions.

Table 6.3. PEP recommendations according to the latest guidelines.

GUIDELINE	ATV/r	LPV/r	DRV/r	DRV/c	EFZ	NEV	RPV	DOR	EVG/c	RAL	DTG	BIC	VERSION LASTEST
EACS										1	2	2	2021
JAPAN							1			1	2		2018
AUSTRALIA										1	1		2016
USA/DHHS			2							1	1		2016
FRANCE			2	2			1		2	2			2017
WHO	2	2	2							2	1		2018
GERMANY			2							1	1		2018
UK	2	2	2							1	2		2021

white boxes represent no current recommendation, red boxes represent alternative regimens, and green boxes represent preferred regimens, BHIVA, British HIV Association; DHHS, Department of Health and Human Services; EACS, European AIDS Clinical Society; RAL, raltegravir; DTG, dolutegravir; DRV; darunavir; /r, ritonavir; LPV, lopinavir; EVG, elvitegravir; /c, cobicistat; ATV, atazanavir; RPV, rilpivirine.

6.5.- General recommendations of PEP use for HIV prevention.

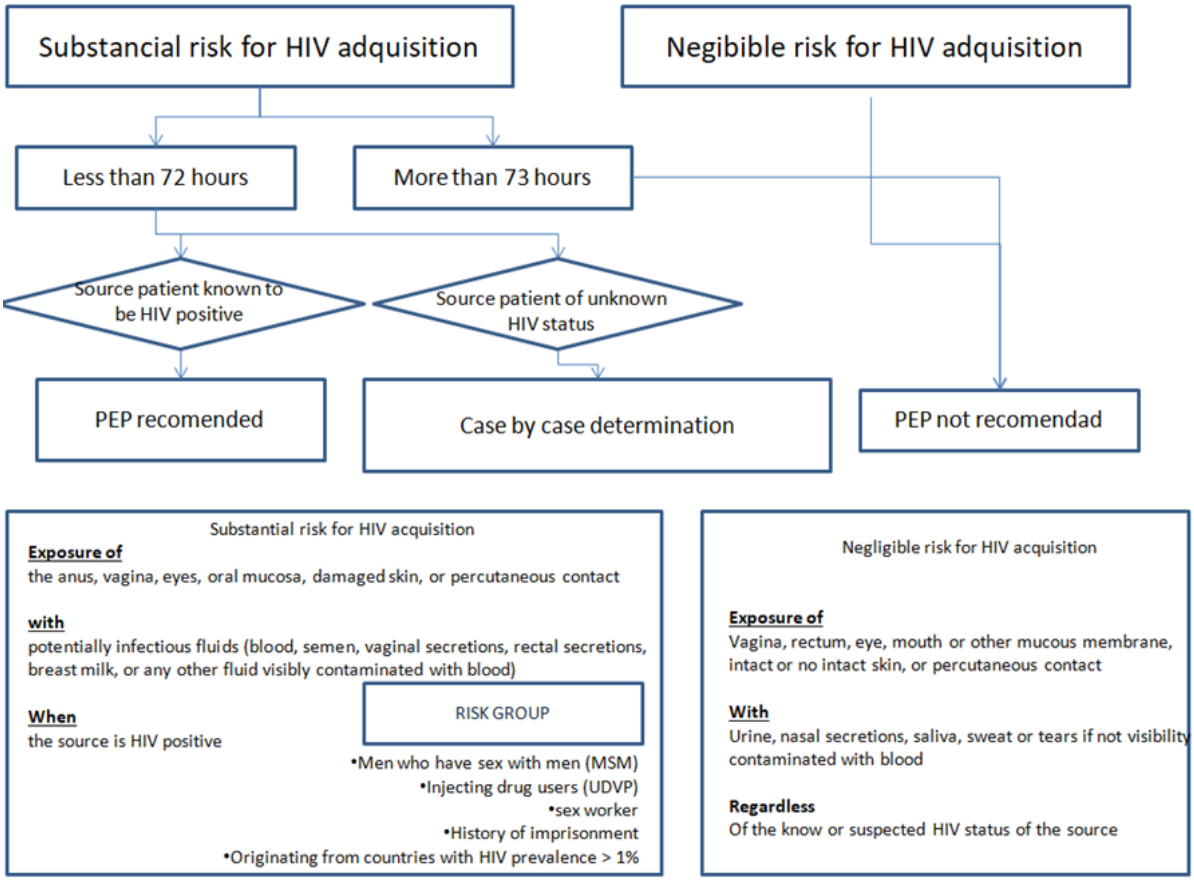
Addressing all patients with risk of exposure to HIV should be necessary; if the risk is considered high, using PEP is desirable in the first 72 hours. PEP recommendations have varied through time and countries; there have been differences between treatment initiation times (48 to 72 hours), the number of drugs (2 or more), type of drug, risk estimation, prescription of initiation packs with 5-7 days of treatment or the prescription of 28 days from the beginning.

The recommendation is to initiate PEP as soon as possible. It is highly suggested to be started before 12 hours, up to 72 hours (152,153).

Consider the risk level according to the exposure, the health status of the source, and the exposed individual. It is essential to address the prevalence of HIV in the population to which the source person belongs.

Risk estimation and recommendations for PEP prescription vary among the different available guidelines. The CDC guidelines on PEP [68] estimate the risk as substantial or negligible (Figure 6.2). In this guide, PEP indication is suitable if the risk is considered considerable; in this case, the evaluation is by case-by-case determination. If the risk is estimated to be zero, there is no need for PEP. Different guidelines recommend using PEP if the risk of contact is considered considerable[52,68,154-155], for example, in receptive anal penetration with the presence of fluids if the source is known as positive for HIV. If the viral load is also high, the risk is considered higher (156).

Figure 6.2. Algorithm for Evaluation and Treatment of possible nonoccupational HIV exposures



Modified from: Centers for Disease Control and Prevention, U.S. Department of Health and Human Services. Updated Guidelines for Antiretroviral Postexposure Prophylaxis After Sexual, Injection Drug Use, and Other Nonoccupational Exposure to HIV – United States, 2016.

The exposure risk depends on the exposure level and severity, the source person's health status, and the exposed individual. It is essential to address the prevalence of HIV in the population to which the source person belongs (high prevalence among MSM, IDUs, and sex workers), especially if their HIV status is unknown. HIV-infected persons with undetectable viral load (defined as < 50 copies) are considered not to transmit infection (if this can be demonstrated, PEP is not recommended) (157-159).

An updated estimation of the per-act risk of HIV transmission in case the source is known to be HIV positive (Figure 6.2). It summarizes the co-factors that could modify the risk of sexual exposure: a high viral load and the presence of genital ulcers could increase the risk, while ART, condom use, circumcision, and taking PrEP could decrease it [160].

6.6.- Follow-up recommendations.

HIV testing has enhanced dramatically since the first generation of tests was available in the 1980s. Individuals exposed to HIV had to wait months for markers to reach detectable levels (161); as a result, initial guidelines recommended a follow-up period of up to six months (162,163). Subsequent generation tests have lowered the detection window considerably and sped up results. 4th generation HIV tests were introduced initially in the U.S market in 2010 and progressively generalized worldwide, with the advantage of a 2 to 4 weeks detection window (164). So, it was not until 2021 that U.K. guidelines recommended shorter follow-up times until four months since PEP can delay seroconversion results. PEP viral suppression can postpone antibody response in case of an HIV infection (165). A 4-month period is a reasonable time to discard other STIs and detect delayed seroconversion.

As a standard procedure, anyone assessed after the risk of exposure to HIV, regardless of whether or not PEP has been prescribed, should be followed up for up to 12 weeks by the UK guidelines (2021) and up to 24 weeks for the GESIDA guidelines (updated 2015); the recommended follow-up and evaluation schedule after a risk exposure, including clinical evaluation, laboratory monitoring, and psychological support (see table 6.4).

When assessing the risk of HIV transmission, it is crucial to take into account other infections that can be transmitted through the same routes, such as; hepatitis B and C, syphilis, chlamydia, gonorrhea, and mycoplasma. It is important to follow the appropriate prophylactic treatment guidelines for these infections, as their presence can increase the risk of acquiring HIV.

While PEP cannot lower the incidence of other STIs, undergoing PEP consultation and follow-up testing can assist in identifying and detecting STIs early, especially those that can be diagnosed through next-generation DNA-based testing for rapid and precise diagnosis (166-167). Conducting periodic laboratory testing is a recommended clinical practice in most PEP care facilities and is a general recommendation in all PEP guidelines, offering a great opportunity to screen for other STIs.

Table 6.4. recommendations are suggested according to the UK guidelines for human post-exposure prophylaxis.

	Day 0 (treatment initiation)	Week 4-8 End of treatment	Week 16
Clinical evaluation	√	√	√
PEP prescription	√		
Hepatitis B vaccination	√		
Biochemistry, liver and pancreatic profile and CBC		√	√
HIV, HBV, HCV, HCA and syphilis serology (**)		√	√
cholesterol, HDL and LDL cholesterol, triglycerides		√	√
Syphilis serology, tetanus vaccination, antibiotic prophylaxis		√	√
Questionnaire on adherence to ART*** and pill count		√	
Adverse events		√	√

(**) Syphilis serology will only be made for sexual exposures until week 12 (&) In special cases according to medical opinion (e.g., sexual assault).(***)SMAQquestionnaire

CHAPTER 7: Pitfalls of PEP use for prevention.

PEP use has several potential pitfals. These include; seroconversions, potential transmissions of drug-resistant strains of HIV, non-completion, adverse event, poor adherence, compliance, and risk compensation behaviours. Understanding these potential pitfalls is crucial to ensuring optimal effectiveness of PEP for HIV prevention.

7.1.- PEP seroconversions.

In our center we performed a case-control study evaluating the predictive factors for HIV seroconversion. We found that MSM, previous PEP, HIV-positive sexual partner, and previous STI were factors associated with seroconversion (167).

Prompt initiation, adherence, and avoiding later exposures are associated with PEP efficacy. The most common cause of seroconversions occurs from an ongoing risk behavior after completing PEP; the reason for PEP failure also includes; deferred initiation, primary infection already recognized at the time of PEP initiation, and poor adherence (see table 7.1) (118,119,168). It is crucial for individuals with multiple exposures within 72 h to address the potential for increased risk.

A large group of exposed subjects in San Francisco were evaluated in a PEP consultation with a follow-up of 3 months; from 702 individuals, seven seroconversions were observed; among the characteristics were men who had received dual therapy and reported high-risk exposures (unprotected anal sex). Half were not adherent and had other risk contacts during treatment (169).

Table 7.1.- shows historical records of PEP failures

STUDY	PEP REGIMEN	SEROCONVERSION	COMMENT
Jochimsen,1997	ZDV	11	
Fournier,2001	ZDV+3TC+NEL	1	Delay between exposure and the beginning of prophylaxis, 70 h
Roland, 2005	ZDV+3TC	7	Multiple exposures(n=4)
Sonder, 2010	AZT+3TC+ATV	5	the virus isolated did not correspond from the source (n=1) unsafe sexual contacts between PEP initiation (n=1); viruses were sequenced and demonstrated no resistance to any PEP drugs (n=3)
Landovitz 2012	TDF+3TC	1	Halted PEP at 16 days; multiple repeats exposures after PEP treatment and laboratory proof of an incident STIs at the time of seroconversion
Landovitz 2014	TDF+3TC	1	Repeat exposures
Thomas 2015	TDF+FTC+LPV/r	1	52 hours
Leal , 2016	TDF+3TC+RAL	1	Numerous potential sexual risk exposures before and after receiving PEP.

7.2.- Potential for transmission of drug resistance (TDR) with the use of PEP

In Europe data from the EuResist Integrated Database, TDR prevalence was 12.5%, and the most prevalent were K103N/S, T215FY, M184I/V, M41I/L, M46I/L, and L90M (170). The prevalence of transmitted drug resistance TDR in Spain globally is 7.8% (3.3% for NTRI, 3.9% for NNTRI, 1.8% for protease inhibitors, and 0.7% for integrase inhibitors, according to the CORIS database (171). The use of ARVs conveys the risk of emerging resistance to recommended drugs. If PEP fails, development of resistant viruses is conceivable. Evidence on PEP failure and whether resistance develops is limited, making it challenging to determine the likelihood of its rate.

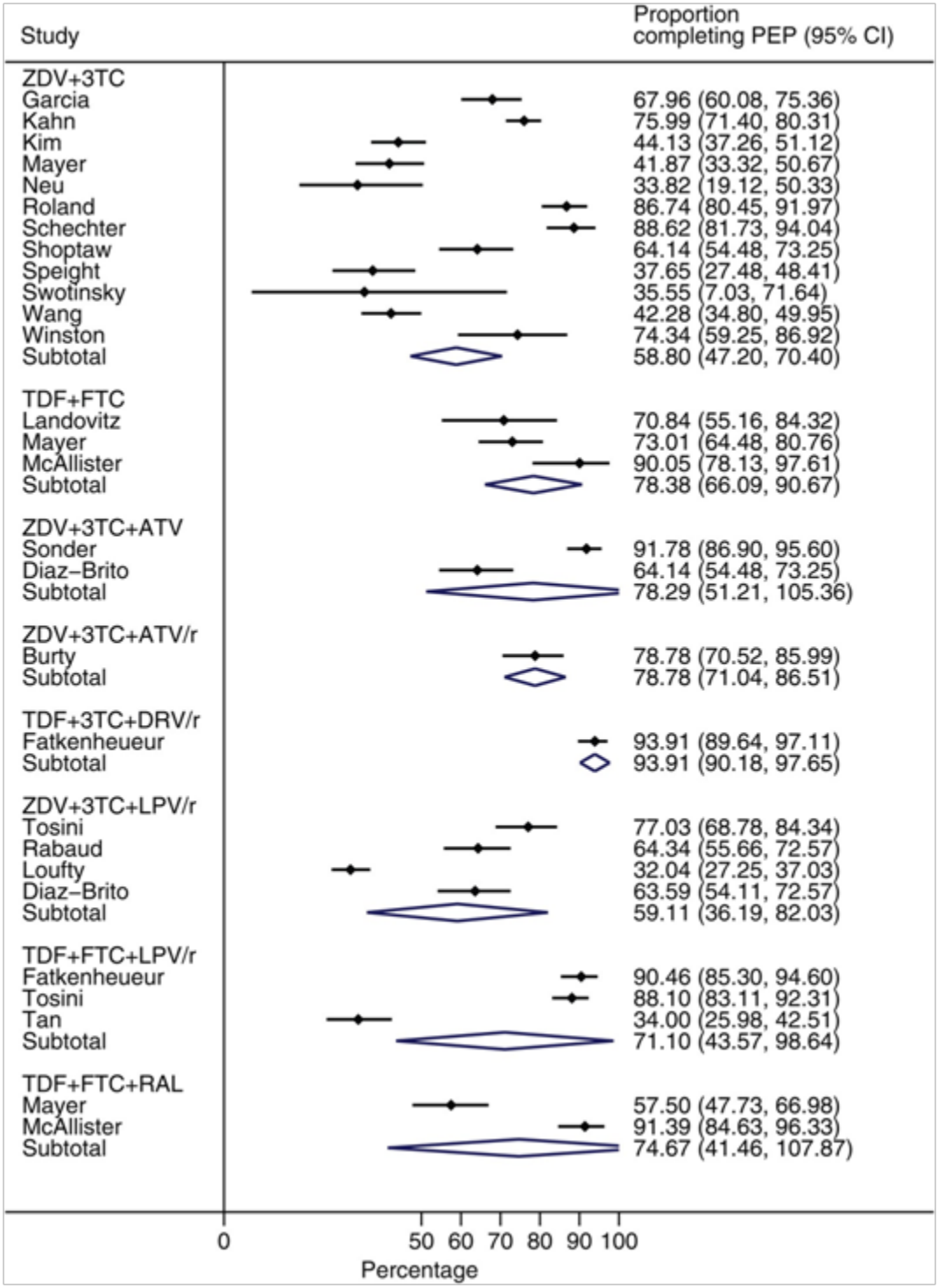
There are a handful of cases of PEP failure possibly associated with TDR. In one case, the known source had a high viral load with genotypic resistance (ZDV, 3TC, and indinavir) was initiated within 2 hours of the penetrating needle stick injury, but seroconversion was confirmed three months later (172). There were two cases with an already acquired HIV infection, undiagnosed initially, and PEP was started with a regimen of two drugs; one of them subsequent analysis revealed M184V mutation (78); this report while Isolated set ground for recommending three drugs regimen instead of a two-drug regimen due to the potential development of resistance. One limitation of MVC as PEP is that HIV might escape using a CXCR4 co-receptor. PRIMO's largest cohort of primary HIV-1 infected (PHI) individuals revealed that 4,9% PHI strains sexually transmitted used a CXCR4(173). Therefore, ongoing studies must be carefully evaluated to use MVC for prevention. Beyond recommended or preferred regimens, if information about resistance profile from source

individual is available, PEP prescription has to be according to it. It is vital that once PEP is prescribed, the link to follow-up is promoted, and carrying out sensitive tests is crucial for an early diagnosis of an HIV infection and genetic testing of the source when it is known (174).

7.3.- PEP completion rates.

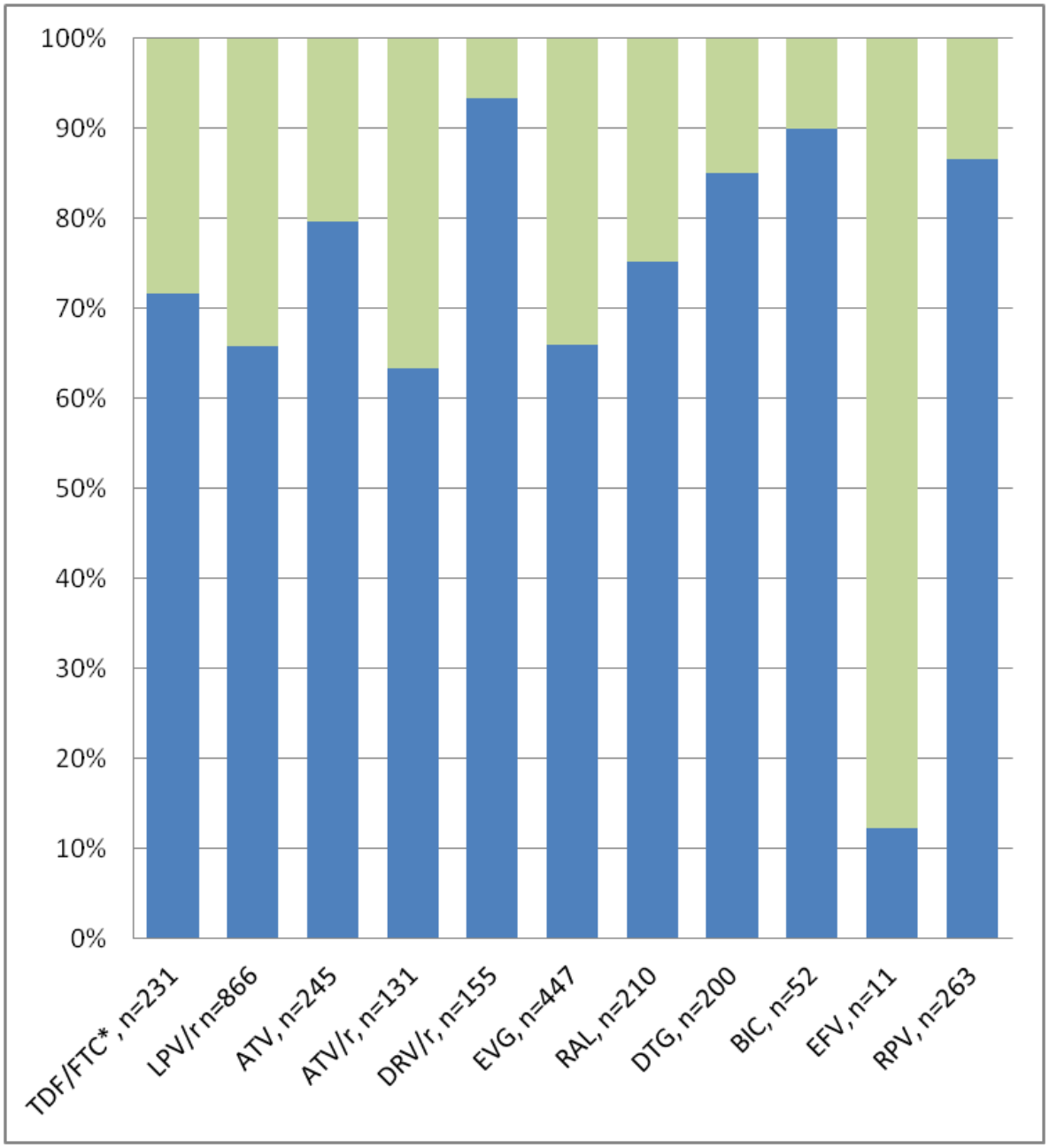
Treatment completion and adherence are among the most critical challenges for individuals receiving PEP. Its failure can affect preventive efficacy and facilitate resistance appearance Failures are often related to adverse events and toxicities, but pill burden, costs, reconsidering risk, stigma, and confidentiality issues may also be considered; noteworthy, the lack of a standardized measurement tool makes adherence assessment and its promotion (175). There are mixed results about PEP completion rates ranging between 38.8%-84% (59,63,97,121,129,176,177,181), (Figure 7.1 and 7.2). A recent meta-analysis found an overall 56,6% completion of the 28-day treatment, with the highest rates (65,6%) in non-occupational PEP studies and the lowest (40,2%) for sexual assault (178).

Figure 7.1. Pooled proportion of individuals completing postexposure prophylaxis (PEP). Not all studies [11] contributed data on completion rates.



Source from: Clin Infect Dis, Volume 60, Issue suppl_3, June 2015, Pages S170–S176, https://doi.org/10.1093/cid/civ092

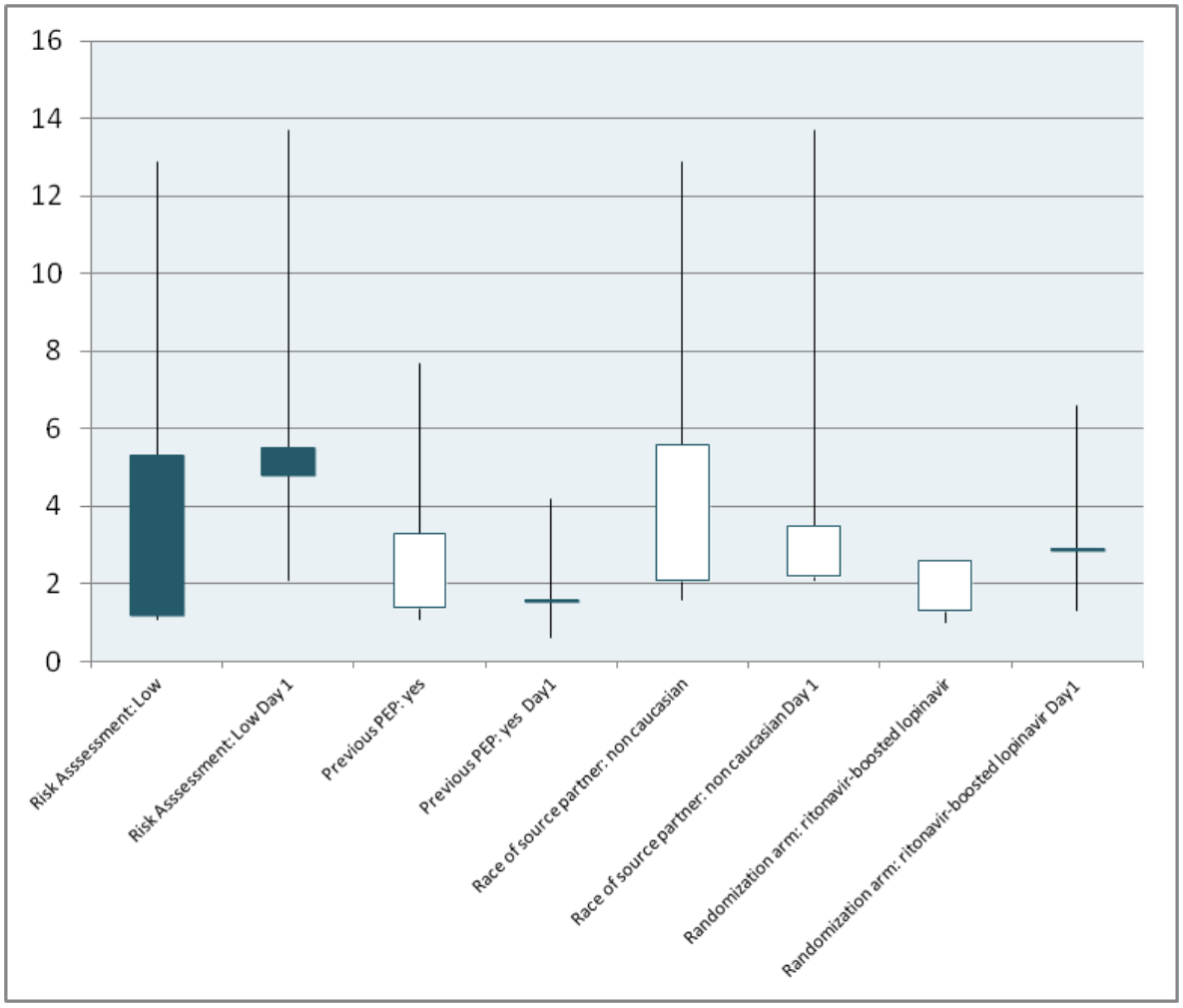
Figure 7.2.- Show PEP completion rates in each different third agent



regimen compiling more than one study at day 28; blue bars indicate PEP completion, green bars indicate PEP non-completion, *two drug regimens. n=represent the total sample size from all different studies.

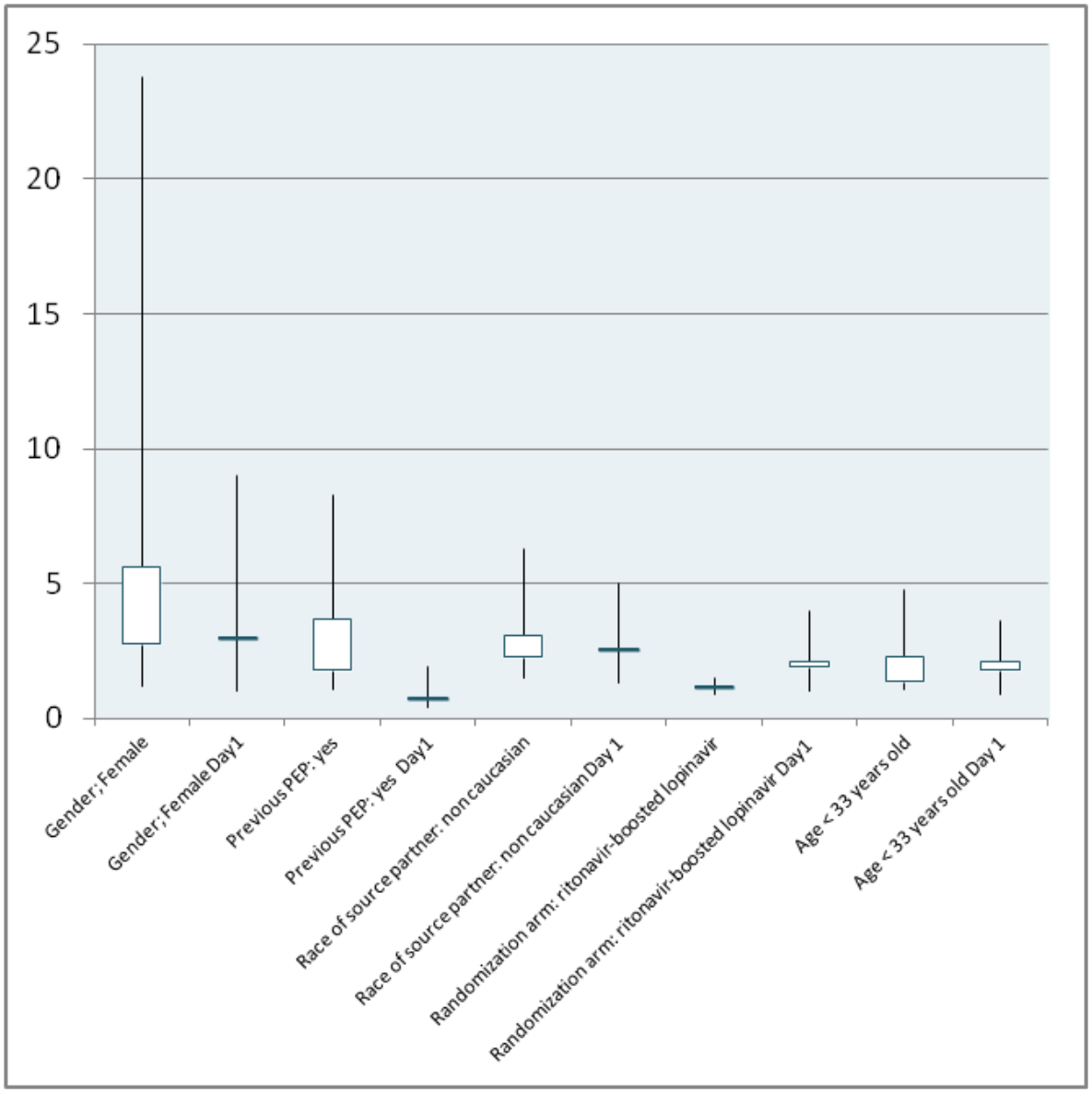
Two clinical trials described factors associated with PEP non-completion; non-caucasian race, previous PEP, and randomization arm to LPV/r were associated with PEP non-completion. Results from these two studies are shown in the following figures 7.3 and 7.4.

Figure 7.3 Factors associated with PEP non-completion in MARAVIPEP trial.



A randomized clinical trial comparing ritonavir-boosted LPV/r versus MVC each with TDF/FTC for post-exposure prophylaxis for HIV infection, Factors associated with PEP non-completion at day 28 due to any cause in the entire cohort (n=237) and individuals coming at least to the day 1 visit (n=243) significant results from multivariate analysis, vertical axis represent Odd ratios.

Figure 7.4.- Factors associated with PEP non-completion in RALPEP trial.



A randomized clinical trial comparing LPV/r versus RAL each with TDF/FTC for post-exposure prophylaxis for HIV infection, Factors associated with PEP non-completion at day 28 due to any cause in the entire cohort (n=243) and individuals coming at least to the day 1 visit (n=191) significant results from multivariate analysis, vertical axis represent Odd ratios. Narrow bars represent in box-plot figure (CI: 95%)

7.4.- Adverse events

Among the most critical challenges for individuals taking PEP are completing the 28 days of treatment and having adequate adherence, while failure to do so may affect its efficacy in preventing new infections and facilitating the emergence of resistance. Reasons for this failure are frequently related to adverse effects and drug toxicity, the burden that the individual has to take the medication, the costs, the reconsideration of the risk, the stigma, and the confidentiality.

A study comparing ART tolerability between HCW in PEP versus HIV-infected individuals on treatment found a higher rate of adverse effects and treatment discontinuation in HIV-negative individuals (179)., this might be due to people who initiate PEP usually do not take any medication and are unexpectedly forced to take it. This may influence them to be more sensitive to side effects or be more prone to attribute any sign to PEP medication.

Most of the observational studies carried out since 2005 have evaluated PEP regimens with ZDV, 3TC, LPV/r, TDF, FTC, and RAL. The adverse effects usually described include fatigue, nausea, headache, diarrhea, and other discomforts at the gastrointestinal level (59,97,180).

In a meta-analysis that included 24 studies related to the prescription of PEP in sexual assaults (predominant female population), AEs such as nausea, vomiting, diarrhea, and fatigue were frequently reported [181).

Another multicenter, randomized study carried out in 6 hospitals in the city of Barcelona comparing ZDV+3TC+LPV/r versus ZDV+3TC+ATV reported 46% AEs among patients, with gastrointestinal symptoms being the most frequent and, in the branch, the most LPV/r[97). There are few studies with NNRTI-containing PEP. This may be due in part to the potential life-threatening risks with first generation NNRTI, particularly NVP. A HCW required a liver transplant due to hepatotoxicity secondary to NVP as PEP, an unusually severe adverse event (182).

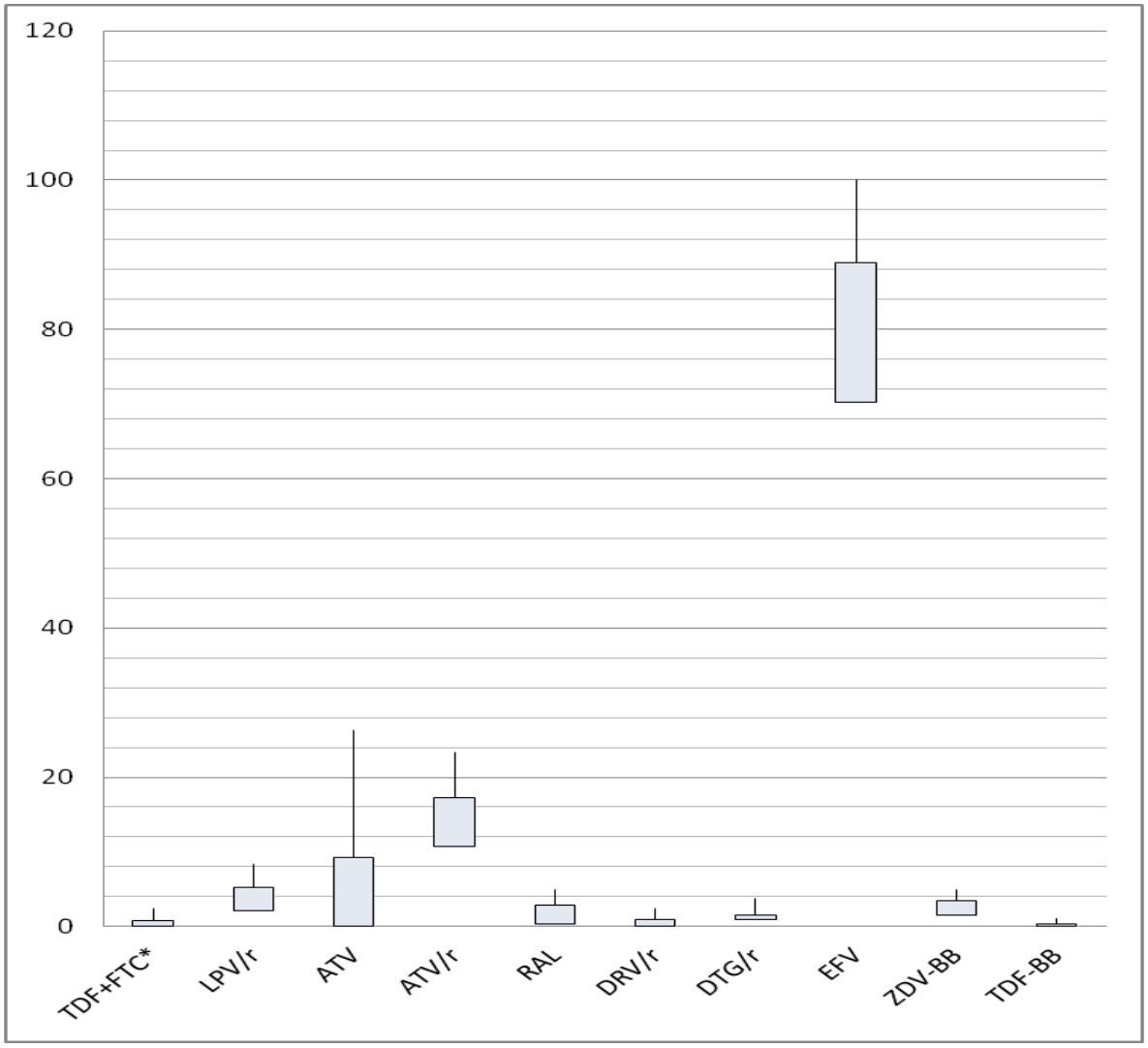
More recently, safer NNRTI drugs have shown better results. A study in Australia that evaluated the use of TDF/FTC/RPV as STR in MSM, in general, had good tolerability and adherence results in general, but one patient developed acute pancreatitis during the first week of treatment that was resolved without complications [123). In a prospective study assessing RPV-based therapy as an STR regimen, 70% of the participants experienced an adverse event, and events leading to discontinuation were in 3% of the cases (122).

For II as third agent; One observational study that evaluated the use of TDF/FTC and DTG as the third agent had a good tolerability profile being, the most common clinical adverse events were fatigue (26%), nausea (25%), diarrhea (21%), and headache (10%) (109). Another study evaluated TDF/FTC/EVG/c as STR in MSM. The following side effects: abdominal discomfort or pain, gas or bloating (42%), diarrhea (38%), fatigue (28%), nausea or vomiting (28%), headache (14%), or dizziness or lightheadedness (6%) (124).

7.5.- Treatment discontinuation

The discontinuation/switching rate of PEP due to adverse events varied among different regimens. The proportion ranged from 0.7% (95% CI 0-2.4%) for both TDF+FTC to 87.8% (70.3-100%) for AZT+FTC+EFV (124,128). LPV/r and ATV(r) protease inhibitors had the highest proportion of discontinuation/switching, particularly ZDV+3TC+ATV/r (21.2%; 95% CI, 13.5%–30.0%) (109, 121,183). Discontinuation rates were below 5% for all other regimens, with gastrointestinal events being the most common (109-112,127). The lowest discontinuation rates were reported for TDF/FTC+RAL (1.9%; 95% CI, 0%–3.8%) and TDF/FTC+DTG (1.4%; 95% CI,0.9-1.1%). EFV was associated with severe dizziness and neuropsychiatric symptoms, while DTG had higher neuropsychiatric events that led to discontinuation (124,139). The discontinuation rate due to adverse events was lower for individuals taking the TDF-backbone regimen (0.3%; 95% CI, 0%–1.1%) than those taking a ZDV-backbone regimen (3.2%; 95% CI, 1.5%–4.9%) (93,121,124,183). Treatment discontinuation in different arms is shown in Figure 7.5. (133).

Figure 7.5. Treatment discontinuation or switching from different studies for post-exposure prophylaxis; horizontal axis shows 3rd agent regimen, expressed in Proportion (CI: 95%).



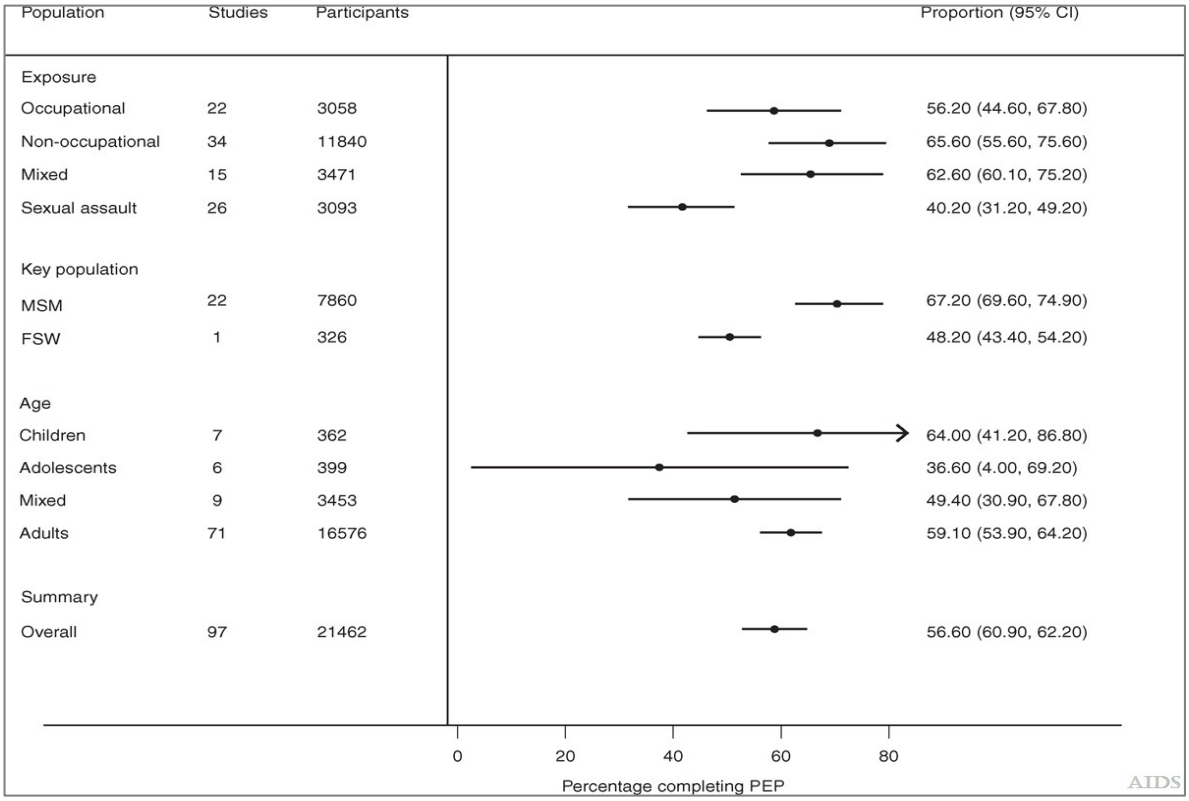
Source: Mayer, 2008 Sonder, 2010. Tosini, 2010. Burty, 2010. Diaz-Brito, 2012. McAllister, 2013. Tan, 2014. Landowitz24. Bogoch, 2015. Leal, 2016. Fatkenheueur, 2016. Wiboonchutikul,
2016. Milinkovic, 2017. McAllister, 2017. Mayer, 2017.

Study design: TDF+FTC, 4 observational studies; LPV/r, 5 RCTs, 3 observational; ATV, 1 RCT, 1 observational; ATV/r Observational; RAL, 1 RCT, 3 observational; DRV/r, 1 RCT; EFV, Observational (retrospective). ZDV- BB 17 observational 1 RTC; TDF-BB, 7 observational, 1 RCT.

7.6.- PEP adherence and compliance.

The assessment of adherence to PEP is challenging due to the absence of a standardized tool. Although a validated tool called the Simplified Medication Adherence Questionnaire (SMAQ) is available to evaluate adherence in HIV-infected individuals, including those from vulnerable populations such as psychiatric patients and minorities, its use is not widely adopted in PEP studies [184-187].

Figure 7.6.- PEP adherence among subgroups studies.



Adapted from: Ford, et al. AIDS, 2014 28(18):2721-2727, Pooled proportion among subgroups of studies.CI, confidence interval; FSW, female sex workers; MSM, men who have sex with men.

A meta-analysis reported that 21,462 PEP prescriptions found a 56.6% treatment completion rate at 28 days, with the highest rates in non-occupational exposures (65.6%)

and the lowest in sexual assaults (40.2%). Previous literature studies show varied results, and PEP completion rates range from 39% to 84%[73,109, 135, 143, 176,177]. Data is shown in figure 7.6.

In a systematic review of adolescents, victims of sexual assault barriers reported by patients/caregivers factors that lower PEP adherence included; side effects, forgetting, stigma/blame, busyness, poor knowledge, and mental health problems. Protector factors associated with good adherence were; HCW encouragement to take PEP, the perpetrator is HIV-positive, transport monetary support, reminders from family/peers to take PEP, and "one-stop" services offering HIV testing and PEP at an initial consultation (188,189).

A randomized study in South Africa evaluated psychosocial support through telephone and a brochure with information that included a diary to record adherence as support for victims of sexual assault. The controls only received the brochure. The intervention group had greater adherence, but the estimated effect was insignificant (190).

A randomized trial in the United States compared the standard intervention consisting of 2 counseling sessions aimed at risk reduction versus an improved one with five sessions in cases of non-occupational exposure. More than 79% of the participants completed the 28 days of treatment in this study, and the difference between the standard intervention versus more counseling sessions was 2.3% (191).

The PEP prescription includes the complete treatment for 28 days from the first visit, while in other centers, the treatment is started with a 3–7-day schedule (starting packs), which implies that the individual has to return at least one more time to collect the rest of the medication. The explanations mentioned for using these starter packs are to facilitate the

initiation of treatment by non-experts, encourage adherence, assess toxicity, provide more counseling, and reassure individuals considering discontinuing. Prescription of PEP starter packs (≤ 7-day treatment) is becoming a more usual practice because it facilitates prescription by non-experts and may encourage adherence since individuals require returning at least one more time to complete 28-day treatment (126).In a meta-analysis that compared outcomes of starter packs versus complete 28-day PEP treatments, it was found that 28% of individuals who received incomplete treatment did not return for the next follow-up visit and therefore did not receive the full PEP course. Conversely, prescribing starter packs was associated with lower adherence and completion rates in the same study (192).

Proactive interventions such as daily reminders through SMS and APPs for medication have shown promising results in some studies (144); telephone calls to reassure continuity and email reminders have not shown favorable results in evaluating the continuum of care from ER to a specialized HIV unit (193). In a multinational American cohort adherence to PEP regimen was found to be associated with the type of regimen used, with patients more likely to be adherent to regimens based on TDF (101). Another intervention that boosts adherence is prescribing simple ARV regimens such as STR instead of MTR (107).

A study conducted in China compared the use of Albuvirtide (ABT) with oral agents to the recommended non-STR for HIV PEP and found that the use of ABT resulted in higher rates of completion and adherence compared to the use of multiple regimens (194). While long-acting regimens used alone for HIV prevention may lead to adherence rates of 100%, concerns exist regarding the prolonged pharmacologic tail, which may make

discontinuation challenging, particularly if exposures or risks are ongoing. This raises the possibility of seroconversion with resistant viral quasispecies, still its use is being mostly considered in PrEP (195,196). Completing 28-day treatment is crucial for achieving efficacy. Therefore, it is a priority to address potential barriers to adherence and find strategies for improvement, especially for populations with lower completion rates, e.g., sexual assault victims and adolescents.

7.7.- Risk compensation

The increasing usage of preventive interventions against HIV might direct to more risky sexual routines and an increase in the transmission of other STIs, also known as risk compensation (197).

The occurrence of syphilis epidemics is often considered as an indicator of risk compensation behavior in HIV/AIDS prevention since syphilis and HIV are commonly tested together in current prevention and control strategies. However, there is no evidence to suggest an immediate increase in syphilis rates related to the use of PEP among the population. While there is a rising incidence of STIs globally, several factors are recognized; new STI agents (HAV, monkeypox,), the emergence of drug resistance, early onset of sexual activity, expanding contraceptives options, increasing sexual risk behaviors, and multiple sex partners, success of antiretrovirals for HIV prevention, chemsex, and sex apps. It cannot be uniquely attributed to preventive measures such as PEP.

Concerns that access to PEP could decrease risk perception and encourage riskier behavior, while most studies that have examined the relationship between PEP use and availability

and risky sexual behaviors during or after use have not documented increases in high-risk sexual behaviors after receiving PEP (198,199). However, other studies found that PEP users had more frequent sex with multiple partners and unprotected anal sex with partners of unknown serostatus or HIV infection at the end of treatment than those who had not used PEP (200).

An Australian cohort of MSM PEP users studied the relationship between PEP use and post-HIV seroconversions and found that among men who had received this treatment, the hazard ratio of subsequent infection was 2.67%. Leading to the conclusion that this subpopulation had a higher prevalence of risky relationships with infected persons, which represented a higher risk of seroconversion, especially after completing PEP (201). In this cohort, the elevated risk of seroconversion to PEP failure but a higher prevalence of unprotected anal sex with HIV-infected partners among PEP users compared to the rest of the cohort who had not used PEP; while this might be true, there is still selection bias on PEP indication on those who are at most risk.

These studies go some way to demonstrating that certain PEP users with ongoing high-risk behaviors may need additional behavioral and biomedical interventions such as PrEP. Therefore, we need broader measures to explore the risk compensation effect, not limited to a particular outcome in a specific area and a specific population.

While PEP might not show an increase in STIs or the risk of condomless sex or numerous sexual partners, the same was demonstrated in male circumcision studies (202). Nevertheless, current investigations indicated that PrEP use might boost risky sexual

behaviors and the risk of bacterial STIs, although earlier analyses did not confirm a precise risk compensation in pivotal PrEP studies. We can understand risk compensation phenomena as a multifactorial social, behavioral, geographic, and technology and not as a direct effect of risk compensations due to HIV prevention measures.

II.- HYPOTHESIS

"Without a hypothesis, a geologist might as well go into the field without a hammer." Proverb

"An hypothesis is a sort of draft in which key words are substituted for blanks in a pattern." - John Dewey

- PEP completion rates for sexual assault victims will be lower compared to other individuals for whom PEP is prescribed.
- TDF/FTC+EVG/c, as a once-daily single tablet regimen, will be a more feasible, and safe option for PEP in terms of improving adherence and completion rates compared to LPV/r prophylaxis regimens.
- When administered as prophylaxis, EVG/c and LPV/r will achieve sufficient concentrations in the rectal mucosa to prevent HIV infection in seronegative individuals.
- TDF/FTC+EVG/c, as a once-daily single tablet regimen, will have a higher completion rate for post-exposure prophylaxis compared to other prophylaxis regimens such as LPV/r, MCV, DRV/c, and RAL.
- DOR/3TC/TDF will be a safe and tolerable single tablet regimen for post-exposure prophylaxis allowing for a higher rate of PEP completion than other reference PEP regimens.

III.- OBJECTIVES

"A goal without a plan is just a wish." - Antoine de Saint-Exupéry

"Setting a goal is not the main thing. It is deciding how you will go about achieving it and staying with that plan." - Tom Landry

GENERAL OBJECTIVE

To comprehensively study the characteristics, safety, tolerability, efficacy, completion, and retention of care while identifying potential factors influencing these outcomes of different PEP regimens among diverse groups receiving PEP.

PRIMARY OBJETIVES

1. To determine the characteristics of PEP users in Barcelona and to analyze the frequency of other STIs and risk factors that render them eligible for PEP treatment.
2. To assess the pharmacokinetics, pharmacodynamics, and immune homeostasis of different PEP treatment regimens to prevent ex-vivo infection.
3. To calculate the rates of non-completion of PEP regimens among different risk groups.
4. To identify the factors linked to non-completion of PEP regimens among diverse risk groups.
5. Analyze the adverse event, adherence, follow-up rates of different post-exposure prophylaxis regimens.

CLASSIFYING AND SUMMARIZING PUBLISHED ARTICLES ACCORDING TO PREDEFINED OBJETIVES.

Although many articles share similar designs and endpoints, which can make it challenging to determine the contribution of each publication for a given objective, the purpose of this section is to attribute a specific weight to each publication based on its alignment with the assigned objectives, regardless of any overlap between them.

The aim of this section is not to provide a detailed account of the results of the published articles, as they are already described comprehensively in each respective work. Instead, this section will briefly summarize the design selected for each study, with regards to achieving the objectives outlined in the doctoral thesis.

This doctoral thesis strives to provide insights and recommendations that can help improve the care and outcomes of PEP treatment in diverse user groups.

For the first objective: *"To determine the fundamental traits of diverse PEP user groups residing in Barcelona and to analyze the frequency of other STIs and risk factors that render them eligible for PEP treatment".* For this Three articles were designated (Article Nº 1, Nº2, and Nº4), all of which share the common goal of describing a group of post-exposure prophylaxis users residing in Barcelona.

For the second objective: *"To assess the effects of different PEP treatment regimens on pharmacokinetics, pharmacodynamics, and immune homeostasis in order to prevent ex-vivo infection".* This article describes an ex-vivo model, developed in collaboration with

international molecular biology and biology research teams, for evaluating the efficacy of PEP, on different regimens.

For the Third objective: "*To calculate the rates of PEP non-completion for various treatment regimens among different risk groups"*. This takes into account the completion rates of five head-to-head clinical trials, one of which is derived from Article No. 2, a network meta-analysis from Article No. 5, and a single-arm clinical trial from Article No. 4.

For the Fourth objective: "*To identify the factors linked to non-completion of PEP treatment with various regimens among diverse risk groups"*. Two of the clinical trials (Articles No. 2 and No. 4) and a large cohort of female sexual assault victims (Article No. 1) underwent multivariate analysis for PEP non-completion.

For the Fifth objective: *"Analyze the adverse event, adherence, follow-up rates of post-exposure prophylaxis treatment using different regimens".* Based on the secondary objectives of four out of the five articles from this doctoral thesis, namely No. 1, No. 2, No. 4, and No. 5.

IV.- RESULTS

"No one can whistle a symphony. It takes a whole orchestra to play it." - H.E. Luccock

"Results are obtained by exploiting opportunities, not by solving problems." - Peter Drucker

FIRST PIECE OF RESEARCH

Post-exposure prophylaxis for HIV infection in sexual assault victims

A Inciarte, L Leal, L Masfarre , E Gonzalez , V Diaz-Brito , C Lucero , J Garcia-Pindado , A León , F García , Sexual Assault Victims Study Group *HIV Med*. 2020;21(1):43-52.

HIV Medicine achieved an impact factor of 3.180 in the ISI Journal Citation Reports, Q1, SUBJECT AREA AND CATEGORY: Infectious disease, Pharmacology and health policies.

DOI: 10.1111/hiv.12797
HIV Medicine (2019)

ORIGINAL RESEARCH

Post-exposure prophylaxis for HIV infection in sexual assault victims*

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Objectives

Sexual assault (SA) is recognized as a public health problem of epidemic proportions. Guidelines recommend the administration of post-exposure prophylaxis (PEP) after an SA. However, few data are available about the feasibility of this strategy, and this study was conducted to assess this.

Methods

We conducted a retrospective, longitudinal, observational study in SA victims attending the Hospital Clinic in Barcelona from 2006 to 2015. A total of 1695 SA victims attended the emergency room (ER), of whom 883 met the PEP criteria. Five follow-up visits were scheduled at days 1, 10, 28, 90 and 180 in the out-patient clinic. The primary endpoint was PEP completion rate at day 28. Secondary endpoints were loss to follow-up, treatment discontinuation, occurrence of adverse events (AEs) and rate of seroconversion.

Results

The median age of participants was 25 years [interquartile range (IQR) 21–33 years] and 93% were female. The median interval between exposure and presentation at the ER was 13 h (IQR 6–24 h). The level of risk was appreciable in 47% (n = 466) of individuals. Of 883 patients receiving PEP, 631 lived in Catalonia. In this group, the PEP completion rate at day 28 was 29% (n = 183). The follow-up rate was 63% (n = 400) and 38% (n = 241) at days 1 and 28, respectively. Treatment discontinuation was present in 58 (15%) of 400 patients who attended at least the day 1 visit, the main reason being AEs (n = 35; 60%). AEs were reported in 226 (56%) patients, and were mainly gastrointestinal (n = 196; 49%). Only 211 (33%) patients returned for HIV testing at day 90. A single seroconversion was observed in a men who have sex with men (MSM) patient at day 120.

Conclusions

Follow-up and compliance rates in SA victims were poor. In addition, > 50% of the patients experienced AEs, which were the main reason for PEP interruption. Strategies to increase follow-up testing and new better tolerated drug regimens must be investigated to address these issues.

Keywords: female, follow-up studies, HIV infections, patient compliance, post-exposure prophylaxis, sexual assault

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*The findings of this study were presented at the HIV4RP Conference on HIV Science. Madrid, Spain, 21–25 October 2018

Introduction

Sexual assault (SA) is a broad term that encompasses non-consented sexual acts, the definition of which includes touching, rubbing and physical coactions as well as rape (penetration with any object without the consent of the victim). There are no accurate data on the prevalence of SA, partly as a consequence of variation in the operational definition applied. Many victims do not identify their experience as rape [1,2]. In spite of this, the World Health

Organization (WHO) reports that one in six women are victims of rape during their lifetime and 35% of women experience some degree of physical or sexual violence [3,4]. This has huge physical, psychological and social repercussions [5–7]. Although SA occurs throughout the world, little information is available in most countries. In Spain, at least 1000 rapes are reported annually, 91% by female victims [8]. There is an important association between SA and the use of alcohol and submission drugs, as has been shown in prospective studies [9]. The most common drug in Barcelona is alcohol (48.8%) [10].

SA victims are vulnerable to a large number of sexually transmitted diseases; the prevalence in cohort studies varies from 8% to 32% [11–15]. In places where there is a high HIV prevalence, 4% of new HIV cases are related to a rape episode. Nevertheless, there are few documented cases of HIV transmission [16–20]. The transmission rate varies depending on the modality of sexual contact; receptive anal exposure carries the highest risk (0.8–3%), followed by receptive vaginal exposure (0.1–0.5%) and oral sex (0.0001–0.01%) [21–23]. Furthermore, any sexual exposure is considered to carry a risk when a condom is not used or is broken. The risk of HIV acquisition increases exponentially in the presence of factors such as genital trauma, genital ulcers, sexually transmitted infections (STIs), high viral load, blood exposure, ejaculation and rape by multiple assailants [24,25]. In cases where the victim of an SA had known the assailant for > 24 h, it was found that the perception of risk was lower and the victim tended to consider the use of PEP unnecessary [26].

The evidence of the efficacy of PEP to prevent HIV infection is based on case–control studies in health care workers, studies of the prevention of perinatal infection in pregnant woman, and animal studies in macaques [27–29]. In populations with a high prevalence of STIs, the use of PEP is recommended as soon as possible in the first 72 h [30–32]. There is a higher rate of completion in nonoccupational consented exposures than in situations of SA, in which completion, follow-up and diagnostic testing rates are low [33,34]. In a meta-analysis of 24 cohort studies, the median adherence to PEP in SA was approximately 40.3% [35]. Factors associated with PEP noncompletion are stigmatization of HIV infection, psychological trauma after rape, adverse events related to medication, limited knowledge about PEP indications, absence of proper multidisciplinary health care support in most Hospitals, and lack of psychological support [36–38].

Currently, there are few studies in Europe that have investigated the rate of treatment discontinuation, the rate of and factors associated with PEP noncompletion, adverse events and the number of seroconversions in SA victims. The purpose of this study was to describe follow-up in a cohort of sexually assaulted victims in the out-patient clinic at the Hospital Clinic in Barcelona, a reference centre in Catalonia.

Methods

We performed an observational, descriptive, longitudinal study. A review was performed of all medical records codified in the emergency room (ER) at the Hospital Clinic from January 2006 until December 2015 as SA, sexual aggression, rape or suspected victim of sexual assault with a potential exposure to HIV.

The assistance circuit for SA victims was standardized and the quality of care was monitored by the committee against gender violence of the hospital. The initial care of the attacked person was multidisciplinary, with the participation of social workers, nurses, gynaecologists, surgeons, traumatologists and forensic specialist psychiatrists, as well as the infectious disease specialists. In this scenario, anamnesis, a physical examination, biological sampling (of blood, urine and genital secretions), and toxicological screening using mass spectrometry (for alcohol, amphetamines, benzodiazepines, cannabis, cocaine, methadone, opiates, gamma hydroxybutyrate and ketamine) were performed together with prophylaxis for STIs (hepatitis B, chlamydial and gonococcal infections, syphilis and *Trichomonas vaginalis* infection). PEP recommendation and prophylactic measures for STIs other than HIV infection were performed according to international guidelines [2006 Centers for Disease Control and Prevention (CDC) PEP guidelines, and 2012 and 2015 updated versions] and national guidelines from Study group for AIDS published in 2015 (Supporting Information Figure S1) [30–32].

A 7-day PEP prescription was given and PEP was initiated immediately in the ER (day 0). HIV testing in the ER was not performed, according to the hospital protocols, and therefore HIV-negative status could not be confirmed before starting PEP. The follow-up procedure was also explained to patients and they were provided with counselling about antiretroviral therapy (ART). Five follow-up visits were scheduled for days 1, 7, 28, 90 and 180 after the ER visit. The primary endpoint was PEP noncompletion at day 28, which was considered to occur when the patient was lost to follow-up before this day or the treatment was discontinued or switched for any reason, including death. Secondary endpoints were loss to follow-up at subsequent visits, discontinuation rate, the number of adverse events and the rate of seroconversion.

The first visit was scheduled with an infectious disease specialist within 72 h of starting PEP (day 1). Demographics, social background, past medical history, characteristics of the assault, risk stratification for HIV acquisition, physical examination, time between SA and first intake of PEP

and blood toxicology screen were recorded and recompiled from ER charts. As part of the risk assessment, information was gathered about the HIV serostatus of the assailant when possible. At day 7, test results from the day 1 visit and possible adverse events were evaluated. Laboratory monitoring and sexual risk exposure counselling were performed and repeated on days 28, 90 and 180. Adverse events were assessed at every scheduled visit.

The hospital's research ethics committee and the competent Spanish authorities approved the protocol describing the project proposed by the researcher (approval number HCB/2014/0346). The ethics committee waived the requirement for written informed consent as all information that directly or indirectly identified patients was removed from the data files, guaranteeing strict anonymity and total confidentiality. The processing, reporting and transfer of personal data for all participating subjects complied with the provisions in Organic Act 15/1999 of 13 December (Spanish Royal Decree 1720/2007 of 21 December), on personal data protection.

Statistical analysis

For data collection, variables were extracted from electronic health records in the SAP 740 Hospital Information System® (Societas Europaea, Walldorf, Alemania, Germany) and the out-patient clinic database. The results obtained were included in a database created with the program MICROSOFT EXCEL® for later analysis with the statistical package SPSS v18.0®(IBM corporation, Armonk, New York ,USA). The primary endpoint of the study, PEP noncompletion, was analysed using Fisher's exact test. Categorical variables were compared between groups using the χ^2 test or Fisher's exact test. A multivariate logistic regression model was used to assess the independent factors associated with PEP noncompletion at day 28. The inferential analysis of continuous variables, such as laboratory values, was performed using parametric tests (Student's *t*-test).

Results

Demographics of the population

From January 2006 to January 2015, a total of 2015 SA victims attending the ER for potential exposure to HIV and meeting PEP criteria were included in the registry. Figure 1 shows the study flow chart. There were 320 erroneous entries. A total of 1695 medical charts were reviewed. The median age of the population was 25 years [interquartile range (IQR) 21–33 years] and 93% (n = 1583) were female. Ethnicity groups were as follows: 72% (n = 1223) were European, mostly Spanish 52% (n = 887); non-Europeans were mainly from Latin America (17%; n = 290), followed by North America (6%; n = 93) and Africa (3%; n = 47). In 76% (n = 1291) of cases, the victim's residency was in Catalonia.

Past medical history was available in 1150 cases. Eleven per cent of these patients (n = 126) had previously experienced an SA and 29% (n = 336) had an active psychiatric disorder, the most frequent of which were depression (33%; n = 110) and anxiety (15%; n = 50). Substance abuse disorder was present in 8% (n = 92) of cases. Disabled persons and sex workers were a minority of the study population: 4% (n = 41) and 2% (n = 24), respectively. The demographic characteristics of the sexually assaulted patients are shown in Table 1.

Characteristics of the assault

The time of day of the SA was reported for 546 people; for 382 of them (70%), this was from 12 pm to 7 am. The assailant was known only in 21% (n = 241) of cases; the assailant was an intimate partner in 37% of these cases (n = 89), had an unnamed known relationship with the victim in 54% (n = 130) and was a neighbour, family member or work partner in the remainder (9%; n = 22). SA with multiple perpetrators was reported in 16% (n = 164) of cases, with a median of 3 (IQR 2–6) perpetrators per assault.

In physical examinations, physical injuries as a result of the assault were observed in 36% (n = 419) of the 1150 individuals. Of these injuries, 11% (n = 121) were genital trauma, 21% (n = 241) haematomas or ecchymosis, 12% (n = 140) lacerations and 0.5% (n = 6) life-threatening lesions (pneumothorax, subarachnoid haemorrhage, pulmonary contusion, cervical fractures, cranial fractures and rib fractures).

Loss of consciousness in the context of drug-facilitated sexual assault (DFSA) was present in 54% of cases (n = 621 of 1150 registered cases). Assault victims self-referred alcohol intake in 54% of cases (n = 544 of 1000 registered cases). In toxicological analysis of 859 samples, alcohol was the most commonly detected substance, being found in 25% (n = 215) of cases, followed by cannabinoids (14%; n = 121), cocaine (12%; n = 101), benzodiazepines (10%; n = 82), amphetamines (7%; n = 56), 3,4-Methyl enedioxy methamphetamine, commonly know as ecstasy (8%; n = 69), morphine (2%; n = 13), GHB (0.4%; n = 3) and ketamine (0.4%; n = 3). The combination of alcohol and other central nervous system active drugs was detected in 11% (n = 95) of the samples. The median alcohol levels were 1.39 g/L (IQR 0.87–2.09 g/L) in positive results. The median estimated blood alcohol concentration was 2.5 g/L (IQR 1.9–3.3 g/L) at the time of the incident. Of those with impaired mental status (n = 528), 30% (n = 158) had

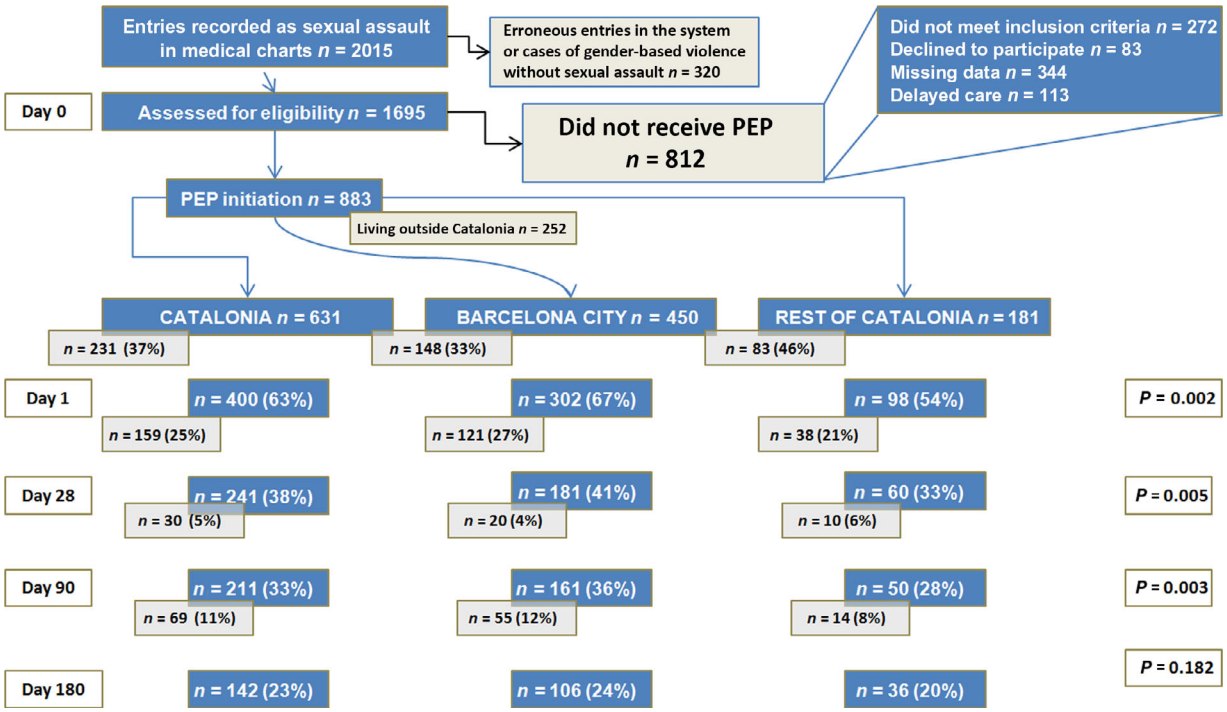

Fig. 1 Study flow chart. On day 0, for patients who met the criteria, treatment was immediately initiated in the emergency room (ER). Blue boxes represent individuals in follow-up according to location; grey boxes represents individuals lost to follow-up according to location. Grey boxes between day 0 and day 1 represent those lost to follow-up before day 1. On day 1, blue boxes represent patients who attended the first follow-up visit scheduled with an infectious disease specialist within the first week; grey boxes represent those subsequently lost to follow-up by day 28. On day 28, blue boxes represent patients who attended the day 28 visit; grey boxes represent those subsequently lost to follow-up by day 90. On day 90, blue boxes represent patients who attended the visit at day 90; grey boxes represent those subsequently lost to follow-up by day 180. On day 180, blue boxes represent patients who attended the visit at day 180 and completed the study. *P*-values are for the comparison between patients living in the metropolitan area and the rest of Catalonia.

positive alcohol blood levels and 67% (n = 354) self-referred alcohol intake.

PEP initiation and treatment regimens

Factors associated with PEP initiation were appreciable risk (53% in those receiving PEP versus 29% in those not receiving PEP; $P < 0.0001$), multiple perpetrators (18% versus 12%, respectively; $P = 0.003$), loss of consciousness (60% versus 44%, respectively; $P < 0.0001$), alcohol consumption (58% versus 47%, respectively; $P = 0.003$), substance abuse disorder (9% versus 5%, respectively; $P = 0.01$), psychiatric disorders (31% versus 25%, respectively; $P = 0.01$), unknown assailant (28% versus 17%, respectively; $P < 0.0001$), being European (89% versus 68%, respectively; $P < 0.0001$) and living in Catalonia (80% versus 73%, respectively; $P = 0.003$).

The median time of PEP initiation was 13 h (IQR 6–24 h) and appreciable risk was presented in 47% (n = 466) of the 1000 documented cases. Antibiotics were administered in all the patients receiving PEP, while vaccination coverage was 53% (n = 610). Excluding the missing data for PEP candidates who did not start the treatment, 42% (n = 196) did not receive it before 72 h or refused it despite it being indicated.

Among the 883 patients receiving ART, 43% (n = 380) were treated with a lopinavir/ritonavir (LPV/r)-containing regimen, 34% (n = 300) with atazanavir (ATV), 21% (n = 185) with raltegravir (RAL) and 2% (n = 18) with elvitegravir. The backbone therapy was variable over the years, but all patients received either zidovudine/lamivudine (77%; n = 680) or tenofovir/emtricitabine (23%; n = 203). For the analysis, these third drugs were categorized as belonging to the ATV, LPV/r or RAL group.

PEP completion rates and loss to follow-up

Among the 631 SA victims with residency in Catalonia, follow-up rates were 63% (n = 400) at baseline (day 1) and 38% (n = 241) and 33% (n = 211) at days 28 and 90,

Table 1 Characteristics of the sexual assault victims in the entire cohort (n = 1695) and those who received post-exposure prophylaxis (PEP) (n = 883) and who did not receive PEP (n = 811)

Variable	Entire cohort	Receiving PEP	Not receiving PEP	*P*-value
n	1695	883	812	
Age (years) [median (IQR)]	25 (21–33)	25 (21–32)	25 (21–33)	0.800
Female gender [*n* (%)]	1583 (93)	817 (93)	766 (94)	0.524
European [*n* (%)]	1223 (72)	597 (68)	726 (89)	0.0001
Catalonia residency [*n* (%)]	1291 (76)	641 (73)	650 (80)	0.003
Lost consciousness [*n* (%)]	621 (54)†	440 (60)	181 (44)	**0.0001**
Received antibiotics [*n* (%)]	1010 (88)†	824 (100)	186 (57)	**0.0001**
Received HBV vaccination [*n* (%)]	610 (53)†	499 (60)	111(34)	**0.0001**
Known assailant [*n* (%)]	241 (21)†	125 (17)	116(28)	0.0001
Appreciable risk [*n* (%)]*	466 (47)‡	384 (53)	82 (29)	**0.0001**
Sex worker [*n* (%)]	24 (2)†	18 (2)	6 (2)	0.217
Disabled [*n* (%)]	41 (4)†	26 (3)	15 (4)	0.577
Previous aggression [*n* (%)]	126 (11)†	79(10)	47 (13)	0.122
Physical trauma [*n* (%)]	419 (36)†	299 (38)	120 (33)	0.082
Multiple perpetrators [*n* (%)]	164 (16)‡	124 (18)	40 (12)	**0.003**
Substance abuse disorder [*n* (%)]	92 (8)†	73 (9)	19 (5)	**0.016**
Psychiatric disorder [*n* (%)]	336 (29)†	248 (31)	88 (25)	**0.019**
Alcohol consumption [*n* (%)]	544 (54)‡	408 (58)	136 (47)	**0.003**
Alcohol blood level [median (IQR)]	1.3 (0.8–2)	1.5 (0.9–2.1)	1.1 (0.7–1.7)	**0.001**

IQR, interquartile range; HBV, hepatitis B virus.
*Defined as any sexual exposure excluding low risk. †Number of nonmissing values was 1150. ‡Number of nonmissing values was 1000.
Bold formatting represents significant *P*-values.

respectively. Statistically significant differences in PEP completion rates were observed between individuals living in Barcelona City and the rest of Catalonia at day 1 (67% versus 54%, respectively; $P < 0.002$), day 28 (41% versus 33%, respectively; $P < 0.005$) and day 90 (36% versus 28%, respectively; $P < 0.003$) (Fig. 1).

In a total of 631 individuals living in Catalonia who initiated PEP, the PEP completion rate at day 28 was 29% (n = 183). The number of individuals completing PEP was taken to be the number who were still in follow-up at day 28 (n = 241), excluding those who did not complete treatment (n = 58). Factors associated with PEP noncompletion were analysed in a multivariate logistic regression model (Table 2). Independent factors associated with higher rates of PEP noncompletion were low risk perception ($P < 0.001$), previous aggression ($P < 0.032$), a known aggressor ($P < 0.006$) and a positive test result for cocaine ($P < 0.026$). PEP treatment group was not associated with PEP noncompletion.

Prevalence and incidence of HIV and other sexually transmitted infections

The prevalence of hepatitis A and B virus protective antibodies was 74% (n = 296) and 82% (n = 328), respectively, in patients who attended the clinic at least on day

Table 2 Factors associated with post-exposure prophylaxis (PEP) noncompletion at day 28 attributable to any cause or to adverse events

	PEP discontinuations attributable to any cause in the entire cohort (n = 883) OR (95% CI)*		PEP discontinuations attributable to any cause in patients living in Barcelona City (n = 631) OR (95% CI)*	
Characteristic	Univariate	Multivariate	Univariate	Multivariate
Known aggressor	**1.29 (1.17–1.43) *P* = 0.001**	**2.87 (1.41–5.84) *P* = 0.004**	**1.28 (1.15–1.42) *P* = 0.0001**	**2.73 (1.34–5.56), *P* = 0.006**
Previous aggression	**1.39 (0.94–2), *P* = 0.017**	**2.73 (1.10–6.78) *P* = 0.030**	**1.17 (1.04–1.32) *P* = 0.021**	**2.67 (1.08–6.55), *P* = 0.033**
Low risk assessment	**2.32 (1.62–3.31), *P* = 0.001**	**3.14 (1.81–5.44), *P* = 0.0001**	**2.55 (1.79–3.62), *P* = 0.001**	**3.05 (1.75–5.29), *P* = 0.001**
Substance abuse disorder	**0.47 (0.25–0.87), *P* = 0.015**		**0.59 (0.31–1.12), *P* = 0.047**	
Location: residency in Barcelona City	**1.45 (1.01–2.08), *P* = 0.044**		1.35 (0.93– 1.96), *P* = 0.106	
European ethnicity	**1.41 (1–1.98), *P* = 0.044**		1.32 (0.92–1.89), *P* = 0.120	
Consumed alcohol	**1.97 (1.22–3.18) *P* = 0.005**		**1.65 (1.13–2.43) *P* = 0.007**	
Positive test for cocaine	**OR = 0.45 (0.24–0.84), *P* = 0.011**	**2.57 (1.12–5.92) *P* = 0.026**	**0.42 (0.21–0.80), *P* = 0.008**	**2.57 (1.12–5.92) *P* = 0.026**
Adverse events			0.83 (0.54–1.27) *P* = 0.396	

*Individuals with an HIV-positive test at baseline were excluded from analysis.
Bold formatting represents significant *P*-values.
CI, confidence interval; OR, odds ratio.

1 (n = 400). Chronic hepatitis B virus infection was presented in 4% of cases (n = 18), and only one case of active hepatitis at the first consultation was detected. Chronic hepatitis C was presented in 2% (n = 10) of the tested patients on day 1 (n = 400). HIV prevalence in the whole cohort was 1.1% (n = 20; three of these were new diagnoses). A single seroconversion was observed in a male in the men who have sex with men (MSM) category at day 120, with multiple potential exposures after PEP. There were no cases of hepatitis B, hepatitis C or syphilis reported during follow-up at day 90.

Adverse events and treatment discontinuation

Adverse events and treatment discontinuation rates were only collected in patients who attended the clinic at least on day 1 (n = 400). Adverse events were reported by 226 (57%) patients and were significantly more common in the LPV/r group compared with the ATV group (65% versus 46%, respectively; P = 0.0001). No differences were observed in the proportion of adverse events when the LPV/r and ATV groups were compared with the RAL group (P = 0.113 and P = 0.167, respectively) (Fig. 2). Gastrointestinal symptoms were the most common adverse events (n = 196; 63%), followed by fatigue (n = 69; 22%) and neuropsychiatric episodes (n = 45; 15%) (Table 3).

Treatment discontinuation was present in 58 of 400 patients (15%), with the main reason being adverse events (n = 35; 60%). There were 44 patients with adverse events who had not finished treatment at day 28 (n = 19 in the LPV/r group, n = 12 in the ATV group, and n = 3 in the RAL group). Discontinuation rates were higher in the LPV/r group compared with the RAL group (18% versus 7%, respectively; P = 0.02). No differences were observed when comparing both groups with the ATV group (Fig. 3).

Abnormal laboratory values for exposed individuals

There were no discontinuations related to clinically relevant abnormal laboratory values. Statistically significant changes were observed in total cholesterol level within each treatment group, with increases in mean level at day 28 compared with baseline [+20 mg/dL in the LPV/r group (P < 0.0001), +8 mg/dL in the ATV group (P < 0.0001) and +7 mg/dL in the RAL group (P = 0.013)]. Statistically significant differences were observed in bilirubin levels in the protease inhibitors with a decrease on the mean levels after day 28 when compared to baseline bilirubin levels (−1.05 mg/dL in the ATV group and −0.6 mg/dL in the LPV/r group) (Table 4). There were no statistically significant differences compared with the normal laboratory ranges except for the ATV group for bilirubin levels (Table 4 shows overall values for the entire cohort).

Discussion

Few studies have described PEP completion rates in SA victims, and most of them lack detailed information regarding PEP regimens, follow-up visits, adverse events and rate of seroconversion. We herein report for the first time these rates in a population group from Catalonia over 10 years. In this study, the PEP completion rate was 29%. Factors associated with a significantly higher risk of PEP noncompletion were low-risk perception, a known assailant, previous aggression and a positive cocaine test.

It should be considered that 42% of those who did not receive PEP had an indication for it. The main reasons

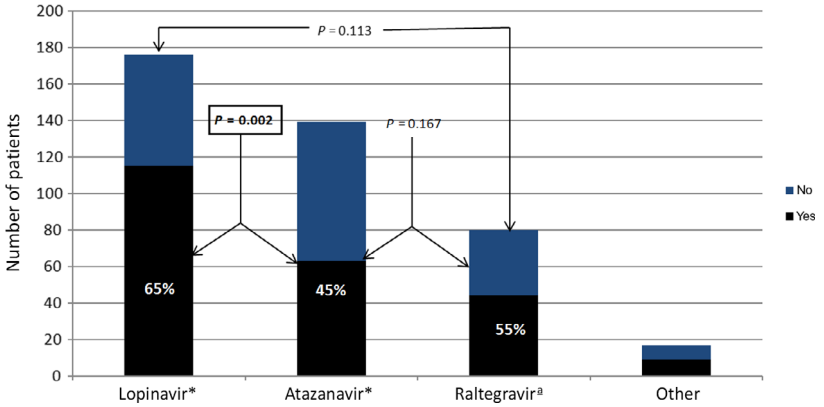

Fig. 2 Adverse effects experienced by sexual assault (SA) victims in the entire cohort coming to at least one follow-up visit (n = 400). [a]Tenofovir/emtricitabine as backbone. *Lamivudine/zidovudine as backbone.

Table 3 Adverse effects (AEs) experienced by sexual assault victims in the entire cohort coming to at least one follow-up visit for each treatment group (n = 400)

	Total	Lopinavir/r*	Atazanavir*	Raltegravir†	Other
Exposed individuals [n (%)]‡	400	172 (43)‡	136 (34)‡	80 (20)‡	12 (3)‡
Individuals with AEs [n (%)]	226 (56)	112 (65)	63 (46)	44 (55)	6 (50)
Type of symptoms [n (%)]					
Gastrointestinal§	196 (63)	100 (63)	54 (61)	38 (66)	4 (57)
Neuropsychiatric¶	45 (15)	22 (14)	15 (17)	7 (12)	1 (14)
Asthaenia	69 (22)	36 (23)	19 (22)	12 (21)	2 (28)

*Lamivudine/zidovudine as backbone. †Tenofovir/emtricitabine as backbone. ‡Overall percentage of the whole cohort. §Such as nausea, vomiting, diarrhoea, abdominal pain and flatulence. ¶Such as headache, insomnia and nightmares.

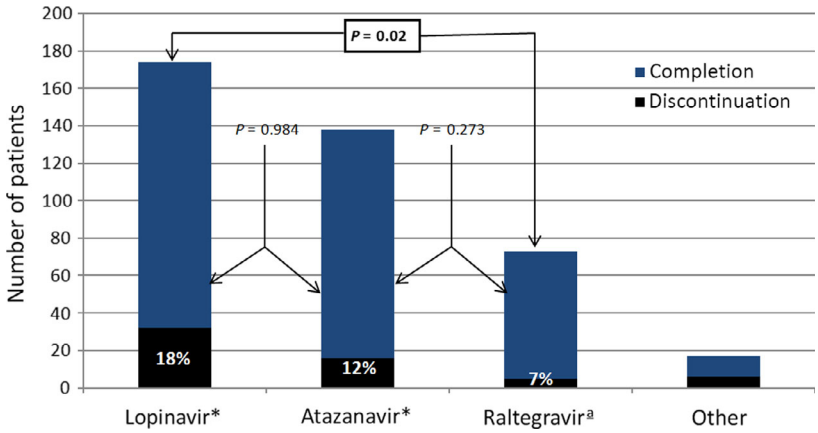

Fig. 3 Discontinuation rates for sexual assault (SA) victims coming to at least one follow-up visit (n = 400). [a]Tenofovir/emtricitabine as backbone. *Lamivudine/zidovudine as backbone.

Table 4 Abnormal laboratory values of exposed individuals in the entire cohort comparing baseline values (day 1) with follow-up values (day 28) for each treatment group (n = 400)

	Lopinavir/r*			Atazanavir*			Raltegravir†		
Laboratory test	Day 15 (3–7)	Day 2834 (30–39)	P	Day 15 (3–7)	Day 2831 (27–35)	P	Day 15 (3–7)	Day 2831 (27–35)	P
Total cholesterol (mg/dL) (normal < 200 mg/dL)	166	186	**0.0001**	161	169	**0.0001**	155	162	**0.013**
Triglycerides (mg/dL) (normal < 150 mg/dL)	98	93	0.291	82	77	0.52	74	79	0.43
AST (UI/L) (normal 5.0–40.0 UI/L)	23	23	0.778	21	22	0.32	22	22	0.78
ALT (UI/L) (normal 5.0–40.0 UI/L)	18	22	**0.010**	18	24	**0.001**	19	19	0.65
BT (mg/dL) (normal 0.20–1.20 mg/dL)	1.2	0.6	**0.0001**	2	0.95	**0.0001**	0.63	0.74	0.11
Leucocytes (cells/μL) [normal 400–1100 cells/μL)	434	635	0.431	460	683	**0.0001**	481	636	**0.0001**
Haemoglobin (g/dL) (normal 120–150 g/dL)	131	127	**0.0001**	130	126	**0.001**	130	130	0.218
Platelets ($\times 10^9$ cells/L) (normal 130–400 $\times 10^9$ cells/L)	276	263	0.111	299	297	0.789	281	289	0.325
Creatinine (mg/dL) (normal 0.30–1.30 mg/dL)	0.71	0.71	0.444	0.79	0.79	0.789	0.70	0.70	0.497

AST, aspartate aminotransferase; ALT, alanine aminotransferase; BT, total bilirubin.
*Lamivudine/zidovudine as backbone. †Tenofovir/emtricitabine as backbone.
Bold formatting represents significant P values.

for not initiating PEP were delayed care, self-refusal and knowing the perpetrator. In this studied cohort, follow-up rates were low: 63% and 38% at baseline and day 28, respectively. These results are similar to those of previous studies on SA with small cohorts in industrialized nations [16,26,33].

In this analysis, follow-up rates were greatly influenced by geographical proximity. Patients living further away from the specialized source of care displayed lower attendance rates than those living nearby. To overcome this issue, health care might be decentralized or be supported by additive interventions such as short message phone

reminders, telephone calls and a full course of PEP, or telemedicine resources could be used to maintain contact with exposed individuals beyond the ER period. The efficacy of these interventions remains unclear [39].

Adverse events were present in 65% of the assault victims in the whole cohort, and were mainly gastrointestinal. Results for PEP discontinuation in SA victims were similar to those in the MSM population, for which there is well-documented scientific evidence from clinical trials and observational studies, while data are scarce in sexually assaulted individuals [40]. The adverse event leads to nonadherence and treatment discontinuation. A recent prospective Belgian cohort study reported that being a sexual assault victim was an independent risk factor for lower adherence [41]. In our study, treatment discontinuation rates were as high as 15%. As RAL discontinuation rates were lower than those of LPV/r and ATV, these results suggest using integrase inhibitors as better-tolerated regimens in this fragile population, as previously demonstrated in the MSM population[40].

This study has a number of limitations. First, it had a retrospective design. Secondly, some of the information collected was incomplete as a consequence of partial amnesia or blackout intervals affecting the victim's recall of the assault at the ER evaluation. Moreover, patients with PEP treatment being lost to follow-up at day 1 (37%) also restricted the recollected information. It is also worth noting that a specific electronic database of sexual contacts was implemented after 2008 with a more detailed medical history. Thirdly, there was no recorded assessment of treatment adherence. Fourthly, the adverse events might also have been related to comedications such as ceftriaxone, azithromycin, metronidazole and progestin contraceptive pills. Finally, the median time between the SA and the arrival of the patient at the ER was 13 h, which is too long an interval for detection of drug use with a standard toxicological test [42].

Conclusions

SA victims displayed low PEP completions rates and poor follow-up rates. Access to a local health care facility at which the necessary resources are available could improve follow-up rates as well as HIV testing rates in these populations. Use of integrase inhibitor regimens might decrease treatment discontinuation rates and the number of adverse events compared with protease inhibitors. The results of this study suggest that it would be beneficial in future studies to further investigate adverse events, discontinuations and tolerance of current regimens in order to improve completion rates and decrease the number of side effects.

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Author contributions

AI, LL, EG, VDB, CL, AL and FG performed clinical assessments. AI and FG designed the study, contributed to data analysis and wrote the first draft of the manuscript. AI, LM and JGP were responsible for data entry. AI, LL, LM, EG, VDB, CL, JGP and FG critically reviewed the manuscript and agreed on its final version.

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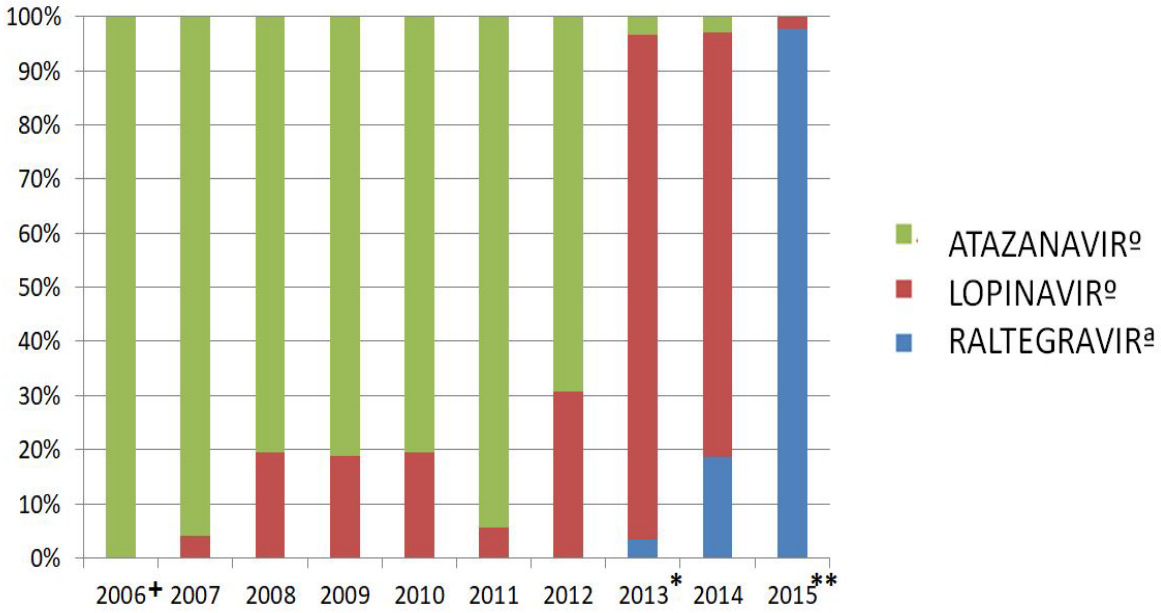
Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Supplementary Figure 1. Percentage of Individuals according to prescribed PEP regimen by year from 2006 and 2015.



Timelines of drug of choice according to Guidelines: + Atazanavir as first drug of choice, *Lopinavir as first drug of choice, ** Raltegravir as first drug of choice ªLamivudine/Zidovudine as backbone, º Tenofovir/ Emtricitabine as backbone.

SECOND PIECE OF RESEARCH

Tenofovir disoproxil fumarate/emtricitabine plus ritonavir-boosted lopinavir or cobicistat-boosted elvitegravir as a single-tablet regimen for HIV post-exposure prophylaxis

A Inciarte , L Leal , E González, A León , C Lucero , J Mallolas, B Torres, M Laguno , J Rojas, M Martínez-Rebollar, A González-Cordón, A Cruceta, J A Arnaiz , J M Gatell, F García, STRIBPEP Study Group . J Antimicrob Chemother. 2017;72(10):2857-2861.

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RESULTS

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Tenofovir disoproxil fumarate/emtricitabine plus ritonavir-boosted lopinavir or cobicistat-boosted elvitegravir as a single-tablet regimen for HIV post-exposure prophylaxis

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Objectives: To assess HIV-1 post-exposure prophylaxis (PEP) non-completion at day 28, comparing ritonavir-boosted lopinavir versus cobicistat-boosted elvitegravir as a single-tablet regimen (STR), using tenofovir disoproxil fumarate/emtricitabine with both of these therapies.

Methods: A prospective, open, randomized clinical trial was performed. Individuals attending the emergency room due to potential sexual exposure to HIV and who met criteria for PEP were randomized 1:3 into two groups receiving either 400/100 mg of lopinavir/ritonavir ($n = 38$) or 150/150 mg of elvitegravir/cobicistat ($n = 119$), with both groups also receiving 245/200 mg of tenofovir disoproxil fumarate/emtricitabine. Five follow-up visits were scheduled at days 1, 10, 28, 90 and 180. The primary endpoint was PEP non-completion at day 28. Secondary endpoints were adherence, adverse effects and rate of seroconversions. Clinical trials.gov number: NCT08431173.

Results: Median age was 32 years and 95% were males. PEP non-completion at day 28 was 36% ($n = 57$), with a trend to be higher in the lopinavir/ritonavir arm [lopinavir/ritonavir 47% ($n = 18$) versus elvitegravir/cobicistat 33% ($n = 39$), $P = 0.10$]. We performed a modified ITT analysis including only those patients who attended on day 1. PEP non-completion in this subgroup was higher in the lopinavir/ritonavir arm than in the elvitegravir/cobicistat arm (33% versus 15%, respectively, $P = 0.04$). Poor adherence was significantly higher in the lopinavir/ritonavir arm versus the elvitegravir/cobicistat arm (47% versus 9%, respectively, $P < 0.0001$). Adverse events were reported by 73 patients (59%), and were significantly more common in the lopinavir/ritonavir arm (90% versus 49%, $P = 0.0001$). A seroconversion was observed in the elvitegravir/cobicistat arm in a patient with multiple exposures before and after PEP.

Conclusions: A higher PEP non-completion, poor adherence and adverse events were observed in patients allocated to the lopinavir/ritonavir arm, suggesting that STR elvitegravir/cobicistat is a well-tolerated antiretroviral for PEP.

Introduction

Post-exposure prophylaxis (PEP) toxicity is the main reason for poor adherence and high rates of discontinuation of treatment.[1] Newly controlled clinical trials comparing lopinavir/ritonavir versus the integrase inhibitor raltegravir, using tenofovir disoproxil fumarate/emtricitabine as backbone for both treatments, observed a significant improvement in tolerance and adherence with raltegravir.[2] Elvitegravir, an integrase inhibitor, with tenofovir disoproxil fumarate/emtricitabine as backbone may be a good choice for PEP.[3–5] A recent pharmacokinetics study in non-human primates showed high and sustained concentrations of elvitegravir in rectal and vaginal mucosa.[6] In addition, elvitegravir can be administered as one pill a day, and a low incidence of side effects and dropouts have been reported.[5] There are no studies comparing single-tablet regimens (STRs) with multiple-tablet regimens (MTRs). Our group has performed a clinical trial comparing cobicistat-boosted elvitegravir versus ritonavir-boosted lopinavir, using tenofovir disoproxil fumarate/emtricitabine as backbone in both cases, to assess PEP completion rates, adherence and adverse effects.

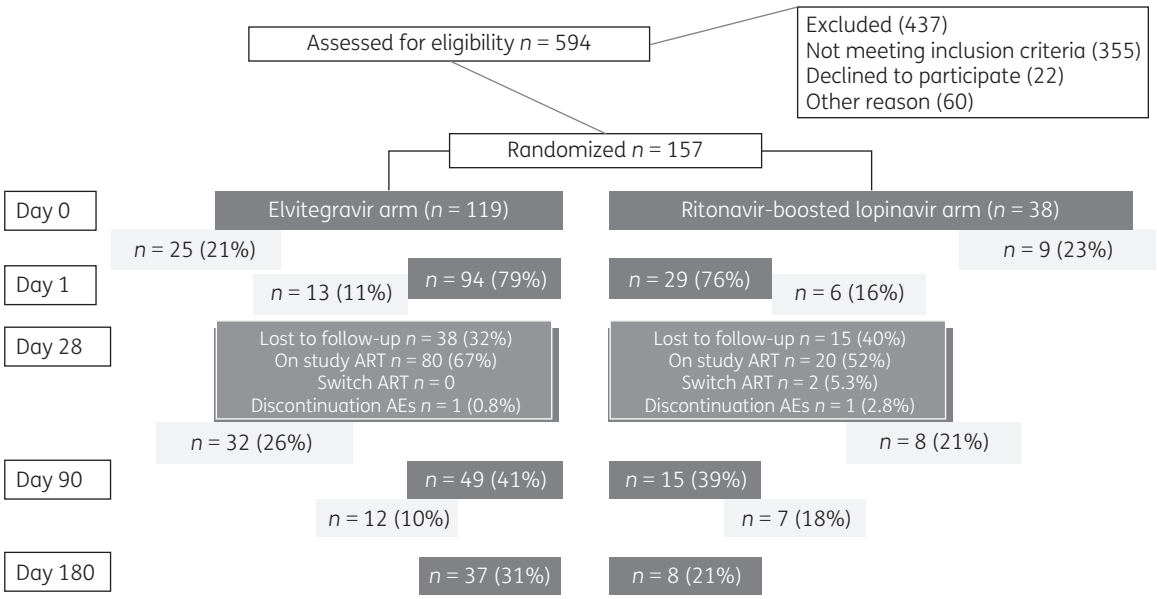

Figure 1. Study flow chart. Day 0: randomization in the ER and treatment immediately initiated. Black boxes represent individuals on follow-up according to arm and grey boxes represent individuals lost to follow-up according to arm. Day 1: patients who attended the first follow-up visit scheduled with an infectious disease physician within the first week and individuals lost to follow-up to day 28. Day 28: patients who attended at day 28 and individuals lost to follow-up at day 90 (including ART patients who continued with the same ART received at day 0, those patients who switched medication but continued to receive medication and attended day 28, and those patients who discontinued treatment due to side effects and attended at day 28). Day 90: patients who attended at day 90 and individuals lost to follow-up at day 180 of the visit. Day 180: patients who attended at day 180 and completed the study. AEs, adverse events.

Methods

We performed an open, randomized clinical trial. Participants were individuals who attended the emergency room (ER) of our hospital between June 2015 and December 2015, due to potential exposure to HIV. PEP recommendations were performed according to Spanish guidelines.[7] Individuals who were ≥18 years old, agreed to participate and signed an informed consent were randomized 3:1 to receive either tenofovir disoproxil fumarate/emtricitabine plus elvitegravir/cobicistat once daily ($n = 119$) or tenofovir disoproxil fumarate/emtricitabine plus lopinavir/ritonavir twice daily ($n = 38$). Figure 1 shows the study flow chart. A full 28 day prescription was given and initiated immediately (day 0). A computer-generated list of numbers was used to randomize the participants. Prophylactic measures for other sexually transmitted infections (STIs) were administered following current recommendations.[7] HIV testing in the ER was not performed due to our hospital protocols and therefore HIV-negative status could not be confirmed before starting PEP. The follow-up procedure was explained to patients, and patients were provided with counselling on ART. After randomization, five follow-up visits were scheduled for days 1, 10, 28, 90 and 180. Treatment adherence was reinforced in the follow-up visits of the first month. Adherence was measured at the 28 day visit using the Simplified Medication Adherence Questionnaire (SMAQ).[8] The degree of adherence was calculated based on each patient's responses and we classified below 94% as low adherence, a cut-off that has been previously implemented by other authors.[8,9] Adverse events were assessed and graded at every scheduled visit, following WHO recommendations.[10] Figure S1 (available as Supplementary data at *JAC* Online) shows the study design. The primary endpoint was PEP non-completion at day 28. PEP non-completion was considered when the patient was lost to follow-up before day 28, or the treatment was discontinued or switched for any reason, including death. Secondary endpoints were lost to follow-up in subsequent visits, adherence to PEP, number of adverse events and rate of seroconversions.

Clinical trials.gov number: NCT08431173.

Ethics

This study was approved by the hospital research committee (approval number HCB/2014/0346) and by the competent Spanish authorities.

Statistical analysis

The sample size was calculated with a $1 - b$ statistical power of 80% and a protection level versus the bilateral Type I error of 5%, assuming treatment discontinuation of 25% in the lopinavir/ritonavir arm and 7% in the elvitegravir/cobicistat arm. Since we had no information about treatment initiation until patients attended the day 1 visit, we hypothesized that reasons for not attending could be independent of the type of medication. Consequently, we also performed modified ITT analysis considering all patients who attended at least the day 1 visit with the aim to better assess the effect of medication on PEP non-completion. Individuals who discontinued PEP because they were found to be HIV positive on day 1 or because the sexual partners subsequently were found to be HIV negative were excluded from this analysis. Continuous variables were compared between groups with Student's *t*-test or a non-parametric Mann–Whitney *U*-test. Categorical variables were compared between groups using the χ^2 test or Fisher's exact test. A multivariate analysis was used to assess the independent factors associated with PEP non-completion at day 28.

Results

Characteristics of exposed individuals and source partners

The characteristics of the exposed individuals are shown in Table 1. The median age was 32 years, 95% were males and 92% were MSM. HIV infection was detected in two randomized patients in

Table 1. Characteristics of exposed individuals from the entire cohort ($n = 157$) and individuals coming at least to the day 1 visit ($n = 123$)

	Entire cohort				Coming at least to the day 1 visit			
	cohort	elvitegravir/ cobicistat	lopinavir/ ritonavir	*P*	cohort	elvitegravir/ cobicistat	lopinavir/ ritonavir	*P*
Number	157	119	38		123	94	29	
Age (years), median (IQR)	32 (27–39)	33 (27–40)	31 (26–38)	0.577	33 (28–40)	33 (28–41)	31 (26–35)	0.189
Male, *n* (%)	149 (95)	113 (95)	36 (95)	0.822	117 (95)	90 (96)	27 (93)	0.585
Caucasian, *n* (%)	124 (79)	96 (81)	28 (73)	0.357	98 (80)	77 (82)	21 (72)	0.266
Time from exposure (h), median (IQR)	19 (9–36)	19 (10–36)	15 (6–20)	0.258	17 (10–36)	18 (10–36)	15 (6–33)	0.347
Type of exposure MSM, *n* (%)	143 (91)	109 (92)	34 (90)	0,689	113 (92)	88 (94)	25 (86)	0.202
Appreciable risk of infection,[a] *n* (%)	126 (82) [153][b]	96 (83)	30 (81)	0.816	101 (83) [121][b]	79 (86)	22 (76)	0.206
Previous PEP, *n* (%)	48 (35) [136][b]	38 (37)	10 (29)	0.407	34 (29) [118][b]	28 (32)	6 (21)	0.266
Previous STI, *n* (%)	67 (50) [134][b]	52 (51)	15 (47)	0.685	52 (44) [117][b]	42 (47)	10 (37)	0.377
Previous HIV test, *n* (%)	134 (98) [137][b]	103 (97)	31 (100)	0.344	111 (97) [114][b]	85 (97)	26 (100)	0.340
Partner HIV positive, *n* (%)	36 (23) [155][b]	26 (22)	10 (27)	0.742	30 (24) [123][b]	22 (23)	8 (28)	0.647

[a]Defined as any sexual exposure excluding those with low risk.
[b]Total of non-missing values.

the serology performed on day 1 (one in the elvitegravir/cobicistat arm and one in the lopinavir/ritonavir arm). These patients were referred to an HIV clinic to continue follow-up.

PEP non-completion and lost to follow-up

PEP non-completion at day 28 was 36% ($n = 57$), with a trend to be higher in the lopinavir/ritonavir arm [lopinavir/ritonavir 47% ($n = 18$) versus elvitegravir/cobicistat 33% ($n = 39$), $P = 0.10$]. Only 123 out of 157 of those who were randomized attended the first scheduled visit, with no significant differences between the two arms ($P = 0.73$). We performed a modified ITT analysis including only patients who attended at least the day 1 visit ($n = 123$) and excluding individuals who discontinued PEP because they tested HIV positive on day 1 ($n = 2$) or because the sexual partner subsequently tested HIV negative ($n = 3$). The characteristics of this subgroup are shown in Table 1. PEP non-completion in this subgroup of patients was significantly higher in the lopinavir/ritonavir arm (9 of 27 patients, 33%) than in the elvitegravir/cobicistat arm (14 of 91 patients, 15%, $P = 0.04$). Of the original cohort, 34% ($n = 53$) was lost to follow-up at day 28 without significant differences between arms [lopinavir/ritonavir 40% ($n = 15$) versus elvitegravir/cobicistat 32% ($n = 38$), $P = 0.39$]. Only a few patients switched or discontinued due to side effects, or reconsideration of risk (Figure 1). The proportion of patients with low adherence to PEP was significantly higher among the patients who completed therapy in the lopinavir/ritonavir arm versus the elvitegravir/cobicistat arm (47% versus 9%, $P = 0.0001$). There was only a single seroconversion in the elvitegravir/cobicistat arm at day 90. This individual reported multiple high-risk exposures before and after starting PEP.

Factors associated with PEP non-completion

The factors associated with PEP non-completion were analysed in a multivariate logistic regression model (Table S1). Independent factors associated with higher rates of PEP non-completion were age below the median ($P = 0.09$), low risk exposure ($P = 0.03$) and previous PEP ($P = 0.05$).

Adverse events

Adverse events were only collected in patients who attended at least day 1. Adverse events were reported by 73 (59%) patients and were significantly more common in the lopinavir/ritonavir arm (90% versus 49%, $P = 0.0001$) (Table S2). There was a higher median of adverse events in the lopinavir/ritonavir arm than in the elvitegravir/cobicistat arm [2 (1–4) versus 0 (0–1), $P = 0.0001$]. There were no potentially life-threating (grade IV) adverse events. Regarding laboratory tests, there were no significant differences between groups. A higher proportion of non-adherent patients presented adverse events when compared with adherent patients (80% versus 52%, $P = 0.04$).

Discussion

To our knowledge, this is the first randomized clinical trial comparing an STR versus an MTR for PEP. Patients attending an ER due to potential exposure to HIV were randomized to receive lopinavir/ritonavir versus elvitegravir/cobicistat, using tenofovir disoproxil fumarate/emtricitabine as backbone in both cases. Patients allocated to lopinavir/ritonavir showed a higher PEP non-completion rate, poor adherence and adverse events. In addition, we found that poor adherence was associated with adverse events. It should be noted that lopinavir/ritonavir was used twice daily; therefore, we cannot know which variables might influence the outcome (number of tablets, number of doses or the drugs themselves). Factors associated with a significantly higher risk of PEP non-completion were low risk exposure, age below the median and previous PEP.

The PEP non-completion rate was higher in the lopinavir/ritonavir arm than in the elvitegravir/cobicistat arm. Similar results have

been found in other studies comparing lopinavir/ritonavir with raltegravir or maraviroc.[2,11] These results suggest overall a very poor PEP completion for PI regimens and support the use of integrase inhibitors in this setting as the most recent guidelines suggest.[12,13] In terms of adherence, patients taking lopinavir/ritonavir were less likely to adhere to treatment as compared with patients taking elvitegravir/cobicistat. Similar results were also observed in several meta-analyses comparing STRs versus MTRs in HIV-positive patients,[14,15] and in a recent prospective single-arm study of elvitegravir/cobicistat for PEP with similar adherence rates for elvitegravir.[16] We also found a higher rate of adverse events in the lopinavir/ritonavir arm compared with the elvitegravir/cobicistat arm, confirming results observed in prospective studies and clinical trials comparing PIs versus integrase inhibitors.[2,17,18]

Several limitations were encountered in this investigation. First, information was not available from patients who were lost to follow-up at the day 1 visit (21%) or at subsequent visits. Second, most of the study population was MSM (92%) with a small number of women included in this analysis (5%). Third, few data were collected about sexual partner HIV serological condition and other STIs because of their unknown status. Finally, HIV fourth-generation testing could not be performed to rule out HIV infection on ER consultation due to our hospital protocols.

In conclusion, elvitegravir might be a suitable drug choice for PEP due to its tolerability profile, low rate of adverse events compared with PIs and low rate of poor adherence when compared with MTRs.

Acknowledgements

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Members of the STRIBPEP Study Group

Hospital Clinic, University of Barcelona, Spain: Eva González, Lorna Leal, Agathe León, Berta Torres, Alexy Inciarte, Constanza Lucero, José L. Blanco, Esteban Martínez, Josep Mallolas, Josep M. Miró, Monserrat Laguno, Jhon Rojas, María Martínez-Rebollar, Ana González-Cordón, Christian Manzardo, Cristina de la Calle, Gerard Espinosa, Joan Albert Arnaiz, Jose M. Gatell, Felipe García, Juan Manuel Pericas, David Nicolás, Marta Bodro, Ana del Río and Celia Cardozo.

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Transparency declarations

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Gilead reviewed a preliminary version of this manuscript for factual accuracy. The authors are solely responsible for final content and interpretation.

Author contribution

A.I., L. L., A. L., J. M. G. and F. G. contributed to the design of the clinical study. A.I., L. L., E. G., A. L., C. L., J. M., B. T., M. L., J.R., M. M.-R., A. G.-C., A. C., J. A. A. and F. G. contributed to the implementation of the clinical protocol. A.I., L. L., A. L., A. C., J. A. A. and F. G. contributed to the data analysis and interpretation of the results. A.I., L. L., A. L., J. M. G. and F. G. contributed to the writing of the manuscript. All authors approved the final manuscript.

Supplementary data

Figure S1 and Tables S1 and S2 are available as Supplementary data at *JAC* Online.

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Supplementary data

Figure S1. Study design.

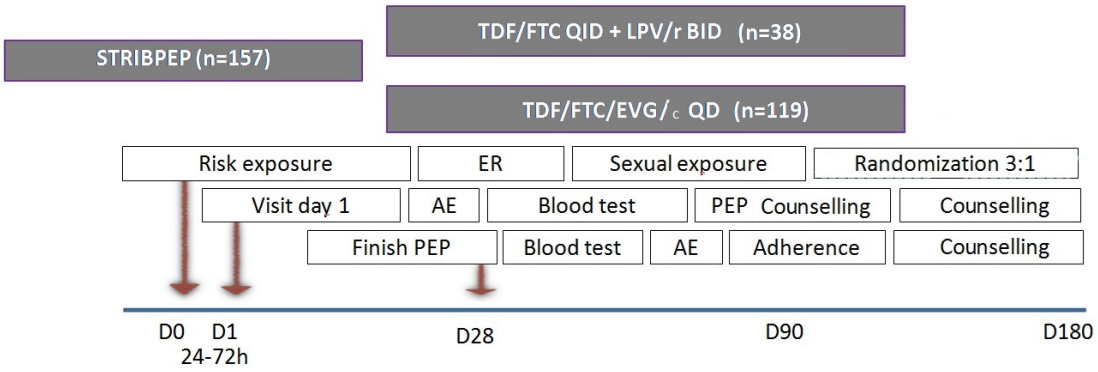

Table S1. Factors associated with PEP non-completion at day 28 due to any cause in the entire cohort (n=157) and individuals coming at least to the day 1 visit (n=123)

Characteristic	PEP discontinuations due to any cause in the entire cohort (n=157), OR (95% CI)		PEP discontinuations due to any cause in patients who attended the day 1 visit (n=118), OR (95%CI)[a]	
Type of analysis[a]	univariate	multivariate	univariate	multivariate
Age[C]: 33 years old or younger	**OR= 0.43 (0.22 – 0.85), P= 0.014**	OR= 2.02 (0.9-4.6) , P= 0.09	**0R= 0.35 (0.14-0.86) , P= 0.019**	0R= 2.72 (0.96 – 7.7), P= 0.06
Type of exposure: Heterosexual	OR= 2.7(0.89 – 8.3), P= 0.06		**OR= 3.9 (1.05 – 14.8), P= 0.03**	
Risk Asssessment: Low	**OR= 3.36 (1.43 – 7.93) P= 0.004**	**OR= 4.7 (1.8-12.1), P=0.001**	**OR = 4.6 (1.69 – 12.5) P=0.002**	**OR=3.70 (1.1-12.4), P= 0.035**
Gender: Female	OR =2.58 (0.55-12) p=0.174		**OR = 6.6 (1.03 – 41.13)P=0.02**	**OR=8.88 (1.02-77.2), P= 0.048**
Previous PEP: yes	**OR= 0.49 (0.22 – 1.05), P=0.06**	**OR=2.2 (1.0-5.1), P= 0.05**	OR= 1.05 (0.39 – 2.8), P=0.92	
Race of source partner: non caucasian	**OR= 1.42 (0.01 - 1.15), P= 0,038**		**OR= 0.1 (0.1 – 1.25), P= 0.05**	
Sexual worker: yes	**OR= 2.96 (2.37-3.69), P= 0,05**		OR = 4.56 (3.26-6.35), P= 0.06	
High adherence to PeP[b]			**OR=81 (6.39-1026.7) P<=.0001**	

Bold formatting represents significant P values.

aIndividuals attending the day 1 visit with an HIV-positive test at baseline or with an HIV-negative partner were excluded from analysis.

bNot measured in patients not attending the day 1 visit

cPopulation was split according to the median value.

Table S2. Adverse effects of exposed individuals from the entire cohort coming at least to one follow up visit (n=126)

	Cohort	EVG/c ARM	LPV/r ARM	P
Number of exposed individuals	123	97	29	
Individuals with adverse events	73 (59 %)	47 (49 %)	26 (90 %)	**P = 0,0001**
Total of adverse Episode*	140	73	67	

Grade I Adverse episode*	107 (76%)	59 (80%)	46 (69%)	
Grade II adverse episode*	13 (9%)	8 (11%)	5 (7,4%)	
Grade III adverse episode *	20 (14%)	4 (5%)	16 (24%)	

Severity degree**	Grade I	67 (54 %)	45 (46 %)	22 (76 %)	**P = 0,005**
	Grade II	9 (7 %)	6 (6 %)	3 (10 %)	P = 0,445
	Grade III	8 (7 %)	3 (3 %)	5 (17 %)	**P = 0,006**

Causal relationship	Events related to PEP	125 (89%)	65 (89%)	26 (89%)	

Gastrointestinal adverse episode*	101 (72%)	53 (73%)	48 (71%)	
Neuropsiquiatric adverse episode*	23 (16%)	14 (19%)	9 (13%)	
Fatigue episode*	14 (10%)	8 (11%)	6 (9%)	

Type of Symptoms***	Gastrointestinal [a]	61 (50 %)	37 (38 %)	24 (83 %)	**P = 0,0001**
	Neuropsiquiatric [b]	15 (12 %)	9 (9 %)	6 (21 %)	P = 0,096
	Fatigue	17 (14 %)	11 (11 %)	6 (21 %)	P = 0,196

* Adverse episodes are defined as the number of total adverse events (the occurrence of an adverse event once and more than once on the same patient or the whole sum of each episode within the entire cohort of patient). ** Number of exposed individuals with symptoms according severity degree.*** Number of exposed individuals according to type of symptoms. Bold formatting represents significant P Values.[a] Such as nausea, vomiting, diarrhea, abdominal pain, flatulence.[b] headache, Insomnia, n

THIRD PIECE OF RESEARCH

PK and effect on HIV ex-vivo infectivity of elvitegravir in postexposure prophylaxis.

Alexy Inciarte, Alberto C. Guardo, Luis M. Bedoya, Cristina Rodríguez de Miguel, Núria Climent, Cristina Rovira, Manuela Beltrán , Josep Llach , Jose Alcamí, Angela D.M. Kashuba , Jose M. Gatell, Montserrat Plana, Felipe García, Josep Mallolas, Esteban Martínez.

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PHARMACOKINETICS AND EFFECT ON HIV EX-VIVO INFECTIVITY OF ELVITEGRAVIR AND LOPINAVIR IN POSTEXPOSURE PROPHYLAXIS

Exploring the Pharmacokinetics of Antiretroviral Drugs: An Innovative Study on the Ex-vivo Effect of Elvitegravir and Lopinavir on HIV Infectivity in Postexposure Prophylaxis

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Short title: PK, effect on immune system and infectivity with PEP

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ABSTRACT

Background: Mucosal tissues are the most common way of HIV transmission. Characterizing pharmacokinetics (PK), ex vivo efficacy on HIV infectivity and effect on immune system of Elvitegravir (EVG) could be informative for optimizing postexposure prophylaxis (PEP).

Method: Substudy of a clinical trial (n=157) comparing the tolerability of 2 PEP strategies: tenofovir/emtricitabine plus ritonavir-boosted lopinavir or cobicistat-boosted elvitegravir received during 28 days. PK (in blood, rectal fluid, and rectal tissue), ex-vivo HIV-1 infectivity (estimated using antigen p24 quantification in HIV-1 strain Bal-1 infected explants), and effect on rectal mucosa immune system of EVG were assessed at day 28 and day 90 (considered as baseline).

Results: EVG concentrations in plasma, rectal fluid and rectal tissue were 1200ng/mL, 770ng/sb, 1124ng/g, respectively. A strong correlation on EVG levels were found between different compartments (r=0.4 ¡, p= 0.028). No significant differences were observed in infectivity between day 28 (last dose of PEP) and 90 (60 days after PEP was discontinued) (p= 0.4). Infectivity was inversely correlated with activation of CD8-T cells in rectal mucosal tissue [CD38+DR+ (r= -0.87, p< 0.005), HLA-DR+ (r= -0.85 p< 0.007), and CCR5+ (r= -0.9 p< 0.002)].

Conclusion: We found that EVG PK levels in different compartments were correlated. However, EVG did not prevent *ex vivo* infection on human rectal explants after 28 days of PEP. On the other hand, activating CD8-T cells in mucosa hinders infectivity in our model. Further studies are needed to validate these results.

INTRODUCTION

According to UNAIDS, the world has achieved a 23% reduction in new HIV infections since 2010, (1) Although this is an improvement, the number of infections is still substantial. In the quest to prevent infection, antiretroviral therapy (ART) has been used for post-exposure and pre-exposure prophylaxis, based on the rationale that if ARV can stop replication in an HIV-positive individual and prevent transmission, it can also prevent HIV infection in a seronegative individual who is exposed to HIV (2,3).

The mucosal tissues, including the colorectum, vagina, and cervix, are the primary gateway for early HIV infection and are the primary target for HIV replication. Therefore, it is crucial to understand the pharmacokinetics and pharmacodynamic role of drug tissue distribution, especially since several factors can alter drug concentrations and dose-response relationships in these tissues (4,53). ART subtherapeutic concentrations in plasma can predict virological treatment failure in HIV-positive patients, and the correlation of genital tract drug exposure in the extracellular and intracellular compartments between drug levels and their efficacy varies, even among drug subclasses. The ability to penetrate tissue can vary significantly, even among members of the same drug class, which may prove crucial in clinical trial efficacy studies for HIV prevention (6,7)

Several studies have established tissue penetration ratios in the male and female genitourinary tract, mainly for non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (3,8-10)

In simian animal models, it has been suggested that combining antiretroviral drugs may be necessary to increase the level of protection. Furthermore, short but potent intermittent PrEP was found to provide protection similar to that of daily PrEP. These findings established the first rationale for the efficacy of PrEP and the current mode of use in humans (11). Based on the PK/PD models for Tenofovir (TDF) in HIV-negative participants, the IPergray and IPrex studies have become the cornerstone of scientific evidence for PreP in preventing HIV transmission among the MSM population (2,8,12).

Due to their mechanism of action in preventing the integration of HIV into newly infected cells, integrase inhibitors have shown promise as a drug of choice in both PrEP and PEP. This step occurs more than 6 hours after infection, which could allow for a wider dosing window, which is essentially important in PEP strategies. In macaque models the penetration of elvitegravir (EVG), RAL, and dolutegravir (DTG) in rectal and vaginal fluids was examined in the absence of pharmacological boosting. Results revealed that elvitegravir had the highest penetration in these fluids, followed by raltegravir and dolutegravir (13). Also given their good tolerability profile, , potency, and dosage administration is a favorable election for its PEP use in humans as previously demonstrated in several studies (14-16). However, few studies have characterized the role of integrase inhibitors on colorectal mucosa in humans (17). Recently raltegravir (RAL) has been found to provide ex-vivo protection and is currently the most recommended third drug for PEP regimens (18-20).

Given that it is not possible to carry out efficacy studies in the PEP, the present study proposes an experimental model of infectivity to evaluate the pharmacokinetics of EVG, Lopinavir (LPV), and Ritonavir (RTV) in tissues. The hypothesis of this study proposes that

concentrations may serve adequately to prevent HIV ex vivo infection and the role of these drugs in the local mucosal homeostasis.

The present study aims to present Pharmacokinetics (PK) and pharmacodynamics (PD) colorectal mucosa data in HIV-negative patients treated with either EVG or LPV for post-exposure prophylaxis, and the results will contribute to our understanding of the pharmacokinetics and pharmacodynamics of these drugs in tissue distribution.

METHODS

This is a sub-study of a clinical trial entitled: "Tenofovir/Emtricitabine plus ritonavir-boosted lopinavir or cobicistat-boosted elvitegravir as a Single Tablet Regimen for HIV postexposure prophylaxis."

The main study recruited 157 participants allocation ratio 3:1; from which 119 individuals were enrolled receiving either elvitegravir/cobicistat/emtricitabine/tenofovir DF 150 mg/150 mg/200 mg/300 mg; (EVG/c/FTC/TDF) or Lopinavir/ritonavir 400 mg/100 mg; (LPV/RTV) twice a day and Emtricitabine/Tenofovir DF 200 mg/ 300 mg once a day (FTC/TDF). Four participants were subsequently excluded, two due to screening failure and two lost to follow-up. The final study population consisted of 18 participants, divided into two study arms: 13 in the EVG arm and 5 in the LPV arm from 08 June 2015 until 15 June 2016. (Supplementary figure I flow chart).

The first visit was scheduled with an infectious diseases specialist within 72 hours of starting PEP (day 1). The substudy subjects were eligible if they were healthy HIV-1 seronegative men who had sex with men (MSM) who accepted to participate and signed informed consent. Those with a basal positive HIV test were excluded. Visits were scheduled for a follow-up on days 7, 28, and 90 after risk exposure. The last visit (day 90) had to be considered baseline.

Demographics, ethnicity, past medical history, and risk stratification for HIV acquisition were assessed. Patients underwent a routine physical examination, sexually transmitted infection (STI) screening, and routine safety laboratory tests, such as a complete blood panel, liver function tests, and serum chemistries. STI screening included testing for hepatitis C antibody, chlamydia, and gonorrhea by polymerase chain reaction (PCR) and for syphilis by serum venereal disease research laboratory (VDRL) with confirmatory

treponemal testing if positive according to PEP Spanish recommendations (21). STI testing was performed at the Center Microbiology Core Lab at the hospital clinic of Barcelona. Any patient with a positive STI at the screening was provided with treatment and then offered re-screening after completing STI therapy. Adherence to PEP was monitored with the medication event monitoring system (MEMSTM AARDEX Group Ltd., Switzerland) (22). Adverse reactions, vital signs, treatment non-compliance, time of dosing, and standard laboratory investigations were monitored and recorded at each follow-up visit.

In order to access rectal mucosa integrity, rectal calprotectin (PreventID® CALDETECT™ 50/200, Sweden) was measured at all-time points through feces sampling, and a result of <50 µg/g was considered negative (23).

Once enrolled they were screened for STIs and have an anal cytology performed. Participants underwent a blood test, fecal calprotectin test, anoscopy and recto sigmoidoscopy on day 7, 28 and 90. A supplementary table was created to visualize the study timeline and assessments (refer to supplementary table II).

To evaluate infectivity, rectal explants from the participants were examined on days 7, 28, and 90. EVG, LPV, and RTV drug levels were analyzed in peripheral blood (PB), rectal fluid (RF), and rectal tissue (RT) on days 7 and 28 after starting PEP. Additionally, changes in immune activation markers were assessed on days 7, 28, and 90 (baseline) after starting PEP to determine the impact of EVG and LPV on immune system homeostasis in RF, FT, and PB.

Infectivity essays were evaluated using rectal explants from participants at day 7, 28 and 90. EVG, LPV, and RTV drug levels were assessed in BP, RF, and RT on days 7, and 28

after starting PEP. In order to determine EVG and LPV effect on immune system homeostasis in BP, RF, and RT, changes in immune activation markers were determined on days 7, 28, and 90 (baseline) after starting PEP.

Blood sample collection

Venipuncture from a superficial vein in the upper limb was performed using an EDTA-tube as a container. The centrifugation process of blood samples was at 910g per 10 minutes. Then plasma was transferred to a 15 ml tube with centrifugation of 1618g. The resulting aliquots were stored and frozen at – 80ºC.

Rectal fluid sample collection

Participant preparation.

Generally, all patients were encouraged to undertake a diet low in fiber and fat for 12 to 24 hours before the procedure. Solutions containing sodium phosphate (NaP) (Casen-Fleet, Zaragoza, Spain) were used for cleansing enemas before anoscopy and sigmoidoscopy preparations.

Sponge preparation

Approximately 0.5 mm was cut off of the narrowest end of the syringe hub, and a Weck-Cel Surgical Spear (Medtronic Ophthalmic, Jacksonville, FL, USA) was inserted 10 mm into the handle of the barrel of the syringe. Each prepared weck was premoistened by placing the tip into the vial with PBS prior to collection to facilitate absorption and minimize epithelial damage with dry weck.

Rectal fluid sampling

Previously a digital clinical examination was performed to exclude any obstruction by the attending physician. Participants were positioned on their left side, and a lubricated

rectal flexible anoscope (Proctoscopes Adultes steriles, Gyneas, Spain) was introduced into the rectum. Once the anoscope was inserted, the obturator was removed, then 5 moistened rectal wecks attached to a syringe were introduced and held against rectal folds for 5 minutes for specimen collection; microflora, cytokines, and EVG, LPV, and RTV levels. Following collection, the sponge was placed in a sterile 5ml cryovial and immediately placed on dry ice for shipment to the laboratory.

Rectal tissue sample collection

Rectal tissue sampling

A total of 20 – 25 biopsy samples were obtained at each biopsy procedure (Microvasive Radial Jaw no. 1589; Boston Scientific, Natick, MA) with an outside diameter of 50 mm. A total of 20 – 25 biopsy samples were obtained at each biopsy procedure. Tissue samples were placed in 15 ml of RPMI 1640 (Gibco BRL, Rockville, MA) with 10% fetal calf serum (designated R10), supplemented with antibiotics (Merck, Whitehouse Station, NJ) and amphotericin B (Gibco BRL). The cells were then used for lymphocyte isolation, flow cytometry, and functional studies.

Patient recruitment and biopsy collection

All volunteers were informed and signed informed consent. Procedures were scheduled in 30-minute time slots. Biopsy samples were acquired via flexible sigmoidoscope between 10 and 30 cm from the anal verge by a board-certified endoscopist, with assistance from a trained nurse, as previously reported (24). Quality assessment for bowel preparation was performed according to the Boston bowel preparation scale

(25). All sigmoidoscopy procedures were performed with high-definition technology devices (CF-HQ190L; EVISEXERA III processor; Olympus Medical, Tokyo, Japan). Seventeen intestinal tissue samples were collected for pharmacokinetics, immunological and ex-vivo infectivity analysis. Rectal samples were obtained according to Dr. Peter Anton's Laboratory SOPs (UCLA Center for AIDS Research (CFAR) Mucosal Immunology Core Laboratory (MICL)). (Refer to supplementary material (XX).

Pharmacokinetics

EVG, LPV, and RTV concentrations were quantified at the University of North Carolina Center for AIDS Research Clinical Pharmacology and Analytical Chemistry Core using liquid chromatography–tandem mass spectrometry (LC-MS/MS). Plasma and tissue samples were shipped on dry ice and stored at -80ºC until analysis.

EVG human plasma samples (30uL) were extracted by protein precipitation by mixing with 270uL of methanol containing the stable, isotopically labeled (SIL) internal standard (EVG-d6). The samples were then vortexed and centrifuged prior to LC-MS/MS analysis. LPV and RTV human plasma samples (25uL) were extracted by protein precipitation by mixing with 475uL of methanol containing the SIL internal standards (LPV-d8 and RTV-d6). The samples were then vortexed, centrifuged, and the supernatant mixed with equal parts water before LC-MS/MS analysis.

EVG, LPV, and RTV tissue biopsies were weighed in Precellys® tubes (Cayman Chemical, Michigan, USA). Following weighing, 0.500mL of 70:30 acetonitrile:1mM ammonium phosphate was added to each tube, and samples were homogenized (5500 RPM, 60 seconds, 3 cycles) and centrifuged (5 minutes at 13,200 RPM). The tissue homogenate

(30uL) was mixed with 150uL of 80:20 methanol: water containing the respective SIL internal standards, EVG-d6, LPV-d8, and RTV-d6. The samples were then vortexed, centrifuged, and mixed with equal parts water before transferring into a 96-well plate for analysis.

A Shimadzu Prominence HPLC system, including pumps (LC-20AD), degasser (DGU-20A), and controller (CBM-20A), supplied from Shimadzu (Columbia, MD, USA) with an API-5000 triple quadrupole mass spectrometer (Sciex, California, USA) was used for all LC-MS/MS analyses. For the EVG plasma analysis, a Waters Atlantis T3 (50x2.1, 3um particle size) analytical column was used under reverse-phase conditions with 10mM ammonium acetate (mobile phase A) and neat acetonitrile (mobile phase B) with a flow rate of 0.500mL/min. The column heater (CTO-20A) was set at 35 °C, and the autosampler (SIL-20AC/HT) was maintained at 15 °C. The injection volume was 7uL. The LC gradient was held at 45% B for 0.25 minutes and increased to 85% B at 2.30 minutes and held for 30 seconds. At 2.90 minutes, the gradient returned to 45% B until a final run time of 4.00 minutes.

An API-5000 triple quadrupole mass spectrometer operated in negative ion TurboIonspray mode was used to acquire data for the EVG method. The source temperature was 400 °C, and the ion spray voltage was 5500V. The declustering potential (DP) was -140V, and the collision energy (CE) was -36V for both the analyte and internal standard. Multiple reaction monitoring (MRM) was used to detect the analyte [precursor/product] transitions (m/z) as follows: EVG [448.0/318.0], EVG-d6 [452.0/322.0]. The MRM transition selected for EVG utilized the natural isotope 37Cl,

while the internal standard did not use the 37Cl isotope, resulting in the parent mass being only 4amu higher than the internal standard.

For LPV, RTV plasma and EVG, LPV, and RTV tissue analysis, a Waters Atlantis T3 (50x2.1, 3um particle size) analytical column was used under reverse-phase conditions with 0.1% formic acid in water (mobile phase A) and 0.1% formic acid in acetonitrile (mobile phase B) with a flow rate of 0.500mL/min. The column heater) was set at 35 °C, and the autosampler) was maintained at 15 °C. The injection volume was 1uL for plasma and 10uL for tissue.

The LC gradient held at 35% B for 0.50 minutes and increased to 80% B at 3.00 minutes, at 3.30 minutes, the mobile phase B percentage was 95 and held for 0.70 minutes until returning to 35% at 4.20 minutes for a total run time of 5.00 minutes.

An API-5000 triple quadrupole mass spectrometer in positive ion TurboIonspray mode with a source temperature was 400°C, and the ion spray voltage of 5000V was used for both the plasma (LPV and RTV) and tissue (EVG, LPV, and RTV) analyses. In the plasma assay, the following MRM transitions were used: LPV [630.4/430.0], LPV-d8 [637.4/429.0], RTV [721.4/171.0], and RTV-d6 [727.4/302.0]. The DP for RTV and RTV-d6 was 140V and 91V, with CE values of 50V and 25V, respectively. For LPV and LPV-d8, the DP was 140V and the CE was 31V. For the tissue analysis, EVG, LPV, and RTV and their isotopically labeled internal standards, used the following MRM transitions with their respective DP and CE as follows: EVG [448.0/273.0] 140V, 60 V; EVG-d6 [454.0/350.0] 140 V, 45 V; LPV [631.4/430.0] 180 V, 3 V; LPV-d8 [637.4/429.0] 180 V, 31 V; RTV [723.4,172.0] 90 V, 50 V; and RTV-d6 [727.4/302.2] 90 V, 25 V.

Linear regression of concentration (x) versus peak area ratio of compound to an internal standard (y) using a 1/(x2) weighting was used with Sciex Analyst software (version 1.6.2) for all analytes. Calibration standards were within 15% (plasma) and 20% (tissue) of nominal values with a dynamic range of 25.0-10,000ng/mL for EVG and 50.0-20,000ng/mL for LPV/RTV while the dynamic assay range for tissue homogenate was 1-10,000ng/ml.

Tissue homogenate concentrations were converted from ng/mL to ng/g tissue by using the following equation: ((ng/mL concentration) x (0.5mL solvent + tissue mass in g)) / tissue mass in g. All plasma and tissue sample concentrations were above the LLOQ.

Immune homeostasis

Immunophenotypic characterization and cell collection.

Fresh blood tubes (less than 1 hour) were collected prior to the isolation of PBMC. Fresh samples of tissue digested by collagenases were used for MMCs. All steps were performed at room temperature.

For PBMCs, three tubes of blood with 10mL EDTA anticoagulant are separated from whole blood to plasma. Afterward, peripheral mononuclear and digested medium with MMCs cells are separated using centrifugation at 1500 g (Megafuge 2.0R) cell isolation using density gradient centrifugation using Ficoll-Hypaque (Sigma Chemical Co., St. Louis, MO), with mesh tubes according to SOP from our center (IDIBAPs, Barcelona. Spain). The PBMC layer was removed and washed twice to eliminate the contaminants before cell type and viability could be confirmed.

Then a comprehensive approach of simultaneous measurement of different immunological parameters was used [12] in CD4 and CD8 T lymphocytes: activation (using CD38 and HLA-DR markers), senescence (using CD28 and CD57 marker), exhaustion (using PD-1 marker), co-receptor expression (CCR5, CXCR4), differentiation stage (using CD45RA and CD45RO markers) and monocyte activation (using CD14, CD16, and CD163 markers). The stained cells were analyzed on a FACSCalibur (Becton Dickinson, San Jose, CA) cytometer. All analyses were conducted using freshly isolated peripheral blood mononuclear cells (PBMCs) or monocyte-derived macrophages (MDMs), without the use of a viability dye. PBMCs were isolated via density gradient centrifugation utilizing Ficoll-Hypaque (Sigma Chemical Co., St. Louis, MO). MDMs were obtained via enzymatic digestion.27,29 The subpopulations of CD4+ and CD8+ T cells were determined through a comprehensive approach of simultaneous measurement34 using a four-color flow cytometry on a FACSCalibur (Becton Dickinson, San Jose, CA) of various immunological parameters including activation markers (CD38 and HLA-DR), senescence markers (CD28 and CD57), co-receptor expression (CCR5, CXCR4), and T cell differentiation stage (CD45RA and CCR7). Monoclonal antibodies such as CD8-peridinin chlorophyll protein (PerCP), CD4-allophycocyanin (APC), CD28-phycoerythrin (PE), CD57-fluoroisothiocyanate (FITC), CD38-PE, HLA DR-FITC, CD45RA-FITC, CCR7-PE, CCR5-FITC, and CXCR4-PE were employed (all from Becton Dickinson, Mountain View, CA, except CCR7-PE from Milteny Biotec B.V. Leiden, NL). Mouse immunoglobulin isotypes conjugated with Per-CP, PE, FITC, or APC served as negative controls for nonspecific binding. The thresholds for positive gated populations were defined using the corresponding isotype controls, unstained samples, and/or fluorescence minus one control (FMO). The data were analyzed using FlowJo v.7.6.5 software (BD Life Sciences).

Data were analyzed using FlowJo Software (Tree Star). The flow cytometry gating strategy for monocytes is shown (refer to figure 1)

Citoquines measurement

For the elution of rectal secretions sponges were used according to SOP from UCLA, CPR (LB-701, 2006). The concentrations of the different cytokines: GM-CSF, TNF-α, IL-1β, IL-4, IL-6, MIP-1β, Eotaxin, RANTES, MIG, IL-12, IL-8, IL-17, MIP-1α, IL-10, IL-1RA, INF-γ, IL-13, MCP-1, IL-7, IL15, INF-α, IL-2R, IP-10, IL-5, IL2 were analyzed in the RF supernatant with a Luminex™ assay, according to the standard protocol (Thermo Fisher Scientific™, Waltham MA).

Infectivity cultures

To evaluate ex-vivo efficacy in using explants of rectal mucosa after starting PEP Infection, endoscopic biopsies were performed with an R5 tropic HIVBal strain (10 ng/well) in 96-well U-bottom sterile plates with two explants per well and in triplicates for 2 hours. Afterward, colorectal explants were extensively washed in PBS and transferred to DMEM pre-wet espongostan rafts in 24 well microplates. Colorectal explants were maintained for up to 14 days in complete medium at 37ºC and 5% CO2. On days 3,7, 10, and 14, supernatants were harvested and cultures re-fed with complete fresh medium. Supernatants were frozen at -20ºC, and quantification of p24was performed with an Elecsys HIV p24 Ag Test system (Roche). Results are represented as p24 quantity vs. time (days)tg and reported as the area under the curve (AUC).

Rectal Microflora

The microflora testing was done at the biomedical Diagnostic Center (CDB) · CORE Laboratory in Barcelona, Spain. Aerobic and anaerobic organisms will be isolated using conventional culture methods and identified using phenotypic tests; *Facultative isolates; Lactobacillus, H2O2-producing, Lactobacillus non-H2O2-producing, Gardnerella vaginalis, Diphtheroids, Bacillus, Gram+ rods, Group B, Streptococcus, Enterococcus aureus, Staphylococcus coagulase-negative, micrococcus, Viridans Streptococcus H2O2-producing, Viridans Streptococcus non-H2O2-producing, gram-positive cocci, E.coli, Proteus, Gram - rods. Anaerobic isolates; Gram – rods, B. Fragilis, Gram – rods non-pigmented, gram+ rods, Clostridium like gram + cocci.* Each organism was quantified using a semi-quantitative method.

Samples will be collected by swab at designated visits at each site, and samples were immediately sent, per SOP, to the Microbiology Laboratory for processing and quantification.

Ethics

This study follows the ethical principles of non-maleficence, beneficence, autonomy, and justice contained in the Declaration of Helsinki, in addition to the Spanish Basic Laws 41/2002on patient autonomy and 14/2007 on biomedical research. Patients asked to participate in the study were given prior oral information and signed a written consent

if they agreed. The institutional review board of each participating center approved the protocol. This protocol was registered in ClinicalTrials.gov under the number NCT08431173.

Statistics

General baseline characteristics from subjects, pharmacokinetics parameters, immunological homeostasis markers, and infectivity values were expressed in median and interquartile ranges.

Significant results of peripheral blood and mucosal mononuclear cells phenotype outcome, RF cytokines, and serum inflammation markers per time point and per arm were assessed using Wilcoxon signed rank test, and asymptotic significances were displayed with a significance level of 0.05.

Infectivity, immunophenotypical markets, and drug concentration in the different compartments were analyzed using Pearson's correlation coefficient, and significant values were represented in a correlation matrix. For statistical modeling Statistical Product and Service Solutions (SPSS) was used v.26.0.

RESULTS

In this study, 24 MSM were screened, and 18 were ultimately enrolled. The participants had a median age of 31 (33-35), with 9 (50%) identifying as Caucasian and X% as Latin-American. A significant proportion of participants had a previous history of STIs and reported having had numerous sexual partners. EVG and LOP/r regimens were well tolerated, and no serious adverse effects, no significant laboratory abnormalities observed. Additionally, all participants tested negative for several sexually transmitted infections during the 6-month follow-up. Two volunteers had positive PCR for *C. trachomatis* and *N. Gonorrhoeae* with no clinical signs. Two patients had on anal cytology low-grade squamous intraepithelial lesion. The calprotectin test showed no high-grade inflammation, and all microflora determinations were saprophytic. While two participants had epithelial erosion or ulceration in their rectal histological evaluation, all five individuals were asymptomatic. Overall, the study found that all participants had high adherence to the medication, as measured by MEMS.

EX-Vivo infectivity

In general, no variations in infectivity were found either between the time points or the treatment groups. Further analysis within each group revealed no significant differences between day 7 and day 28 for either LPV/r or EVG/c. Additionally, no differences were found within the LPV/r or EVG arms individually, as shown in Figure III.

Pharmacokinetics.

The different compartment concentration ranges were as follow; plasma values ranged 1170 (198-1502) mg/mL for EVG, 7615 (2880-13305) mg/mL for LPV and 582 (328-1851)

mg/mL for RTV at day 28. Tissue concentrations were: 1124 ((880-1508) ng/g for EVG, 6266 (4668-6188) ng/g for LPV and 2579 (2131- 2821) ng/g for RTV. For RF concentration were estimated 1613 (661-12507) ng/sb for EVG, 2127 (1433-3782) ng/sb for lopinavir and ng/sb for RTV. All the plasma and tissue samples were above the LOQ, being possible to quantify the different analytes. The only exception was the fluid sample SPEP-006-02. Detailed pk parameters are shown in table 1.

Generally, both EVG and RTV achieve high concentrations in the rectal plasma. AUC ratios are greater than 1.00 in both drug concentrations. In contrast, the LPV ratio is lower than 1.00. The penetration ratios across the time post-ARV dose stratified by the drug are shown in figure 1 and figure 2. A strong correlation on EVG, LPV, RTV levels were found between different compartments (r=0.4, p= 0.028). EVG and RTV appear to penetrate the tissues to a greater extent compared to LPV.

Immune system homeostasis

Immunophenotypic characterization during treatment (day 28) and after treatment (day 90)

In PBMCs the expression of CD4+38+ (57 vs. 55, p= 0.012), CD4+ CD45RA-CCR7+ T (39 vs. 24, p= 0.012) cells was significantly higher in patients receiving EVG at day 28 than in baseline, with also a higher CD4/CD8 ratio (2.1 vs 1.8, p=0.025). For CD8+ subtype cells a higher expression of CD8+ CD45RA-CCR7+ (7 vs. 4 p= 0.012) and CD8+CCR5+ (8 vs 2, p= 0.036) coreceptors were observed on EVG when compared with baseline.

In MMCs the expression of coreceptors CD4+CD28+, CD163+, CD11c+, HLADR+[(100 vs 98, p= 0.012), (5 vs 0.1, p= 0.001), (5.7 vs 3.9, p= 0.027), (72 vs 65, p= 0.027)], were higher at baseline (day 90) than (day 28) with EVG,

No differences were observed in LOP/r Immunophenotypic markets in PBMCs and MMCs. Results are shown (Supplementary Tables II and III)

Immunophenotypic characterization in different treatments arms

In PBMCs CD4 cells subsets CD4+DR+, CD4+CD57+, CD4+28-57+ and CD4+CD45RA+CCR7- (terminally differentiated) levels were lower in patients on EVG -based treatment than LOP/r -based treatment, [(5.9 vs 8.3, p= 0.027), (1,7 vs 6.8, p= 0.027), (0.7 vs 5.4, p= 0.027), (2.7 vs 5.3, p= 0.027)]. In CD8 cells subsets expression of CD8+CD57+, CD8+28-57+ in EVG arm [(25 vs. 29, p0-=028), (20 vs 35, p=028)], was lower than than in LOP/r arm. inversely a higher expression of CD8+CD28+, (71 vs. 51, p= 0.028) was observed in patients EVG-based treatment when compared with LOP/r-based regimen.

A Higher expression of dendritic cell CD11c+ coreceptor was also observed in EVG/arm. The CD163 expression levels on PBMCs subsets were lower on EVG/arm than LOP/r arm (0.02 vs. 0.05, p= 0.028), significant PBMCs and MMCs values are shown in table (DIAPO 3 Y 4) . In MMCs CD4+CD57+, CD8+28-57+, CD???CD45RA+CCR7-, CD14+, HLADR+, lower levels of coreceptor expression were observed in EVG arm when compared with LOP/r arm.

With the exception of CD8+28-57+ marker in MMCs, no differences were observed in different cell subtype populations at baseline (day 90) between treatment arms, both in PBMCs and MMCs. Non-significant and significant values are shown in supplementary table (refer to supplementary table II and III).

Citoquines levels on rectal fluid

Regarding citoquines levels; INFa levels (164 vs. 162, p`= 0.036) were higher during EVG-based treatment than at baseline, on the contrary TNFa, and Il-4 levels were lower [(6.6 vs 8.5, p= 0.017, (109 vs 122, p=0.036)].

In different treatment arms baseline Il-4 and IL13 levels on patients were higher in EVG based treatment than LOP/r-based treatment. Results regarding citoquines levels are (refer to suplemantary table IV).

Correlations between PK, infectivity and immunological changes

No significant differences were observed on infectivity between day 28 (last dose of PEP) and day 90 (60 days after PEP was discontinued) (p= 0.4). Infectivity in EVG was inversely correlated with activation of CD8-T cells in rectal mucosal tissue [CD38+DR+ (r= -0.87, p< 0.005), HLA-DR+ (r= -0.85 p< 0.007), and CCR5+ (r= -0.9 p< 0.002)]. we also observed significant correlations in activation CD8-T cells [CD28+ (r= -0.681, p= 0.03), CD57+ (r= 0.790 p= 0.005), 28-57+ (r= 0.790 p= 0.006)] and monocyte activation of coreceptors CD11c+ CCR5+ (r= 0.730 p= 0.016) HLADR+ (r= -0.692 p= 0.027) in PBCMs (DIAPO 6 Y 7)

In LOP/r arm a positively correlation was observed between infectivity and the expressions of the following coreceptors; 4+CXCR4, CD163, CD11c-CD163+, CCR5+, CD163+ GM CD11C+, conversely, a negative correlation was found between CD11c-CD163+ and CD14+ markers and infectivity, these associations were observed both in PBMCs. (diapo 6 y 7)

When citoquines were analyzed in different treatments arms; In LOP/r arm citoquines levels were positively correlated with infectivity; IL-1b (r=0.9, p=0.001), IL5 (r=0.9, p=007), iL-8(r=0.9, p= 0.009), IL-12 (r=09, p=0.008), IL-13 (r= 0.9, p=0.003), IL-17 (r= 9,

p= 0.048), MCP-1 (r=0.9 p= 0.04), No significant changes were observed in EVG/arm between infectivity and citoquines levels. (Supplementary table V)

In RT drugs concentrations had a positive correlation between Il -10 and IP-10 in EVG/arm, on the contrary no significant correlations RT drugs concentration and the LOP/r arm. RF drug concentration was associated with significantly with higher MIP-1b levels in LOP/r arm, with no correlation in EVG/c arm.

DISCUSSION

Comparisons of PK/DP profiles and their impact on preventing ex-vivo infections in the context of HIV prevention are limited. The pharmacokinetics of antiretroviral drugs in the rectal tissue have not been fully elucidated. Our study's main findings are as follows: Firstly, neither EVG nor LPV/r demonstrated the ability to prevent ex-vivo infection of the rectal tissue. However, our findings indicated a correlation between plasma and colorectal tissue for EVG and LPV with penetration rates above 1, indicating that effective drug concentrations were available to prevent or mitigate infection.

EVG boosted with COBI is a potent ARV combination and is active in macaques in vivo models in a peri-coital modality to be taken shortly before or after sex. Displays heightened protection of about 91 to 100% to rectal SHIV infection when the regimen is delivered four hours before or two hours after exposure (26]. This efficacy level is equivalent to daily TAF/FTC or TDF/FTC in the MSM population cohort for PrEp (27,28).

The effectiveness of RAL, DTG, and EVG in preventing the transmission of HIV through rectal secretions was assessed in a macaque model. Rectal secretions collected from treated macaques were found to block the infection of TZM-bl cells at certain dilutions (X), with dilutions of 1/1000 for RAL, 1/800 for DTG, and >1/30 000 for EVG. These findings suggest that these drugs, particularly elvitegravir, may be effective in reducing or preventing the transmission of HIV through rectal secretions(29). The outcomes from our research differ from the findings reported above, although animal models had shown higher penetration rates than our ex-vivo models, still EVG and RTV penetration ratios were above 1, levels still considered protective in ART treated PLWH (30,31).

Our ex-vivo model did not demonstrate the efficacy of EVG or LPV/r in preventing HIV-1 infection. However, other models utilizing maraviroc on MSM successfully inhibited HIV-1 infection while other show lack of HIV ex-vivo infection (32,33). Additionally, several other studies have found that TDF effectively prevented HIV-1 infection of explant cultures both topically and systemically [34]. .

In this study ex-vivo models exhibited lower penetration rates than the animal studies; nonetheless, the penetration ratios for EVG and RTV were greater than 1, and there have been no prior investigations characterizing the penetration ratios of EVG in human tissues. In contrast, the tissue penetration of LPV was inferior to that of EVG and RTV in our research. Nevertheless, it is still higher than the levels detected in previous studies examining seminal fluid and cervicovaginal tissues in humans [35-38] Several studies have established tissue penetration ratios for raltegravir (RAL) and dolutegravir (DTG) in mucosal tissues, including the colorectum, vagina, and cervix. In one study, RAL levels were found to be higher in cervicovaginal tissue (CT) than plasma (39), in another study DTG levels in rectal tissue (RT) were lower than those in plasma (40), compared to the rest integrase inhibitor EVG/c had showed higher levels when compared with previous studies.

Regarding LPV/r, we observed no differences in inflammation and activation markers in the blood and mucosal tissue. This is consistent with the findings of a recent PEP study conducted on MSM seronegative individuals, as well as historical studies on people living with HIV, which compared the effects of integrase inhibitors and protease inhibitors on activation markers (41).

When analyzing the immunophenotype across different treatment groups, CD8 subsets in the EVG arm expressed higher levels of CD28+ CD57+ and CD28-57+ compared to those in the LPV arm. These observations collectively imply that the group treated with EVG exhibits enhanced activation of the immune system and cellular functionality relative to the group treated with LPV.

we found a correlation between ex-vivo infectivity for monocyte activation and CCr5 co-expression in peripheral blood samples. The CCr5 co-expression is linked to infectivity and disease progression in several studies (42,43). Also, ex-vivo infectivity was correlated with CD4 T-cell activation and inflammation in the rectal compartment and lower levels of T-cell terminally differentiated markers. It is possible to infer that viruses with a greater capacity to induce inflammation and immune activation in the rectal compartment, may have a greater likelihood of infecting their target cells (44). However, it is crucial to verify these observations in further investigations to confirm their validity

The interpretation of the results of this study can be considered exploratory but does not establish a strong association. The main limitation of the study is the small sample size to make a correlation between groups. Second is the need for more standardization of the methods, ex-vivo models are not validated for general use outside the research, and ex-vivo models need to reflect accurately in vivo. Due to the timing of the PEP administration, which varied among participants and sometimes included midnight doses, the tests were performed only in the morning, Besides the different distribution profiles in tissues compared with plasma, single time point concentration ratios could miscalculate accurate tissue exposure when calculating plasma tissue/penetration (10). As a result, we obtained a diverse range of concentrations in different tissues. Moreover,

in the absence of any prior research in RF, it is difficult to compare our results with any previous studies. It is also worth noting that the amount of mucosal lining fluid on the sponges differed among the participants, contributing to the heterogeneity of the results. Therefore, it is essential to approach our conclusions with caution, as the heterogeneity of our sample makes it difficult to draw definitive conclusions.

EVG PK levels on different compartments were correlated. However, EVG did not prevent *ex vivo* infection on human rectal explants after 28 days of PEP. On the other hand, activating CD8-T cells in mucosa hinders infectivity in our model. Further studies are required to validate these results. To ensure the validity of our findings, further research is needed. Additional studies would help to confirm our results and provide a more comprehensive understanding of the impact of PEP administration on different tissues in RF. Further research could also help to minimize the effects of participant heterogeneity and facilitate more accurate conclusions. Thus, our study underscores the importance of continued research to better understand the effects of PEP administration on different tissues in RF.

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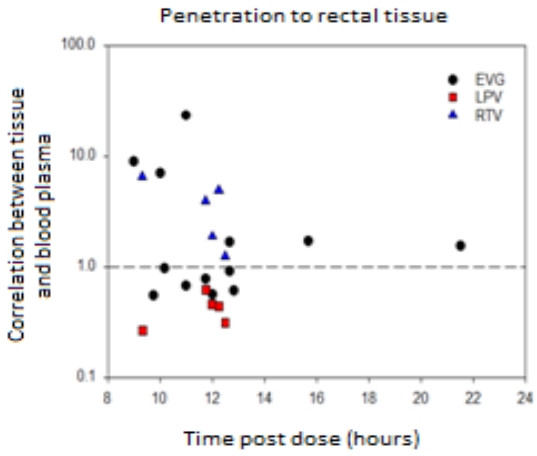
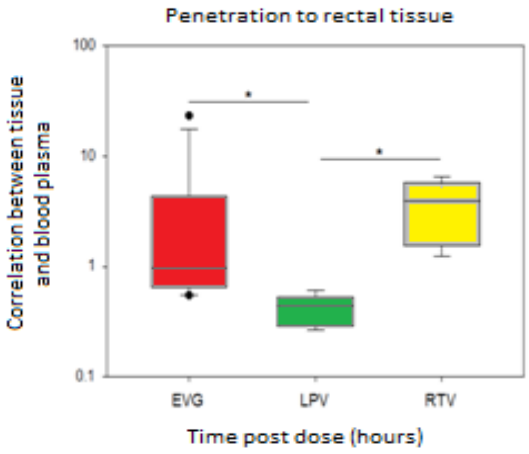
Table 1. Pharmacokinetics concentrations in plasma, rectal fluid and rectal tissue with different post-exposure prophylaxis treatment at day 7 and 28.

Drug	Plasma (ng/mL) day 7	Plasma (ng/mL) day 28	Rectal tissue (ng/g)	Rectal fluid (ng/sb)
EVG	1170 (198-1502)	1200 (217-1632)	1124 ((880-1508)	1613 (661-12507)
LOP	1	7615(7280-13305)	6266 (4668-6188)	2127 (1433-3782)
RIT	582 (328-1851)	508 (328 - 1851)	2579 (2131- 2821)	, 1124ng/g

Figure 1. Penetration ratios according to different PEP regimens.

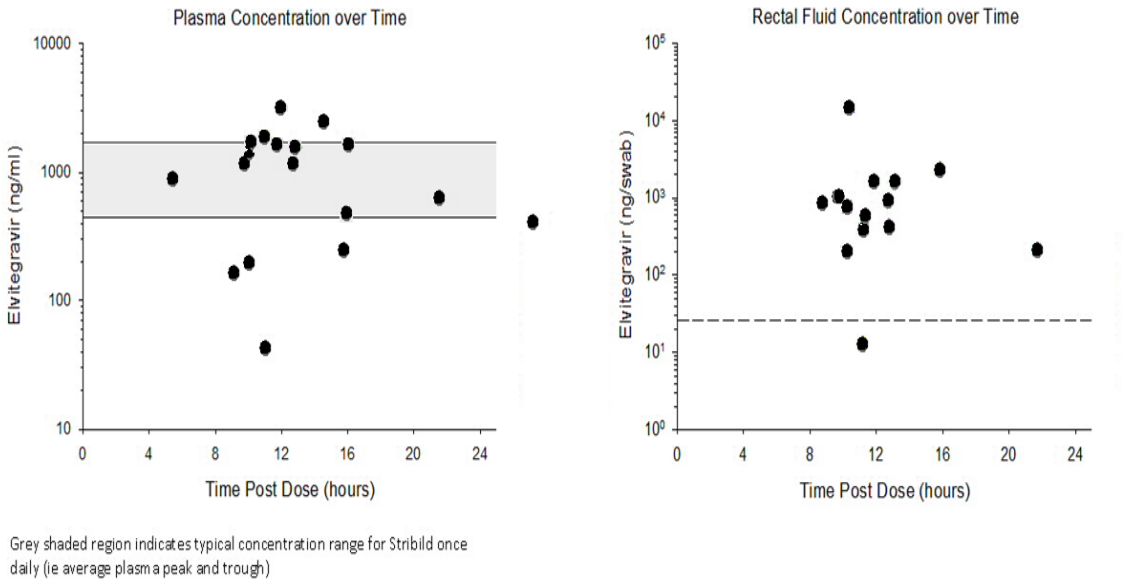


PK expected concentrations for any of the study drugs. Black dots represents Elvitegravir PK in rectal tissue. Red and Blue icons represents Ritonavir-boosted lopinavir, in rectal tissue.



Represent penetrations ratios of the study drugs Red boxes for Elvietravir, Green boxes for Lopinavir and Yellow boxes for ritonavir.

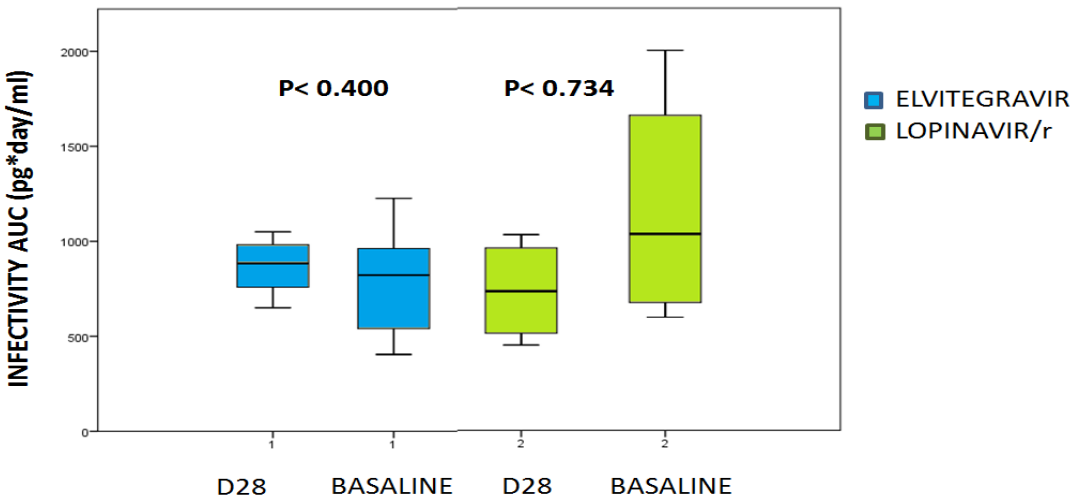
Figure 2. PK of elvitegravir according to time points



Black dots represent Elvitegravir concentration in plasma and rectal fluid. Grey-shaded regions indicate typical concentration ranges for EVG+c/TEF/FTC once daily plasma .peak and trough.

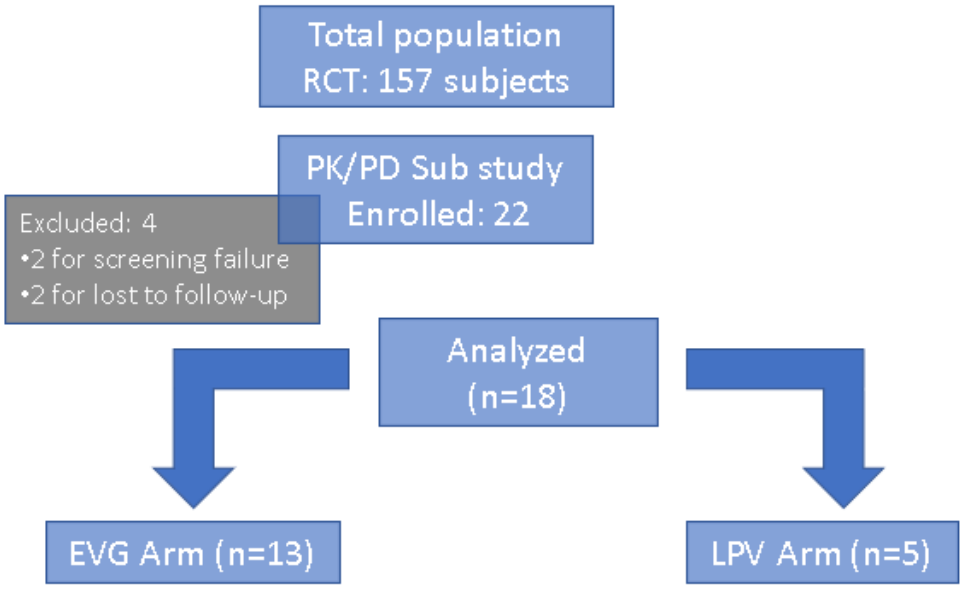
Figure XX. HIV infectivity AUC in rectal tissue according to study drug between timepoints (baseline D90 - no treatment, D7 - treatment initiation, D28 - end of treatment).

Figure 03. EX VIVO EFFICACY ON HIV INFECTIVITY



AUC in rectal tissue according to the study drug comparing between time points (baseline D90,no treatment, D28 end of treatment).

Supplementary figure 01. Flow chart describing the participants' distribution



Supplementary table 01: different assessments performed during the study.

Procedure	Day 7	Day 28	Day 90
Blood test	X	X	X
PK in plasma	X	X	
Anal cytology	X		
Rectal swabs for STIs	X		
Fecal calprotectin	X	X	X
Anoscopy	X	X	X
PK in rectal fluid	X	X	
Rectosigmoidoscopy	X	X	X
PK in rectal tissue	X	X	

Supplementary table 02: Cellular markers of different immune cell according to cell type and main function.

	Cell Type	Role
CD4	T helper cells	Co-receptor expression
CD8	Cytotoxic T cells	Co-receptor expression
CD4/CD8	T cells	Co-receptor expression
CD4+38+	T helper cells	Activation
CD4+DR+	T helper cells	Activation
CD4+38+DR+	T helper cells	Activation
CD4+CD28+	T helper cells	T cell differentiation stage
CD4+CD57+	T helper cells	T cell differentiation stage
CD4+28-57+	T helper cells	T cell differentiation stage
CD4+RA+CCR7+	T helper cells	T cell differentiation stage
CD4+RA-CCR7+	T helper cells	T cell differentiation stage
CD4+RA-CCR7-	T helper cells	T cell differentiation stage
CD4+RA+CCR7-	T helper cells	T cell differentiation stage
CD8+38+	Cytotoxic T cells	Activation
CD8+DR+	Cytotoxic T cells	Activation
CD8+38+DR+	Cytotoxic T cells	Activation
CD8+CD28+	Cytotoxic T cells	T cell differentiation stage
CD8+CD57+	Cytotoxic T cells	T cell differentiation stage
CD8+28-57+	Cytotoxic T cells	T cell differentiation stage
CD8+RA+CCR7+	Cytotoxic T cells	T cell differentiation stage
CD8+RA-CCR7+	Cytotoxic T cells	T cell differentiation stage
CD8+RA-CCR7-	Cytotoxic T cells	T cell differentiation stage
CD8+RA+CCR7-	Cytotoxic T cells	T cell differentiation stage
CCR5+	T cells	Co-receptor expression
CD11c+	Dendritic cells	co-receptor expression
CD83+	Dendritic cells	Activation
CD163+	Monocytes/macrophages	Activation
CD11c-CD163+	Monocytes/macrophages	Activation
CD11c+CD163+	Monocytes/macrophages	Activation
CD11c+CD163-	Monocytes/macrophages	Activation
CD11c-CD163-	Monocytes/macrophages	Activation
CD45+DR+	Monocytes	Activation
CD14-11C+	Monocytes	Activation, co-receptor expression
CD14+11C+	Monocytes	Activation, co-receptor expression
CD14-11C-	Monocytes	Activation
% CD11c+ CCR5+	Dendritic cells	Co-receptor expression
GM CCR5	T cells	Co-receptor expression
CD14+CD11c+HLA-DR+	Monocytes	co-receptor expression
GM HLA-DR	T cells	Activation

GM CD11C+	T cells	Activation
HLADR+	T cells	Activation
CD11C+	T cells	Co-receptor expression

Supplementary table II. Significant results of peripheral blood mononuclear cells according to phenotype outcome, per time point (D28 and D90) and per treatment arm (EVG vs LPV).

PBMCs	EVG	LOP/r	p		EVG	LOP/r	p
CD4/CD8				**CD4+38+**			
D90	**1,8(0,9-2,6)**	1,4(1-1,9)	ns	D90	**55(43-62)**	51(43-58)	ns
D28	**2,1(1,1-3,3)**	1,1 (1,1-1,5)	ns	D28	**57,4(53,9-68)**	**49,3 (47,3-51,3)**	**0.027**
Overall p	**0.025**	ns		Overall p	**0.012**	ns	
CD4+DR+				**CD4+CD28+**			
D90	4,3(3,7-5,9)	6,1(5,8-7,4)	ns	D90	98(97-98)	92(86-97)	ns
D28	**5,9(3,9-7,6)**	**8,3 (7,7-9,5)**	**0.027**	D28	**97,9(94-98)**	**92,5 (83,2-93,3)**	**0.027**
Overall p	ns	ns		Overall p	ns	ns	
CD4+CD57+				**CD4+28-57+**			
D90	2,1(1,4-3,7)	8,7(3,1-15,9)	ns	D90	1(0,2-1,3)	7(1,7-13,3	ns
D28	**1,7(1,1-4,7)**	**6,8 (6,8-15,6)**	**0.027**	D28	**0,7(0,2-2,4)**	**5,4 (5-12,6)**	**0.027**
Overall p	ns	ns		Overall p	ns	ns	
RA-CCR7+				**RA+CCR7-**			
D90	**24,1(19,6-31,4)**	34,4(26,05-43,5)	ns	D90	4(2,5-5,8)	3,8(1,85-9,6)	ns
D28	**39,4(27,4-53,9)**	34 (22,4-42,6)	ns	D28	**2,7(2,16-3,9)**	**5,3 (4- 7,6)**	**0.027**
Overall p	**0.012**	ns		Overall p	ns	ns	
CD8+CD28+				**CD8+CD57+**			
D90	80,3(63-83)	57,1(39-67,6)	ns	D90	21,2(11,5-32,7)	40(32-56)	ns
D28	**71(49-77)**	**51 (33-51)**	**0.028**	D28	**25(16-32)**	**39 (36-40)**	**0.028**
Overall p	ns	ns		Overall p	ns	ns	
CD8+28-57+				**RA-CCR7+**			
D90	11,8(7,91-26,1)	36,5(27,85-52,3)	ns	D90	**4,1(3,4-5,6)**	5,7(3,7-6)	ns
D28	**19,9(14,5-26,8)**	**35,3 (33,5-35,9)**	**0.028**	D28	**7(5,22-9,8)**	6,1 (4,5-7,4)	ns
Overall p	ns	ns		Overall p	**0.012**	ns	
8+CCR5+				**CD11c+**			
D90	**2,1(1,4-2,3)**	3,5(2-5,2)	ns	D90	2,9(0,7-26,6)	3,3(1,2-16,4)	ns
D28	**7,6(1,8-8,7)**	4,2(1-4,7)	ns	D28	**2,5(1,3-3,2)**	**1,2(0,8-1,3)**	**0.028**
Overall p	**0.036**	ns		Overall p	ns	ns	
CD11c-CD163-				**CD163+**			
D90	**89,5(24,1-90,1)**	94,1(59,5-95)	ns	D90	0,02(0,01-0,12)	0,03(0,02-0,11)	ns
D28	**93,8(90,7-96)**	93,5(57,9-97,2)	ns	D28	**0,02(0,02-0,1)**	**0,05(0,004-0,32)**	**0.028**
Overall p	**0.05**	ns		Overall p	ns	ns	
GM CCR5				**HLADR+**			
D90	**19,9(18,7-20,9)**	24,2(19,6-29,75)	ns	D90	**18(10-80)**	17(15-57)	ns
D28	**22,3(20,5-27,6)**	34,3(24,2-40,5)	ns	D28	**22(18-32)**	18(18-40)	ns
Overall p	**0.012**	ns		Overall p	**0.012**	ns	

Bold formatting represent significant values.

Suplementary Table III. Significant results of Mucosal mononuclear cells according to phenotype outcome, per time point (D28 and D90) and per treatment arm (EVG vs LPV).

MMCs	EVG	LOP/r	p		EVG	LOP/r	p
CD4+CD28+				**CD4+CD57+**			
D90	**100(99.3-100)**	99.4(28.9-99.7)	ns	D90	8.9(4.6-12.4)	13(8.7-18.1)	ns
D28	**98.1(88.9-99.2)**	99.6(69.5-99.6)	ns	D28	**4.7(3.6-11)**	**11.2(10.5-25.2)**	**0.027**
Overall p	**0.012**	ns		Overall p	ns	ns	
CD8+28-57+				**RA+CCR7-**			
D90	**1.2(0.6-1.5)**	**4.2(1.4-5.9)**	**0.042**	D90	17.6(6.5-29.7)	15.6(2.4-42.6)	ns
D28	**1.2(0.7-1.4)**	**5.3(1.1-7.6)**	**0.027**	D28	**0.5(0-2.5)**	**4.4(0.8-7.3)**	**0.027**
Overall p	ns	ns		Overall p	ns	ns	
CD163+				**CD11C+**			
D90	**5.1(2.8-11.7)**	0(0-0.2)	ns	D90	**5.7(3.3-8.3)**	9.4(3-18.1)	ns
D28	**0.1(0-0.1)**	0.1(0-1.5)	ns	D28	**3.9(2.3-7.7)**	6.9(3.4-20.5)	ns
Overall p	**0.001**	ns		Overall p	**0.027**	ns	
CD14+				**HLADR+**			
D90	0.4(0.2-1.4)	0.3(0.3-3.2)	ns	D90	**72.7(51.3-98.6)**	59(15.2-88.1)	ns
D28	**0.4(0.1-2.1)**	**2.9(1.1-6.7)**	**0.027**	D28	**65.3(52.9-75.3)**	**82.6(41.7-84.4)**	**0.027**
Overall p	ns	ns		Overall p	**0.027**	ns	

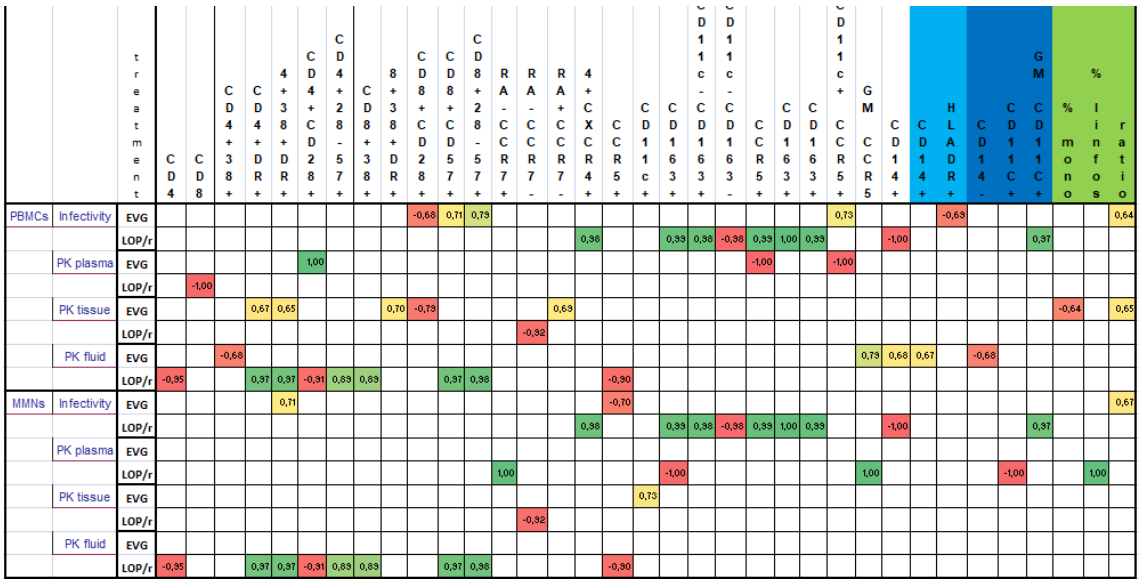
Bold formatting represent significant values.

Supplementary table IV. Significant results of citoquines levels per time point and prm.

Citoquines	EVG	LOP/r	p		EVG	LOP/r	p
IFN-a				**IL-13**			
D90	**162.2(139.5-343.4)**	86.8(116.8-146.3)	ns	D90	**31.4(22.7-52.3)**	**16.8 (12.5-19.6)**	**0.002**
D28	**163.6(69.4-219.9)**	98.4(126.2-144.6)	ns	D28	27.8(16.3-57.9)	21.4 (10.5-52.3)	ns
Overall p	**0.036**	ns		Overall p	ns	ns	
TNF-a				**IL-1RA**			
D90	**8.5(6-15.2)**	1.3(2.6-7.8)	ns	D90	**2.4(1.6-4.8)^**	**0.7(0.4-12)^**	ns
D28	**6.6(1.4-11.9)**	4.3(6.6-8.5)	ns	D28	**2.2(1.1-3.3)^**	16(8.6-18)^	ns
Overall p	**0.017**	ns		Overall p	**0.05**	ns	
IL-2				**IL-4**			
D90	14(9.1-23.2)	7.2(8.8-15.2)	ns	D90	**122.3(98.4-172.4)**	**76.5(60.5-90)**	**0.002**
D28	**10.7(9.4-14.6)**	**7.1(7.5-12.2)**	**0.027**	D28	**108.7(62.7-148)**	4.3(6.6-8.5)	ns
Overall p	**0.017**	ns		Overall p	**0.036**	ns	

Bold formatting represents significant values.

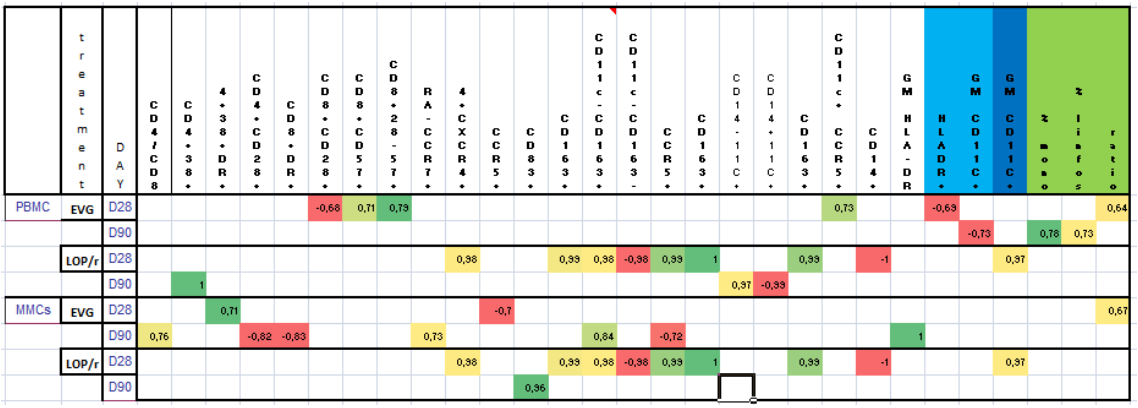
Supplementary Table V. Correlation matrix between PBMC, MMC, infectivity and drug concentrations per treatment arm.



		treatment	CD4	CD8	CD4+38+	CD4+DR+	4+38+DR+	CD4+CD28+	CD4+28-57+	CD8+38+	8+38+DR+	CD8+CD28+	CD8+CD57+	CD8+28-57+	RA-CCR7+	RA-CCR7-	RA+CCR7-	4+CXCR4+	CCR5+	CD11c+	CD163+	CD11c-CD163+	CD11c-CD163-	CCR5+	CD163+	CD163+	CD11c+CCR5+	GM CCR5	CD14+	CD14+	HLADR+	CD14-	CD11C+	CD11C+	% mono	% infos	ratio
PBMCs	Infectivity	EVG										-0,68	0,71	0,73													0,73			-0,63						0,64
		LOP/r																0,98			0,93	0,98	-0,98	0,93	1,00	0,93			-1,00				0,97			
	PK plasma	EVG						1,00																-1,00			-1,00									
		LOP/r		-1,00																																
	PK tissue	EVG				0,67	0,65				0,70	-0,73					0,69																	-0,64		0,65
		LOP/r														-0,92																				
	PK fluid	EVG			-0,68																						0,73	0,68	0,67		-0,68					
		LOP/r	-0,95			0,97	0,97	-0,91	0,83	0,83			0,97	0,98					-0,90																		
MMNs	Infectivity	EVG					0,71												-0,70																	0,67
		LOP/r																0,98			0,93	0,98	-0,98	0,93	1,00	0,93			-1,00				0,97			
	PK plasma	EVG																																		
		LOP/r													1,00						-1,00							1,00				-1,00			1,00	
	PK tissue	EVG																		0,73																
		LOP/r														-0,92																				
	PK fluid	EVG																																		
		LOP/r	-0,95			0,97	0,97	-0,91	0,83	0,83			0,97	0,98					-0,90																		

Color squares represent significant values, positive correlation to negative from green to yellow to red

Supplementary table VI. Correlation matrix between infectivity and coreceptors per time point and treatment ARM.



	treatment	DAY	CD4/CD8	CD4+38+	4+38+DR+	CD4+CD28+	CD8+DR+	CD8+CD28+	CD8+CD57+	CD8+28-57+	RA-CCR7+	4+CXCR4+	CCR5+	CD83+	CD163+	CD11c-CD163+	CD11c-CD163-	CCR5+	CD163+	CD14-11C+	CD14+11C+	CD163+	CD11c+CCR5+	CD14+	GM HLA-DR	HLADR+	GM CD11C+	GM CD11C+	% mono	% lin os	ratio
PBMC	EVG	D28						-0,68	0,71	0,79													0,73			-0,63					0,64
		D90																									-0,73		0,78	0,73	
	LOP/r	D28										0,98			0,99	0,98	-0,98	0,99	1			0,99		-1				0,97			
		D90		1																0,97	-0,99										
MMCs	EVG	D28			0,71								-0,7																		0,67
		D90	0,76			-0,82	-0,83				0,73					0,84		-0,72							1						
	LOP/r	D28										0,98			0,99	0,98	-0,98	0,99	1			0,99		-1				0,97			
		D90												0,96																	

Color squares represent significant values, positive correlation to negative from green to yellow to red.

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Infectious disease unit; Eva González, Lorna Leal, Agathe León, Berta Torres, Alexy Inciarte, Constanza Lucero, José L. Blanco, Esteban Martínez, Josep Mallolas, Josep M. Miró, Monserrat Laguno, Jhon Rojas, María Martínez-Rebollar, Ana González-Cordón, Christian Manzardo, Cristina de la Calle, Gerard Espinosa, Joan Albert Arnaiz, Jose M. Gatell, Felipe García, Juan Manuel Pericas, David Nicolás, Marta Bodro, Ana del Río and Celia Cardozo. Microbiology department; Jordi Vila, Miriam Alvarez, Juan Carlos Hurtado, Pathology department; Teresa Ribalta, Immunology; Montserrat Plana, Alberto Crespo, Núria Climent, Manel Bargallo, laboratory department; Cristina Rovira Carmen Hurtado, endoscopy department; Josep Llach, Cristina Rodríguez, Instituto de Salud Carlos III. Infectivity: José Alcamí, Luis Miguel Bedoya, University of North Carolina at Chapel Hill. For pharmacokinetics; Angela Kashuba, Mackenzie Leigh Cottrell, Ruili Wang

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Contributorship statement : AI, LL, performed clinical assessments. LL , and FG designed the study, AI,AC,NC, collaborated with data entry AI, contributed to data analysis and wrote the first draft of the manuscript. AI, were responsible for data entry. AI, CGV, JAM, IA, AS, LM, EG, VDB, CL, JGP, FG, critically reviewed the manuscript and agreed on its final version.

Transparency statement: All the information displayed in the present manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Data sharing statement: Extra data will be available by emailing ajinciar@clinic.cat

Patient and public involvement: Patients were not involved in the study described; there will be an enlisting of patients to disseminate the research findings to the general population in primary care settings.

FOURTH PIECE OF RESEARCH

Evaluation of Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate for Non-occupationalPost Exposure Prophylaxis, a Prospective Trial (DORAVIPEP)

Inciarte, Alexy; Ugarte, Ainoa; Torres, Berta; Martinez-Rebollar, Maria; Laguno, Montse; Ambrosioni, Juan; Chivite, Ivan;Berrocal, Leire; González-Cordón, Ana; Puerta, Pedro; De La Mora, Lorena; De lazarri, Elisa; Herrera, Sabina;Fernández, Emma; Barrero, Laura; Solbes, Estela; Martinez, Esteban; Blanco, José Luis; Miró, José M; Soriano, Alex; Mallolas, Josep

Open forum infectious disease achieved an impact factor of 6 in the ISI Journal Citation Reports. Accepted, Q1. SUBJECT AREA AND CATEGORY: Infectious disease.

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21 March 2023

Re: DOR/FTC/TDF for HIV-1 post-exposure prophylaxis

Dr.Barrocas
Editor-In-Chief
Open Forum Infectious Diseases

Dear Dr. Barrocas

Please find enclosed our manuscript entitled, "Doravirine/Lamivudine/TenofovirDisoproxil Fumarate for Non-occupational HIV-1 Post-Exposure Prophylaxis: A Prospective Open-Label Trial (DORAVIPEP Trial)"by Alexy Inciarte et al. to be considered for publication in the *OP Infectious Diseases* as Major Article.

Our study aimed to evaluate the safety and efficacy of DOR/3TC/TDF as a non-occupational HIV-1 post-exposure prophylaxis (PEP) regimen. We conducted a prospective, open-label trial in which participants received the DOR/3TC/TDF regimen within 72 hours of exposure. DOR/3TC/TDF is an appealing combination for this indication, given the low drug-drug interaction potential; the co-formulation of the regimen; and its relatively low cost compared to other combinations. The primary endpoint was non-completion rates at the 28-day follow-up period.

We are pleased to report that our study found that DOR/3TC/TDF was well-tolerated and demonstrated safety as a PEP regimen, with minimal side effects reported and a very low rate of discontinuation. This study found no cases of HIV-1 seroconversion, even though it was not specifically designed as an efficacy study.

We are submitting our manuscript to *OFID*, as we believe that the data presented would further guide clinicians involved in managing post-exposure prophylaxis. We feel that our results are relevant and, therefore, worthy of publication in a reputable journal like *OFID.* Moreover, clinical trials in this setting are very scarce.

None of the paper's contents have been previously published, and the manuscript is not being considered for publication elsewhere, in whole or part, in any language. None of the authors have any conflicts of interest to disclose regarding the work presented in this manuscript. All authors have agreed to the final version of the manuscript. Furthermore, all authors have seen and approved the manuscript, contributed significantly to the work.

We are pleased to confirm that we are willing to bear the cost of reproducing our color figures, and would like to request that the journal use color in the final version of our publication

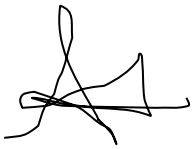
Preliminary results of this paper have been presented at Glasgow HIV Drug Therapy 2022.

If you require any further information, please do feel free to contact us.

We look forward to hearing from you at your earliest convenience.

Yours sincerely,

On behalf of all authors,



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Subject: Decision Notification: Ms. No. OFID-D-23-00476R2

Ref.: Ms. No. OFID-D-23-00476R2
Doravirine/Lamivudine/TenofovirDisoproxil Fumarate for Non-occupational HIV-1 Post-Exposure Prophylaxis: A Prospective Open-Label Trial (DORAVIPEP Trial)
Open Forum Infectious Diseases

Dear Dr Inciarte,

We are pleased to tell you that your work has now been accepted for publication in Open Forum Infectious Diseases and that we will soon be sending the manuscript files to Oxford Journals for processing and immediate publication on Advance Access. Any additional comments from the editor (if applicable) are included at the end of this email.

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Additional comments from the editor:

Dear Dr. Inciarte,

Thank you for your revised manuscript. I understand your rationale for inclusion for completion/adherence and believe that you have properly referenced other manuscripts with similar decisions. I am happy to recommend your manuscript for acceptance.

Sincerely,
Josh Barocas, MD
Associate Editor

With kind regards,

Dr Joshua A Barocas
Associate Editor

Dr. John Baddley, MD, MSPH
Editor-in-Chief

Dr. Andrej Spec, MD, MSCI
Editor-in-Chief
Open Forum Infectious Diseases

_____

Open Forum Infectious Diseases

Doravirine/Lamivudine/TenofovirDisoproxil Fumarate for Non-occupational HIV-1 Post-Exposure Prophylaxis: A Prospective Open-Label Trial (DORAVIPEP Trial)

--Manuscript Draft--

Manuscript Number:	OFID-D-23-00476R2
Full Title:	Doravirine/Lamivudine/TenofovirDisoproxil Fumarate for Non-occupational HIV-1 Post-Exposure Prophylaxis: A Prospective Open-Label Trial (DORAVIPEP Trial)
Article Type:	Major Article
Section/Category:	Transfer from CID
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Manuscript Region of Origin:	SPAIN
Abstract:	BackgroundNew regimens may provide better tolerability, convenience, and safety for non-occupational HIV post-exposure prophylaxis (PEP). For this reason, we evaluated the single-tablet regimen (STR) Doravirine/Lamivudine/Tenofovir disoproxil fumarate (DOR/3TC/TDF) for 28 days.Methods and materialsProspective, open-label, and single-arm trial. We included individuals with potential HIV-1 exposure within 72 hours. The primary endpoint was non-completion 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. The trial is registered at clinicaltrials.gov number: NCT04233372.ResultsBetween September 2019 and March 2022, the study enrolled 399 individuals. Median age was 30 (27-36) years and 91% (n=364) were males. 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 (13-40) hours. Non-completion of PEP was 29% (n=114) (95%CI:24-33) and 20% (n=72) (95%CI: 16-25) per modified ITT. Main reasons for non-completion 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<0.001). One hundred and twenty-three (31%) participants reported adverse events—mostly mild and self-limited (82%); discontinuation occurred in eight cases (2%). Adherence to PEP in the assessed users was 96%. There were no HIV seroconversions.ConclusionsDOR/3TC/TDF is a well-tolerated option for non-occupational PEP.
Suggested Reviewers:	Kenneth Mayer Harvard Medical School kmayer@fenwayhealth.org Expertise and research in HIV prevention strategies among them post exposure prophylaxis.
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Opposed Reviewers:	
Response to Reviewers:	Dear Dr. Barocas, Thank you for taking the time to carefully review our manuscript and provide us with such detailed and insightful feedback. We understand and appreciate your candidness, and we recognize that some aspects of our response to the initial reviews may not have been as thoroughly addressed in the manuscript as they should have been. We sincerely apologize if this oversight gave the impression of disregard for the valuable suggestions and concerns raised by Reviewers. Our intention was solely to convey our research findings, and any lapses in clarity or completeness were not deliberate. We acknowledge the importance of thoroughly examining data from multiple angles, especially in the context of a single open-label study. Your comments on understating the limitations of the regimen, the inadequacy of the current conclusion language, and the need for more objective measures of adherence are all incredibly valuable insights. In line with your suggestions, we have made substantial changes in our manuscript. We appreciate your guidance in making our manuscript more comprehensive and reflective of our study's findings and limitations. We hope that the revised manuscript now meets your expectations, and we look forward to your further comments.

	Once again, thank you for your thorough and thoughtful feedback Sincerely, Alexy Inciarte.
Additional Information:	
Question	**Response**
Are any of the co-authors a member of IDSA?	Unknown
Are you or any co-authors a Fellow of the IDSA (FIDSA)?	Unknown
Manuscript Classifications:	Antiviral; HIV I - Prevention; Viruses
Secondary Full Title:	

Doravirine/Lamivudine/TenofovirDisoproxil Fumarate for Non-occupational HIV-1 Post-Exposure Prophylaxis: A Prospective Open-Label Trial (DORAVIPEP Trial)

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Running title: PEP with DOR/3TC/TDF for HIV-1 Infection

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ABSTRACT WORD COUNT: 233

Background: New regimens may provide better tolerability, convenience, and safety for non-occupational HIV post-exposure prophylaxis (PEP). For this reason, we evaluated the single-tablet regimen (STR) Doravirine/Lamivudine/Tenofovir disoproxil fumarate (DOR/3TC/TDF) for 28 days.

Methods and materials: Prospective, open-label, and single-arm trial. We included individuals with potential HIV-1 exposure within 72 hours. The primary endpoint was non-completion 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. The trial is registered at clinicaltrials.gov number: NCT04233372.

Results: Between September 2019 and March 2022, the study enrolled 399 individuals. Median age was 30 (27-36) years and 91% (n=364) were males. 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 (13-40) hours. Non-completion of PEP was 29% (n=114) (95%CI:24-33) and 20% (n=72) (95%CI: 16-25) per modified ITT. Main reasons for non-completion 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<0.001). One hundred and twenty-three (31%) participants reported adverse events—mostly mild and self-limited (82%); discontinuation occurred in eight 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 non-occupational PEP.

Summary WORD COUNT: 39

The study evaluated the safety, tolerability, and adherence of DOR/3TC/TDF as a single-tablet-regimen for non-occupational HIV-1 PEP in 399 individuals. Results showed non-completion rates of 29% and 20% (per ITT and mITT) and a low discontinuation rate due to adverse effects.

Background.

According to the Joint United Nations Programme on HIV/AIDS (UNAIDS), there were 1.5 million new 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 post-exposure prophylaxis (PEP). It is used after occupational or non-occupational exposure. PEP was initially provided in the occupational context (2) but it has now been implemented in non-occupational 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 two nucleotide reverse transcriptase inhibitors (NRTI) 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 three-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 (DDI) potential, treatment-associated toxicities, and a lack of convenience (i.e., bedtime dosing or calorie intake requirements) have prevented the use of older non-nucleoside-reverse-transcriptase-inhibitors (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/TDF for non-occupational

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 one or more of these aforementioned properties. Doravirine (DOR) is a novel NNRTI that has hit the market as a once-a-day STR in combination with lamivudine and tenofovir disoproxil fumarate. Studies in people living with HIV (PWLH) 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-naïve and antiretroviral-experienced PLWH in Spain and other European countries (22,23). Altogether, these characteristics make DOR-3TC-TDF an appealing combination choice for PEP. This study evaluated DOR-3TC-TDF STR for non-occupational PEP.

Materials and Methods:

We performed a phase 4, single-center, open-label, single-arm and prospective study addressing safety and tolerance of DOR-3TC-TDF STR as PEP. We included those individuals who visited the emergency room (ER) 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 older than 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 flow chart.

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), weeks 4 (3-5) and 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 (VDRL) test; IgM and IgG antibody testing for *T. pallidum* (syphilis); and antibody testing for HAV, HBV, and HCV. Participants consulted results a week after the blood tests during a follow-up visit with either the nurse or physician. (see 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 two 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 (ICH, MedDRA). AE could belong to one of two 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 six-item scale that measures ART adherence in PLWH. The questionnaire considers patients as treatment-adherent if they answer four qualitative questions correctly and respond less than or equal to 2 times and 2 days to questions 5 and 6 (see references), respectively. Patients' answers determine the adherence score, and a score below 94% is considered as low adherence. (24,25).

The primary endpoint was the proportion of participants not completing the 28-day PEP regimen. PEP non-completion 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 non-completion, the identification of factors associated to non-completion, proportion of subjects that 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 GCP, 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. Information regarding patients' identities was codified. Clinicaltrials.gov number: NCT04233372.

Statistical Analysis.

Considering that a population of approximately 1400 individuals attends our center for PEP yearly, a sample of 400 individuals produces a two-sided 95% confidence interval (CI) with a precision of 0.04 when the actual proportion of non-completion (our primary outcome) is near 40%. We performed the sample size calculation using PASS 15 (PASS 15 Power Analysis and Sample Size Software (2017). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.)

We performed summary statistics using absolute frequency and percentages for qualitative variables and mean (SD) or median (IQR) for quantitative variables. Wilcoxon Rank Sum test was used to analyze differences between groups for quantitative variables. Chi-squared test was used to analyze differences between groups for qualitative variables. In case of low frequency for some category of a variable, Fisher's 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 one dose of PEP, and in the modified-ITT (mITT) population, which meant a selection of those who had at least one follow-up measurement. We defined non-completion as participants who did not attend at least one follow-up visit. For the secondary objectives, we evaluated baseline characteristics associated with PEP non-completion using a logistic regression model, selecting variables

using clinical judgment and a stepwise process. We reported the incidence rate (IR) of AE as the number of AE per 100/person-months and its 95% CI, differentiating those leading to discontinuation, 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 IR 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 mixed-effects regression model. All tests were two-tailed, and the significance level was set at <0.05. We conducted the statistical analysis using Stata (StataCorp. 2021. Stata: Release 17. Statistical Software. College Station, TX: StataCorp LLC).

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

Results

Baseline characteristics of the study population

Demographics

A total of 1,535 subjects received PEP prescriptions between September 2019 and February 2022. Of these, 399 individuals who met PEP criteria and visited the emergency room with possible exposure to HIV were included in the study.(Supplementary Figure 1). The median age was 30 years [interquartile range (IQR) 27-36], and 91% (n=364) were male. HIV acquisition risk was 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 and 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 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 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 *N. gonorrhoeae* infection; 58 (32%), syphilis; and 44 (24%), *Chlymadia trachomatis* infection. Of the patients with basal-reported STIs, 26% (n = 33) reported two episodes and 8% (n=10), three episodes. Throughout the follow-up period, there were a total of four asymptomatic syphilis diagnoses; four cases of *N. gonorrhoeae* infection; and two cases of *C. trachomatis* infection. Supplementary figure number 2 shows previous STIs.

Seroprevalence of Hepatitis and Syphilis.

At baseline, among the 345 participants, 85% (n=291) were HAV IgG pos, 69% (n=239)

were HBVs Ab positive, 7% (n=24) were IgG HBVc Ab positive and 1% (n=3) have HBVs Ag positive; 1% (n=3) were HCV Ab 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). 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 in 33% (n=128) of the participants. Most cases (n=361, 92%) had a risk of transmission via anal sex, either insertive or receptive. Unprotected oral sex was reported in 91% of cases (n=343). In a smaller proportion Unprotected vaginal sex was reported 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 exposure.

Previous drug use and co-medications.

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), 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 treatments 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 non-completion.

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 eight days (IQR 0, 14). Reasons for non-completion 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 modified ITT, PEP non-completion percentage at day 28 was 20% (n=72) [95%CI: 16%; 25%). 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 non-completion.

In the multivariable logistic regression model including all enrolled patients, the unique independent factor associated with PEP non-completion was younger age [OR 0.94 (95%CI 0.91;0.97) p<0.001]. Restricting the sample only to those patients who came at least one visit after enrollment, the independent factors associated with PEP non-completion in the multivariable logistic regression were younger age [OR= 0.94 (0.91 – 0.98), p<0.001] and the emergence of any AE during PEP [OR = 1.96 (1.13-3.38), P= 0.016]. Table 2 shows factors associated with PEP non-completion in both samples and unadjusted and adjusted logistic models.

Adverse events.

A total of 123 (31%) patients reported adverse events, with 183 AE episodes overall. The incidence rate was 60.09 cases per 100 person-months (95%CI: 51.98; 69.45). Adverse events 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 (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 (14,9%), asthenia (n=9, 12.2%), headache (n=9, 12.2%) There were no potentially life-threatening (grade IV) adverse events related to the medication, and no serious adverse events. Discontinuation due to AEs accounted for 8 (7%) cases among all types of PEP non-completion. 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 while administration or cessation of the study medication. Laboratory abnormalities were not the reason for PEP non-completion 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 (weeks) 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 seven and week 4, respectively, with corresponding pill count data. The number of non-adherent 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 non-occupational PEP. DOR/3TC/TDF seems appealing as a PEP regimen for several reasons: the co-formulation of their components, the low DDI potential, the higher genetic barrier of DOR compared to other NNRTIs, and the good tolerance reported in pivotal naïve and switch randomized controlled trials (RCT) exploring this regimen (26,27). The DORAVIPEP trial aimed to investigate non-completion rates of post-exposure prophylaxis for HIV.

Results of DORAVIPEP trial can be compared to three RCTs conducted at our center: MARAVIPEP, RALPEP, and STRIBPEP (28-30). While these studies are two-arm trials, in contrast with DORAVIPEP, a single-arm trial, they are methodologically similar in an equivalent population with consistent PEP non-completion rates. An examination of the results from these studies indicates that combination therapy of DOR/3TC/TDF has lower PEP non-completion rates than those of regimens belonging to the ritonavir-boosted lopinavir (LPV/r), Maraviroc (MVC), 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 + 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 (31).

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 (32), while another study included 102 participants but

lacked a comparison group (33). Although both studies yielded important results, their relatively limited sample sizes might have prevented to detect subtle variances or infrequent adverse effects. Nevertheless, PK/PD studies noted reduced levels in cervical and vaginal tissues for TAF compared to TDF (34). This limitation could influence the treatment's prophylactic effectiveness, emphasizing the need for additional exploration. A subject's younger age has consistently been identified as a significant factor in multiple studies examining PEP non-completion. Furthermore, adverse events contribute to non-completion in the intention-to-treat analysis of these studies (28-30).

Previous studies have identified female sex as a factor for PEP non-completion, perhaps due to a higher risk perception among males. However, in our studies, being female was not associated with non-completion. 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 (35). 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 (36). 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 non-completion 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 (37). In old PEP studies, the recommendation was to wait until six months for discharge, making it more feasible for higher dropout rates to be present. With the introduction of 4th generation HIV tests in 2010 (with a shorter detection window of up to four weeks), recent guidelines recommended shorter follow-up periods until four months as a measure of precaution because of a potential delay in seroconversion due to PEP use (38).

PEP efficacy can be jeopardized due to early discontinuation and low adherence. Adverse events and PEP discontinuation are often described when using ritonavir-boosted protease inhibitors such as LPV/r, atazanavir (ATZ/r), or darunavir (DRV/r) (39-41). With the appearance of very well-tolerated, new antiretroviral agents for HIV treatment, like integrase strand transfer inhibitors (InSTI), current guidelines recommend RAL as the third drug in PEP regimens; PI as an alternative; and, to a lesser extent, some other InSTI (8,42,43). The incidence of adverse events 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 (28,44).

An adherence meta-analysis including three RCTs, nine prospective and five retrospective studies (45) 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 (44,46,47).

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 UK, 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 (44). 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. Secondly, 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 two-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 COVID-19 pandemic may have contributed to less follow-up, fewer testing opportunities, and underreporting of adverse events 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. Lastly 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 Self-reported Medication-taking Adherence Questionnaire (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 adverse events, and treatment discontinuation. A randomized clinical trial may reinforce the results of this single-arm trial.

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Transparency Statement: All the information displayed in the present manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

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

Table 1. Characteristics of individuals with HIV exposure from the entire cohort (intent-to-treat ITT population) (n=399) and individuals coming to at least one follow-up consultation (m-ITT population) (n=356)

	Whole Cohort				Coming at least to one follow-up consultation			
	Cohort	**Completion**	**Non-completion**	**P**	**Cohort**	**Completion**	**Non-completion**	**P**
Number	399	285	114	<0.001[a]	356	284	72	0.004[a]
Median age in years (IQR)	30 (27 ; 36) [399]	31 (27 ; 37) [285]	29 (24 ; 33) [114]	0.017[b]	31 (27 ; 36) [356]	31 (27 ; 37) [284]	29.5 (25 ; 32.5) [72]	0.291[c]
Male (%)	367 (92%) [399]	268 (94%) [285]	99 (87%) [114]	0.523 [b]	330 (93%) [356]	265 (93%) [284]	65 (90%) [72]	0.913[b]
European origin (%)	231 (60%)[382]	175 (61%) [285]	56 (58%) [97]	0.758 [a]	217 (61%) [355]	174 (61%) [284]	43 (61%) [71]	0.760 [a]
Median time from exposure (IQR)	24 (13 ; 40) [388]	24 (14 ; 40) [285]	24 (12 ; 36) [103]	0.972[b]	24 (13 ; 40) [355]	24 (13.5 ; 40) [284]	24 (12 ; 36) [71]	0.420[b]
Type of exposure MSM (%)**	331 (84%) [395]	246 (87%) [284]	96 (86%) [111]	1.000 [c]	309 (87%) [354]	245 (87%) [283]	64 (90%) [71]	0.693[c]
Evaluable risk of infection * (%)**	385 (97%)[397]	275 (97%) [284]	110 (97%)[113]	0.809[b]	345 (97%) [355]	274 (97%) [283]	71 (99%) [72]	0.878[b]
Previous PEP (%), yes	138(35%)[392]	101 (36%) [284]	37(34%) [108]	0.948[b]	126(35%) [355]	101 (36%) [283]	25 (35%) [72]	0.664[b]
Previous STI (%)	125 (33%) [383]	91 (33%) [278]	34 (32%) [105]	0.200[b]	115 (33%) [348]	90 (32%) [277]	25 (35%) [71]	0.092[b]
Source known to be HIV infected (%)	45 (11%) [399]	36 (13%) [285]	9 (8%) [114]	<0.001[a]	43(12%) [356]	36 (13%) [284]	7 (10%) [72]	0.004[a]

* Total of non-missing values

** Men who have sex with other men

***Defined as any sexual exposure excluding those with low-intermediate risk

[a]Wilcoxon Rank Sum test

[b]Chi-squared test

[c]Fisher's exact test

Table 2. Factors associated with PEP non-completion at day 28 due to any cause or adverse events

Characteristic	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 one follow-up visit (n=356), OR (95%CI)[a]	
Type of analysis	Univariable	Multivariable	Univariable	Multivariable
Age: one-year increase	**OR= 0.94 (0.91 – 0.97), P= 0.0003**	**OR= 0.94 (0.91 – 0.97), P= 0.0002**	**OR= 0.94 (0.90 – 0.97), P= 0.0012**	**OR= 0.94 (0.91 – 0.98), P= 0.003**
Type of exposure: homosexual; yes vs. no	OR= 0.99(0.52 – 1.88), P= 0.972		OR= 1.42 (0.60 – 3.33), P= 0.422	
Risk Assessment: high vs. intermediate/low	OR=1.2 (0.32 – 4.52) P= 0.787		OR = 2.33 (0.29 – 18.77) P=0.426	
Sex: male vs. female	**OR = 0.42 (0.20 – 0.87)P=0.019**			
AE during PEP treatment: yes vs. no	OR= 1.04 (0.63-1.70), P= 0.885		**OR = 2.06 (1.20-3.54), P= 0.008**	**OR = 1.96 (1.13-3.38), P= 0.02**
Adherence to PeP[b] : high vs. low	**OR=0.23(0.08-0.67) P=0.007**		**OR=0.23(0.08-0.67) P=0.007**	**OR= 0.21 (0.07; 0.67), P=0.008**

Factors associated with PEP non-completion at day 28 in the unadjusted model. Baseline characteristics associated with treatment non-completion are identified using a logistic regression model. **The dependent variable is 'Have discontinued the 28-day treatment'**

Bold formatting represents significant P-values.

a Attending individuals with an 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.

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Supplementary table 1. Study procedures during follow-up

	Day 0 Treatment initiation	Day 7	Weeks 4	Week 12
Compliance with inclusion and exclusion criteria	X			
Clinical evaluation	X	X	x	x
Biochemical, liver, and CBC	x (1)		x	x
HIV, HAV*, HB*, HCV*, and syphilis serology (**)	x (1)	X(2)	x	x
Cholesterol, HDL, and LDL	x (1)		x	x
Pregnancy test	x (4)		X(5)	
Questionnaire of adherence to ART (3)		x	x	
Pill count		x	x	
Reporting adverse event.	x	x	x	x

*Day 0 and weeks 10 to 14.

(1) This analysis can be performed within 10 days of exposure.

(2) Syphilis serology to be performed in cases of sexual exposure until day 28.

(3) Evaluated with a simplified medication adherence questionnaire-SMAQ.

(4) In special cases, per medical assessment, pregnancy tests in women of childbearing age.

Supplementary Table 2. Adverse effects of individuals with HIV exposure from the entire cohort coming to at least one follow-up visit (n=355).

		Cohort	Related	Unrelated
Number of exposed individuals		399	-	-
Individuals with adverse events		123 (31 %)	55 (44.4%)	82 (66.6%)
Total of adverse event episodes*		183	78 (43%)	105 (57%)
Grade I adverse episode*		150 (82%)	63 (81%)	87 (83%)
Grade II adverse episode*		26 (14%)	12 (15%)	16 (15%)
Grade III adverse episode *		5 (3%)	3 (4%)	2 (2%)
Severity degree**	Grade I	108	-	-
	Grade II	22	-	-
	Grade III	4	-	-
Gastrointestinal adverse episode*		63 (35%)	45 (58%)	18 (17%)
Neuropsychiatric adverse episode*		37 (21%)	18 (23%)	19 (18%)
Systemic adverse episode*		9(5%)	7 (9%)	2 (1%)
Type of Symptoms ***	Gastrointestinal [a]	50	-	-
	Neuropsychiatric [b]	29	-	-
	Fatigue	11	-	-

* Adverse episodes are defined as the total number of adverse events (the occurrence of an adverse event once and more than once in the same patient or the whole sum of each episode within the entire cohort of the patient). Bold formatting represents significant P-values.

** Number of exposed individuals with symptoms according to severity degree.

*** Number of exposed individuals according to the type of symptoms.

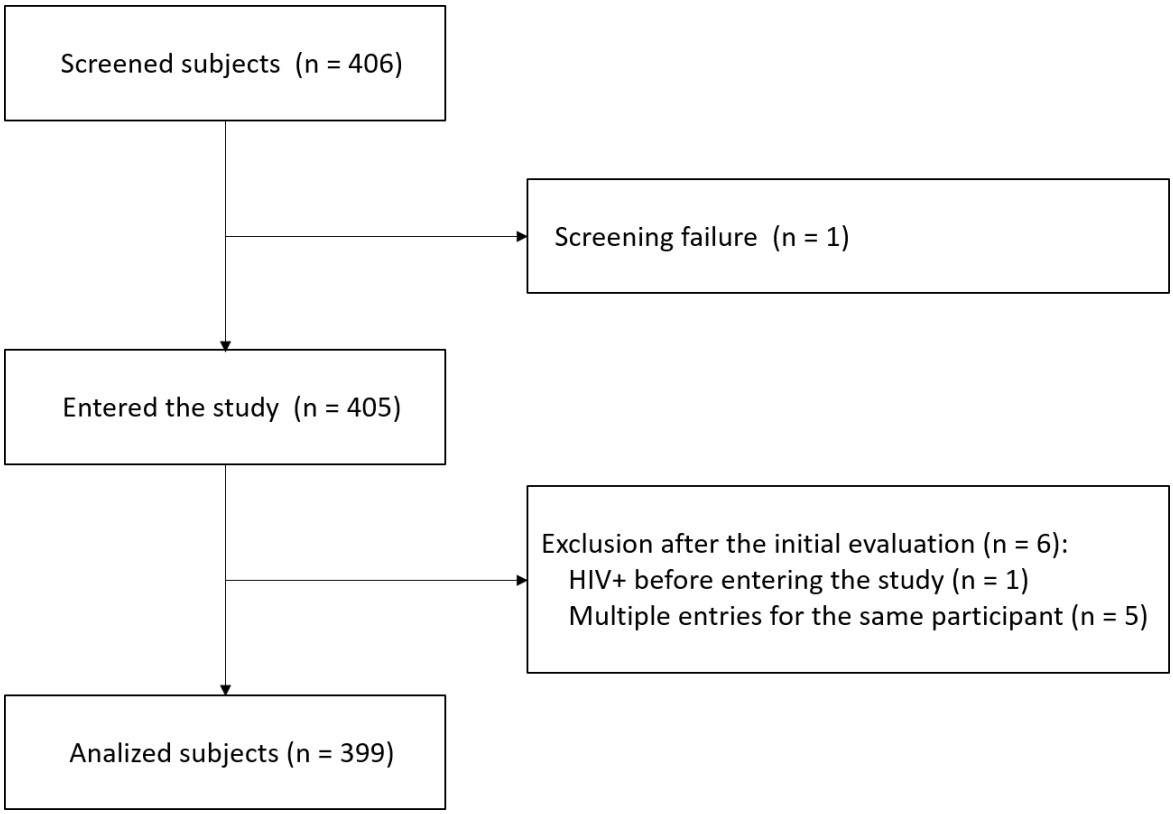
[a] Such as nausea, vomiting, diarrhea, abdominal pain, and flatulence. [b] headache, insomnia, and nightmares.

Supplementary Table 3 Laboratory parameters of the study population during follow-up.

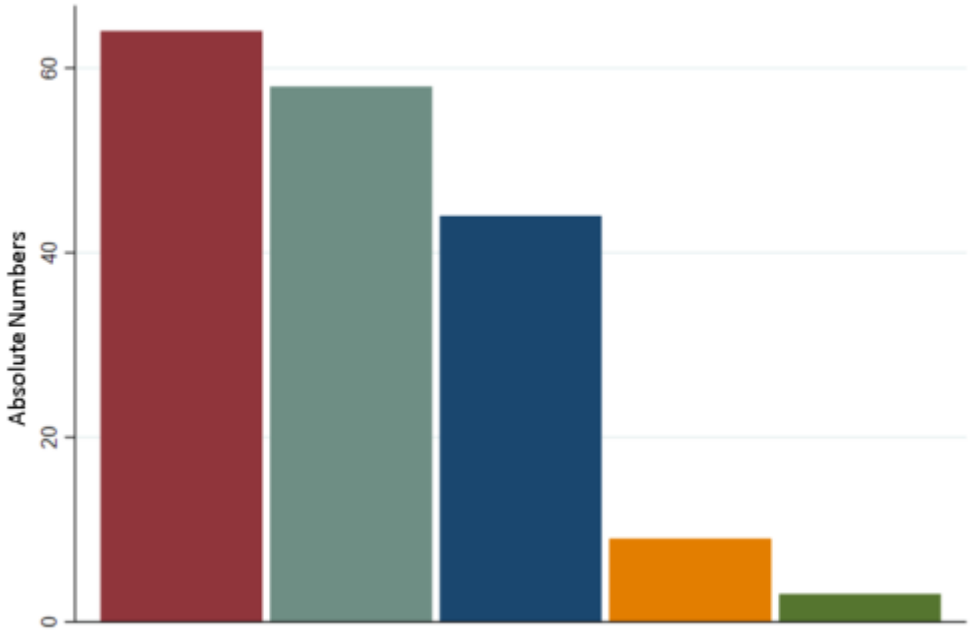
VARIABLE Unit [normal range]	Day 7	Week 4	Week 12
Total Cholesterol mg/dL [<200]*	166 (144 ;187) [350]	172 (154 ; 192) [272]	166 (150 ; 186) [233]
Triglycerides mg/dL [<150]*	56 (31 ; 81) [2]	115 (96 ; 131) [3]	76 (58 ; 93) [3]
AST UI/L [5.0 - 40.0]*	24 (19 ; 30) [352]	24 (19 ; 29) [270]	24 (20 ; 29) [234]
ALT UI/L [5.0 - 40.0]*	22 (17 ; 30) [353]	22 (17 ; 30) [353]	22 (17 ; 30) [353]
GGT mg/dL [0.20 - 1.20]*	18 (14 ; 25) [353]	18 (14 ; 25) [353]	18 (14 ; 25) [353]
Leucocytes *10^9L [4.00 - 11.00]*	7.105 (5.84 ; 8.44) [354]	7.105 (5.84 ; 8.44) [354]	7.105 (5.84 ; 8.44) [354]
Neutrophils *10^9L [2.5 - 7.0]*	4.2 (3.2 ; 5.3) [354]	4.2 (3.2 ; 5.3) [354]	4.2 (3.2 ; 5.3) [354]
Linfocytes*10^9L [0.9 - 4.5]*	2 (1.6 ; 2.5) [354]	2.1 (1.7 ; 2.6) [274]	2.1 (1.8 ; 2.6) [234]
Hemoglobin g/dl [120 - 150]*	152 (144 ; 158) [354]	153 (145 ; 159) [274]	152 (145 ; 159) [234]
Platelets 10^9/L [130 - 400]*	228.5 (204 ; 273) [354]	228.5 (200 ; 268) [274]	232.5 (201 ; 275) [234]
Creatinine mg/dL [0.30 - 1.30]*	.94 (.86 ; 1.03) [354]	.95 (.87 ; 1.03) [274]	.94 (.85 ; 1.04) [234]
Glomerular filtration rate (GFR), > 90**	285 (81%)	216 (79%)	190 (81%)
Glomerular filtration rate (GFR)**	82 (75 ; 86) [69]	83 (72 ; 87) [58]	82 (72.5 ; 86) [44]
Sodium, meq/L [135 - 145]*	140 (139 ; 141) [354]	140 (139 ; 141) [273]	140 (139 ; 142) [232]
Potassium, meq/L [3.5 - 4.5]*	4.2 (4 ; 4.4) [354]	4.3 (4.1 ; 4.6) [273]	4.3 (4.1 ; 4.5) [232]

AST: Aspartate amino tranferase. ALT: Alanine amino tranferase. GGT: gamma-glutamyl transferase *: Median (IQR) [n]
**: n (Column percentage)

Supplementary Figure 1. Subject disposition flow chart

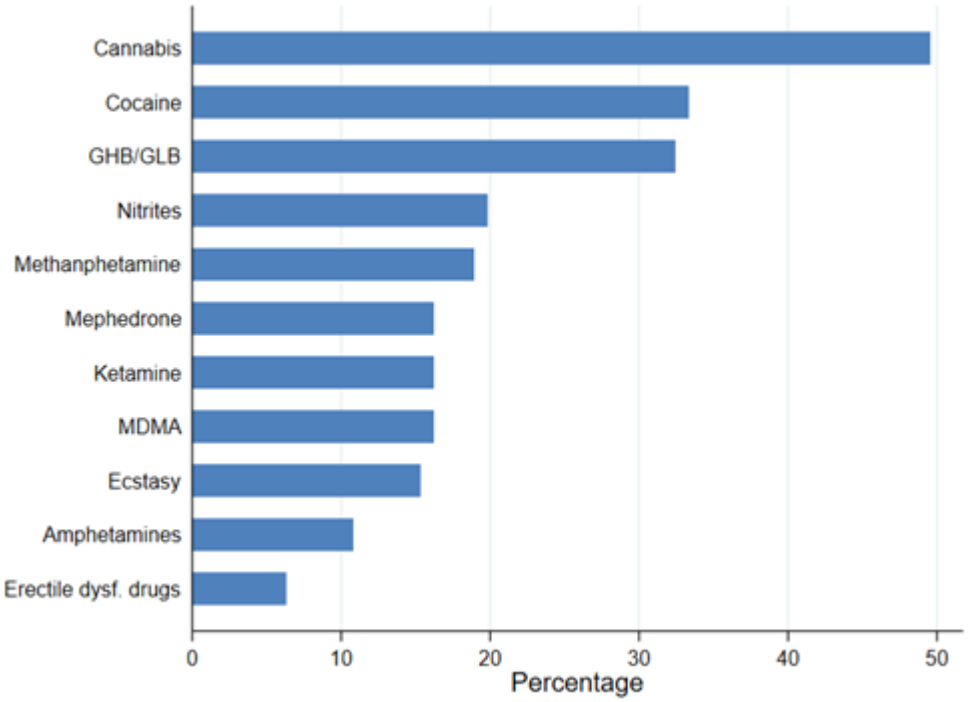


Supplementary Figure 2. Previous STIs among individuals receiving PEP in absolute numbers.



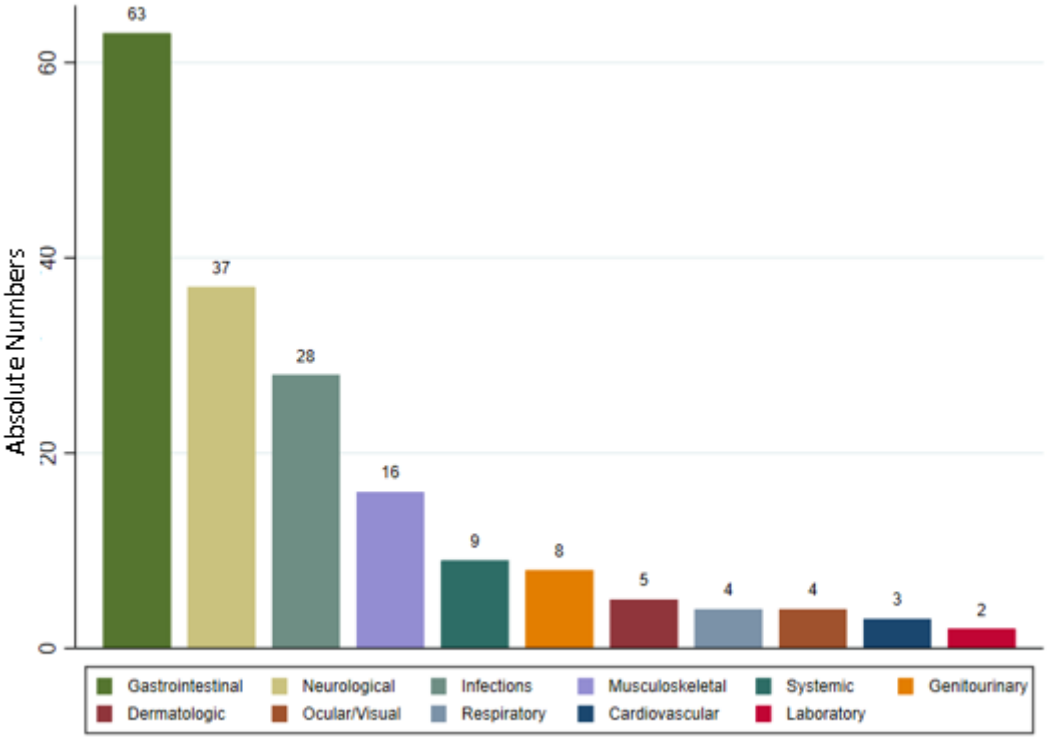
The color of the bars corresponds to the color of the organism in the legend; *N. gonorrhoeae* (red bars), *T. pallidum* (gray bars), C. *trachomatis* (blue bars), HPV: human papillomavirus, (orange bars), HSV 2: herpes simplex virus (green bars)

Supplementary Figure 3. Drug use among individuals receiving PEP.



GHB, gamma hydroxybutyrate; GLB, gamma-butyrolactone; MDMA, N-Methyl-D-aspartate.

Supplementary Figure 4. Adverse event according to Primary Organ System classification in absolute numbers.



FIFTH PIECE OF RESEARCH

Network meta-analysis of post-exposure prophylaxis randomized clinical trials

I Fernández, E de Lazzari**, A Inciarte** , V Diaz-Brito , A Milinkovic , A Arenas-Pinto , F Etcheverrry , F García , L Leal , HIV-PEP Group. HIV Med. 2020 Jan;21(1):43-52.

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SHORT COMMUNICATION

Network meta-analysis of post-exposure prophylaxis randomized clinical trials

I Fernández,[1] E. deLazzari,[1] A. Inciarte,[2] V. Diaz-Brito,[1] A. Milinkovic,[3] A. Arenas-Pinto,[3] F. Etcheverrry,[1] F. García [1,4] and L Leal on behalf of the HIV-PEP Group the HIV-PEP Group

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Objectives

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) *vs.* atazanavir (ATV) (one study), cobicistat-boosted elvitegravir (EVG/c) (one study), raltegravir (RAL) (one study) or maraviroc (MVC) (two studies). We estimated the probability of each treatment of being the best based on the evaluation of five 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.

Conclusions

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

Keywords: completion, HIV, integrase inhibitors, post-exposure prophylaxis

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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 three antiretroviral drugs (ARVs) for 28 days. To maximize the desired preventive effect, PEP compliance seems essential. Toxicity and/or side effects leading to frequent drop-outs and loss to follow-up have been frequently described during this type of treatment. Higher rates of ARV toxicity and discontinuation have been reported as a result of the use of PEP regimens when compared with people living with HIV receiving treatment with the same ARV combination. Due to ethical constraints and sample size, PEP efficacy studies cannot be performed, and therefore its prescription is based on data from animal studies [1],

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retrospective analysis of occupational PEP [2] and prophylaxis of maternal–fetal transmission [3].

Previous PEP regimens consisted on zidovudine (AZT)/lamivudine (3TC) as the backbone and a third drug, preferably a protease inhibitor (PI). As tolerability was an issue with these nucleoside reverse transcriptase inhibitors (NRTIs), more recent PEP combinations are based on a backbone, including tenofovir (TDF)/emtricitabine (FTC). Until very recently the third recommended ARV was ritonavir-boosted lopinavir (LPV/r) or atazanavir (ATV) [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 (MVC) [6] or the nonnucleoside transcriptase inhibitor (NNRTI) rilpivirine [7] have been reported, suggesting that these alternative regimens have better completion outcomes than PI. Updated guidelines (based on expert opinion) now recommend INSTIs as first-line treatment (e.g. in the UK, raltegravir; in the 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 five randomized clinical trials (RCTs) comparing different PEP regimens and reporting completion outcomes on 1105 PEP initiations [10–14].

Methods

We performed a systematic search (September 2019) of 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 two PEP three-drug regimens in adults and with reports on completion rates or discontinuation at the 28-day follow-up visit. We excluded any study that was not randomized, that compared PEP with one- or two-drug regimens, where the studied population were newborns or minors, that had inadequate data, 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 potential effect modifiers. Outcome data for completion rates at 28 days, treatment discontinuation, switching, lost to follow-up and total adverse events were collected. We accepted each study's definition of adverse events, but the different definitions of adverse events allow the comparability. Following rigorous examination, we identified six RCT candidates to include in the NMA. Nevertheless, 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.* non-occupational) and there were significantly more occupational exposures (21%) than in the other five trials which included manly non-occupational exposures [10–14]. We assumed that the threshold of tolerance and/or risk perception of health workers and men who have sex with men 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 five selected RCTs compared previous standard of care (SOC) ritonavir-boosted lopinavir (LPV/r) with a different ARV in each trial: atazanavir (ATV) [10], cobicistat-boosted elvitegravir (ELV/c) and raltegravir (RAL), and *vs.* MVC in two RCTs. 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 (ORs) 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. Values of OR <1 correspond to beneficial treatment effects of the first drug relative to the second one (the comparator). As there was only more than one RCT for comparisons that involved MVC, only the OR for MVC relative to LPV/r is a pooled estimate. For each outcome, 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 numbers of studies involved in each treatment and comparison, respectively. Ranking probabilities of each treatment being at a particular order (the best, second, third, fourth and the worst) were reported in tabular form 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 1105 PEP initiations from five RCTs, four conducted in Spain and one in England, were included in the clinical trials analysed [10–14]. The study participants in all studies were principally men (n = 941, 85%) and men who have sex with men (n = 832, 75%); 247 (22%) were non-Caucasian, 261 (24%) reported previous sexually transmitted infections (STIs) 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%), and this was an inclusion criterion in four studies. In the remaining study, 30 occupational exposures were described. A three-drug regimen was prescribed in all studies, where TDF-disoproxil/FTC was the most frequently used backbone. All studies followed European recommendations on prescription and follow-up [15].

In all, 454 (41%) PEP non-completion cases were reported for any reason. The ORs for ARVs compared with LPV/r were: 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 (Table S1; Fig. 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 = 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 sub-analysis was performed including DRV/r (see Table S6), the rankogram showed that DRV/r and EVG/c have 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 ORs for ARVs compared with LPV/r were: 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) (Table S2; Fig. 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 rates

Table 1 General characteristics of studied populations

Study_ author	Backbone	Arm	Cohort	Per_arm	Male	MSM	Non- Caucasian	PEP*	STI†	HIV test‡	HIV partner§
Leal_MRV	TDF + FTC	LPV/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	LPV/r	243	121	218	196	31	28	26	109	31
Leal_RAL	TDF + FTC	RAL		122			39	31	32	107	43
Milinkovic	TDF + FTC	LPV/r	213	106	208	200	17	41	48	96	38
Milinkovic	TDF + FTC	MVC		107			15	32	33	98	60
Inciarte	TDF + FTC	LPV/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	LPV/r	255	131	147	96	21	15			23
Diaz_Brito	AZT + 3TC	ATV		124			28	15			18

3TC, lamivudine; ATV, atazanavir; AZT, zidovudine; EVG/c, cobicistat boosted elvitegravir; FTC, emtricitabine; LPV/r, ritonavir-boosted lopinavir; MSM, men who have sex with men; MVC, maraviroc; RAL, raltegravir; TDF, tenofovir.
*Previous post-exposure prophylaxis.
†Previous sexually transmitted infection.
‡Previous HIV test.
§Known HIV-positive sexual partner.

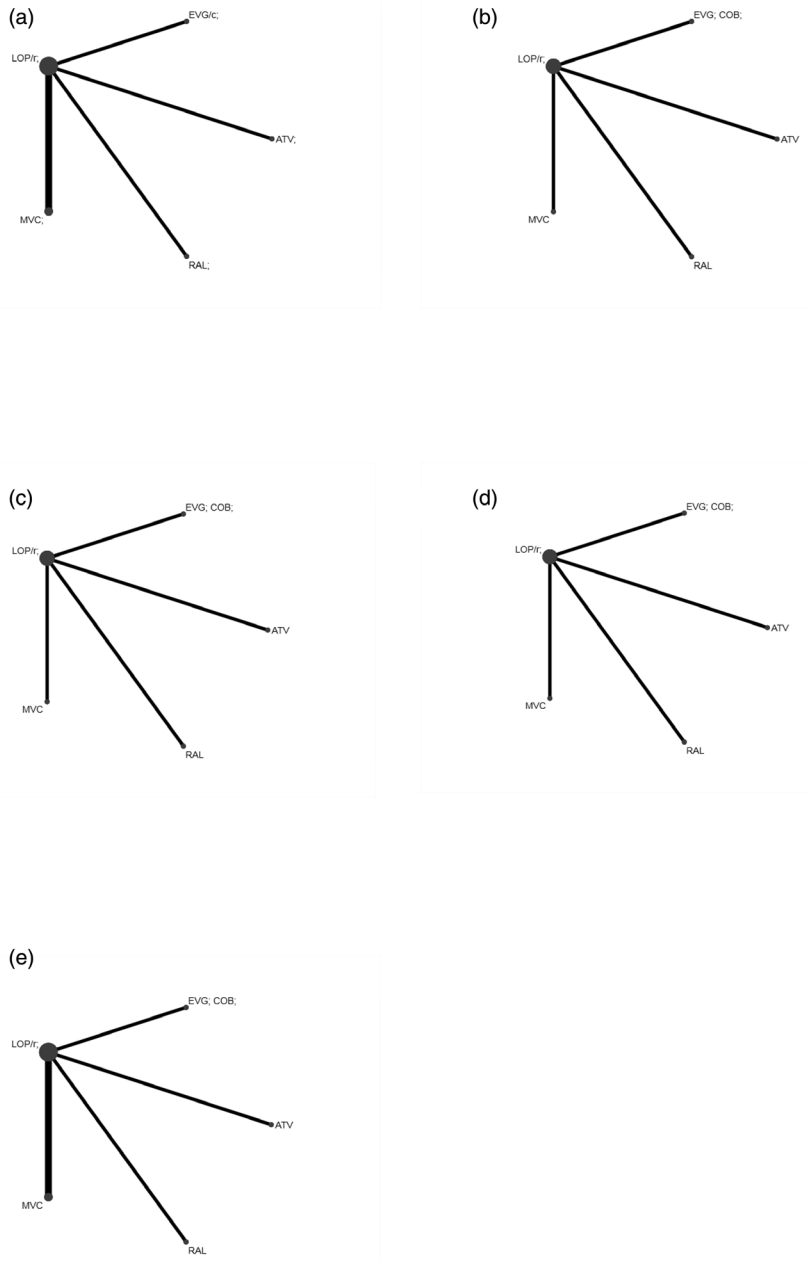

Fig. 1 Network map for post-exposure prophylaxis (PEP): (a) PEP completion at day 28; (b) PEP discontinuation due to adverse events; (c) PEP switching due to any cause; (d) PEP lost to follow-up; (e) PEP adverse events.

of switching, lost to follow-up or adverse events (79%, 100% and 98%, respectively) (Table S3–S5; Fig. 1c–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 frequently used in the past 10 years, probably because they were the less expensive option, particularly in resource-limited settings. Other ARVs prescribed as the third drug are the NNRTIs such as nevirapine that have reported more acute adverse events such as severe hepatotoxicity. When used as antiretroviral

therapy, INSTIs 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, PIs 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 five RCTs, 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, the rate of those lost to follow-up was high, ranging from 25% to 80% in French cohorts [18], and in a meta-analysis of 2014 only 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 rates lost to follow-up could be lower. When a sub-analysis 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 treated with caution given that in this study subjects were stratified by type of event (occupational *vs.* non-occupational) and there were significantly more occupational exposures (21%) than in the other five 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, which has better adherence than multiple-tablet regimens (MTRs); missing doses were frequently reported when ARVs 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 as compared with MTRs [20]. This safety profile could explain the good results in our meta-analysis.

Maraviroc was the best option in relation to discontinuation due to adverse events, and RAL and EVG/c were the second and third best options for this endpoint. Méchai *et al.* [6] 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 of between 11.7% and 21% [21,22]. Adverse events seem to be the principal cause of non-compliance, so ARVs with a good safety profile should preferably be used.

Our study has a number of limitations. First, there are only a few RCTs comparing PEP regimens, so our analysis only has information from five studies. In addition, none of the five include dolutegravir, despite this being considered a first-line option, or 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 used for PEP and shows the advantages of INSTIs over the rest of the PEP regiments, especially the EVG/c-containing regimen, which had the best completion rate at day 28.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 Treatment and corresponding ranking probabilities, mean rank and SUCRA for post-exposure prophylaxis non-completion at day 28.

Table S2 Treatment and corresponding ranking probabilities, mean rank and SUCRA for post-exposure prophylaxis discontinuation due to adverse events.

Table S3 Treatment and corresponding ranking probabilities, mean rank and SUCRA for post-exposure prophylaxis switching due to any cause.

Table S4 Treatment and corresponding ranking probabilities, mean rank and SUCRA for post-exposure prophylaxis lost to follow-up.

Table S5 Treatment and corresponding ranking probabilities, mean rank and SUCRA for post-exposure prophylaxis adverse events.

Table S6 Treatment and corresponding ranking probabilities, mean rank and SUCRA for post-exposure prophylaxis non-completion at day 28, including the study by Fatkenheuer *et al* [1] with a darunavir/ritonavir-containing regimen.

Appendix S1

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

V.- DISCUSSION

"The only way to do great work is to love what you do." - Steve Jobs

"We cannot solve our problems with the same thinking we used when we created them." -

Albert Einstein

Post-exposure Prophylaxis is a well-known preventive strategy and is widely prescribed in case of a potential risk of HIV acquisition.

There are several differences between guideline recommendations that make its prescription difficult. Side effects, low adherence, discontinuations, lack of retention in care, and no universal access limit its efficacy. Overcoming challenges and improving limitations is a priority to achieve preventive effectiveness.

Improving access to PEP and to better tolerated and simpler regimens promote linkage to care, and prompt diagnosis of HIV infection are top priorities in this field. Recently there have been several changes in PEP recommendations to overcome challenges, guarantee effectiveness, and limit possible risks.

Here It is explained an overview of each article's key elements that summarize the discussion's more relevant facts

In the first article of this thesis **(Inciarte et al)**, we select sexual assault victims as the study population. Sexual assault victims with potential exposure to HIV are a particular population among the PEP users not only due to the nature of the population itself (stigma, self-rejection, blame, and barriers to disclosure) and the poorly standardized attention of their care (underreporting, and neglection), factors that might also conditionally lower the proportion of PEP completion (203-205).

In the second study **(Inciarte et al)** we report the first prospective trial using an TDF/FTC/EVG/c STR for PEP comparing the LPV/r + TDF/FTC standard of care in all guidelines until 2015 and is still a preferred regimen in the guideline that covers low-income countries due to its availability.

In the third study **(Inciarte et al),** we evaluated the effect of infectivity on human rectal explants, the pharmacokinetics and the immunological impact. Since no study in humans can be achieved to assess PEP efficacy due to methodological difficulties and ethical concerns. We have to rely on animal models and ex-vivo models. Few studies assess PK/PD dynamics on rectal tissues of different ART used for PEP, and most studies are derived from PrEP research.

For the fourth study **(Inciarte et al),** the use DOR In a single ARM clinical trial on mostly MSM population, DOR is a drug formulated as an STR, and post-marketing information regarding safety and tolerability remains undefined for PEP users .

The last manuscript of this doctoral thesis involves a network meta-analysis of the main clinical trials of PEP available so far **(Fernandez et al),** This study examined five randomized clinical trials; 4 of them were conceived in the same center, in different historical timelines but with similar follow-up patterns.

The first objective: *"To determine the fundamental traits of diverse PEP user groups residing in Barcelona and to analyze the frequency of other STIs and risk factors that render them eligible for PEP treatment."* Three articles were designated (Article Nº 1, Nº2, and Nº4), all of which share the common goal of describing a group of post-exposure prophylaxis users residing in Barcelona.

In comparing STRIBPEP (Article 2) and DORAVIPEP (Article 4), both of which focus on MSM populations, there are several demographic, HIV acquisition risk, ethnicity, and gender similarities, as well as some differences in age and time from exposure until PEP initiation. Article 1, on the other hand, examines a sexual assault population and is distinct in demographics and HIV acquisition risk.

STRIBPEP and DORAVIPEP trials share similarities in demographics, with both studies focusing on MSM populations. The median age in DORAVIPEP were similar slightly younger than reported in STRIBPEP, and predominantly male populations. With high proportion of MSM population for both trials, these results are similar to previous studies performed in MSM population (109-112). In contrast, sexual assault victims were a younger and predominantly female, reflective of the sexual assault context.

Ethnically, populations from DORAVIPEP and STRIBPEP have similar compositions, with most participants being of European descent and caucasian. Latin Americans make up for most of the participants in the DORAVIPEP and STRIBPEP trials, while non-Europeans in the sexual assault victims were mainly from Latin America. This highlights the diverse ethnic backgrounds in these study populations, which may influence HIV risk factors and prevention strategies, and concerns about the care linkage in more vulnerable populations.

Regarding the time from exposure until PEP initiation, there is a difference between the MSM population from STRIBPEP and DORAVIPEP trials, reporting a day from the exposure to treatment initiation, while sexual assault victims had a shorter time of just 13 hours. This discrepancy in initiation times could impact the efficacy of PEP, as earlier administration generally leads to better outcomes (65). One possible explanation for the shorter initiation time in the sexual assault population is the presence of a center with a historical and standardized multidisciplinary approach for sexual assault victims. Held by forensics, gynecology, infectious diseases specialists, and psychiatric specialists, could streamline the process of PEP initiation, ensuring that sexual assault victims receive treatment as soon as possible.

A significant proportion of sexual assault victims refuse to initiate PEP in our study despite of having indication, sexual assault victims with potential exposure to HIV are a particular population among the PEP users not only due to the nature of the population itself (stigma, self-rejection, blame, and barriers to disclosure) and the poorly standardized attention of their care (underreporting, and neglection) , factors that might also conditionally lower the proportion of PEP completion (203-205).

Factors influencing PEP initiation in sexual assault victims include appreciable risk, multiple perpetrators, loss of consciousness, alcohol consumption, substance abuse disorder, psychiatric disorders, unknown assailants, being European, and living in Catalonia. These factors highlight the complexities surrounding PEP prescription in this population and emphasize the need for healthcare providers to consider various individual and contextual factors when deciding whether to initiate PEP in sexual assault victims. A discussion of these

factors provides insights into the circumstances that influence healthcare providers' decisions to prescribe PEP and the unique challenges this population faces.

An appreciable risk of HIV transmission was a decisive factor associated with PEP initiation, with greater proportion of those receiving PEP experiencing appreciable risk compared to those not receiving PEP. This finding indicates that healthcare providers prioritize prescribing PEP to those with a higher risk of HIV acquisition due to the nature of the exposure.

Multiple perpetrators, another factor associated with PEP initiation, could increase the risk of HIV transmission due to potential increased exposure to different sources of infection. Loss of consciousness is another factor that might contribute to uncertainty about the nature of the assault and increase the perceived risk of HIV acquisition, thus leading to PEP prescription.

Unknown assailants represent a significant factor in PEP initiation, as the HIV status of the perpetrator may be uncertain, increasing the perceived risk of transmission. Alcohol consumption and substance abuse disorder could impair the victim's ability to consent or recall the details of the assault, further contributing to the decision to initiate PEP. Psychiatric disorders might also play a role in the vulnerability of victims and the perceived risk of HIV transmission.

Also, Previous STIs and PEP use were factors associated with seroconversion in a study published in our center (167). Previous STIs and PEP use are in half, and a third of the DORAVIPEP and STRIBPEP trials, suggesting that these MSM populations may benefit from initiating PrEP according to Spanish guidelines to reduce their risk of HIV acquisition (226).

Conversely, the sexual assault population may require different interventions tailored to their unique circumstances and needs.

STRIBPEP and DORAVIPEP participants exhibit similarities in their MSM populations, demographics, HIV acquisition risk, ethnicity, and gender, with some differences in age and time from exposure until PEP initiation. The substantial proportion of participants with previous STIs and PEP use in these studies indicates the potential need for PrEP initiation in these at-risk populations. In contrast, the sexual assault population represents a distinct demographic requiring targeted intervention strategies.

For the second objective: *"To assess the effects of different PEP treatment regimens on pharmacokinetics, pharmacodynamics, and immune homeostasis in order to prevent ex-vivo infection".* This article describes an ex-vivo model, developed in collaboration with international molecular biology and biology research teams, for evaluating the efficacy of PEP, on different regimens.

The main problem with PEP is that it needs an adequate model to validate human efficacy. No study in humans can be achieved to assess PEP efficacy due to methodological difficulties and ethical concerns. We have to rely on animal models and ex-vivo models. Few studies assess PK/PD dynamics on rectal tissues of different ART used for PEP, and most studies are derived from PrEP research.

Knowing the PK/PD profile is critical to determine, at least hypothetically, the window of effectivity of PEP; as demonstrated in previous macaque studies, the time from SIV inoculation to PEP initiation determines the level of protection (65). In this study, we

evaluated the effect of Infectivity on human rectal explants, the pharmacokinetics, and the immunological impact.

As a result, Infectivity was not evaded in this model despite adequate levels in rectal tissue with a good penetration ratio from RT/BP. More interestingly, EVG plasma levels exceeded those from LPV. In both treatments, ex-vivo infection was not avoided. In contrast, in another study performed in our center, Individuals who received twice-daily MVC for PEP displayed a decline in viral replication in ex-vivo RT explants. At the same time, no such decrease was observed in the LPV/r or RAL arms.

While ex-vivo models can give supplementary information about a drug effect, it does not correlate totally with a human model (217). Regarding animal models, previous PK analyses in macaques revealed that EVG concentrations in rectal fluids without COBI exceeded the PA-IC90 for up to 48h and were acceptable to stop SHIV infection *in vitro*. This study evaluated PK concentrations in rectal tissue between macaques and humans; EVG, FTC, and TFV concentrations were also similar between macaques and humans. Both groups initiate treatment 24h before analysis (218). In our study, we evaluated EVG as part of PEP follow-up. In contrast, we calculated EVG levels at initiation at 24 days of treatment in a larger population group.

Regarding LPV/r, no discrepancies were found in inflammation and activation markers in the blood, as previously reported (219,220). But there was a significant increase of activation markers in blood samples in the EVG arm. It might be expected that with a higher immune activation, HIV acquisition can be facilitated (221).

Our study has several limitations. Owing to the nature of enrollment, we lacked accurate baseline samples, and the potential impact of HIV risk exposure on immunology and subsequent results cannot be ignored. Additionally, there were differences in baseline immune markers between the arms. The ex-vivo HIV infection was performed in cryopreserved rectal tissue, raising concerns that frozen samples may not yield reliable infectivity data. While participants began PEP at various times, including midnight, and all tests were performed in the morning, we obtained a wide range of concentrations across different tissues.

Moreover, no previous studies in RF are available to compare our results, and the amount of mucosal lining fluid on the sponges differed among participants. Given this variability, drawing firm conclusions is complex, and caution is necessary. Further research is needed to confirm our findings.

Despite these findings, EVG had a good tolerability profile, but further research is needed to validate PEP efficacy with this treatment in experimental models.

The Third objective: "*To calculate the rates of PEP non-completion for various treatment regimens among different risk groups."* This considers the completion rates of five head-to-head clinical trials, one derived from Article No. 2, a network meta-analysis from Article No. 5, and a single-arm clinical trial from Article No. 4.

This discussion aims to compare different studies on patient populations regarding PEP completion rates, considering the nature of the studies and the populations involved. The

STRIBPEP and DORAVIPEP studies are clinical trials, while the sexual assault victim population represents a different context.

In the STRIBPEP study, a modified ITT analysis focusing on patients who attended day 1 revealed that PEP non-completion was higher in the LPV/r arm compared to the EVG/c arm. Similarly, the DORAVIPEP study reported a PEP non-completion rate similar to EVG/c arm from the STRIBPEP study, in both ITT analysis, while this was a single-arm analysis, not a head-to-head study as STRIBPEP, which can impact the reliability of the comparisons made between them, on contrast, the study populations in both studies are similar in terms of demographic characteristics. The meta-analysis (Fifth article) of five RCTs suggested that EVG/c-based PEP demonstrated the lowest treatment non-completion rate by day 28, followed by MVC, RAL, and ATV-based combinations. At the same time, data from the metanalysis might differ in the case of MVC from being pooled data.

For the STRIBPEP study PEP non-completion rate was in the spectrum of non-completion rates for other newly authorized STRs when used for PEP (121,123,213). Furthermore, different single-center evaluations of TDF/FTC/EVG/c as STR reported PEP non-completion ranging from 33% to 8%. The completion rate of PEP with TDF/FTC/EVG/c was similar to data from TAF/F/EVG/c and DTG+TDF/FTC from other studies (124,214). Terminating the 28-day course of PEP is a challenge to the efficacy of PEP for HIV prevention. PEP non-completion was not attributed directly to /TDF/FTC /EVG/cbut primarily to a loss of follow-up, which is expected with other PEP regimens (109).

In contrast, the PEP non-completion rate at day 28 for sexual assault victims was substantially higher, at 61%. This difference in completion rates between clinical trials and

the sexual assault population can be attributed to several factors. First, clinical trials, such as STRIBPEP and DORAVIPEP, typically have higher retention in care due to the nature of the study design and the close monitoring of participants. This increases the likelihood of patients adhering to and completing the PEP regimen. Conversely, sexual assault victims may face challenges that hinder their ability to complete the PEP regimen, such as emotional trauma, difficulty accessing healthcare services, or limited support systems. Second, the populations involved in the clinical trials and the sexual assault study are different, with the latter group experiencing unique circumstances that may affect PEP completion rates. Factors like mental health, stigma, and fear of retribution may negatively impact adherence to PEP in the sexual assault population. Third, it is essential to consider the differences in PEP regimens between the clinical trials (STRIBPEP and DORAVIPEP) and the sexual assault victim population. The latter group, which comes from historical controls, predominantly receives PI treatments. These PI-based regimens are often considered less tolerable than the newer regimens investigated in the STRIBPEP and DORAVIPEP trials

comparing PEP completion rates across different studies, and patient populations reveal that clinical trials like STRIBPEP and DORAVIPEP generally report higher completion rates due to the nature of the study design and patient care. In contrast, sexual assault victims face unique challenges, resulting in lower PEP completion rates. Therefore, it is crucial to consider the context and patient populations when interpreting and comparing PEP completion rates in various studies.

The Fourth objective: "*To identify the factors linked to non-completion of PEP treatment with various regimens among diverse risk groups.*" Two clinical trials (Articles No. 2 and No.

4) and a large cohort of female sexual assault victims (Article 1) underwent multivariate analysis for PEP non-completion.

The comparison of PEP non-completion factors across three studies - a head-to-head study (STRIBPEP), an open-label single-arm study (DORAVIPEP), and a retrospective study in sexual assault victims - provides valuable insights into the challenges faced by different populations in adhering to PEP regimens.

In the retrospective study of sexual assault victims, factors independently associated with PEP non-completion included low-risk perception, previous aggression, a known aggressor, and a positive test result for cocaine. Interestingly, the specific PEP treatment group was not associated with PEP non-completion. This suggests that factors related to the individuals experiences, perception of risk, and substance use may play a more significant role in their adherence to PEP.

The DORAVIPEP study found that younger age was the only independent factor associated with PEP non-completion in the multivariable logistic regression model that included all enrolled patients. When restricting the sample to patients who attended at least one visit after enrollment, younger age and the emergence of any AE during PEP were the independent factors associated with non-completion. These findings indicate that age and the occurrence of AEs may be crucial in influencing adherence to PEP regimens.

This and previous studies highlight the role of age and risk perception in determining PEP adherence. In the STRIBPEP study, independent factors associated with higher PEP non-completion were age below the median, low-risk exposure, and previous PEP, as stated in previous studies (111,112). Furthermore, previous PEP experience may affect individuals

willingness to complete the treatment, potentially due to their prior experiences with side effects or challenges in adherence.

The comparison of PEP non-completion factors across the three studies reveals that age, risk perception, and the occurrence of adverse events are common factors influencing adherence to PEP regimens. However, each study population faces unique challenges, such as experiences of aggression or substance use in the sexual assault victim population. Understanding these factors can help inform targeted interventions to improve PEP adherence and completion rates in different populations.

The Fifth objective: *"Analyze the adverse event, adherence, and follow-up rates of post-exposure prophylaxis treatment using different regimens".* Based on the secondary objectives of four out of the five articles from this doctoral thesis, namely No. 1, No. 2, No. 4, and No. 5.

The different treatment regimens of PEP across the sexual assault study, STRIBPEP, DORAVIPEP, and the meta-analysis, it is essential to compare the AEs and discontinuation rates among the various regimens.

In the sexual assault study, AEs were more common in LPV/r group compared to the ATV group, with gastrointestinal symptoms being the most frequently reported. The STRIBPEP trial also found AEs to be significantly more common in the LPV/r arm than the EVG/c arm, with non-adherent patients experiencing more AEs than adherent patients. These findings suggest that LPV/r may have a higher incidence of AEs compared to other regimens, potentially affecting adherence and completion rates.

Concerns about safety and tolerance between different ART used for PEP regimens exist. Most clinical data on ART tolerance and safety derives from PLWH and the predominantly male population (208,209). However, there is evidence of greater discontinuation rates due to toxicities in Women LWH (210,211,212), so previous clinical data on the safety and pharmacology of the more commonly PEP regimens are not fully described in females, considering that most PEP cohorts are predominantly male. With over 90% of the individuals in our cohort being women, adverse events were reported in 65% of individuals, which is consistent with findings in male PEP users. However, when compared to similar regimens used by the MSM population, PEP discontinuation rates due to toxicity were higher (121,122). Differences in BMI, hormonal levels, and body fat distribution in women suggest that there may be distinct PK/PD dynamics, which cannot be dismissed and require further investigation.

In the STRIBPEP trial adverse events were only collected in patients who attended at least one day, reported by 59% of patients; equivalent results were observed in a French open-label single-arm study in 68% and 59% of the participants receiving EVG/c/F/TAF on days 14 and 28 (214). A high frequency of mild adverse events was observed and adverse event rates were higher in PEP users than in individuals with HIV (215).

The upheaval of newer regimens that are better tolerated, using a tenofovir backbone and INSTIs, has been associated with increased levels of tolerability. (216) This allows justifying the higher regimen completion rates in this study. In addition to better-tolerated regimens, another purpose of PEP is to make the regimens as simple as possible. In this study, 64% of individuals completed the STR regimen as prescribed. also, LPV/r+TDF/FTC, an MTR

regimen, had been associated with lower adherence and more adverse events when compared with EVG/c/TDF/FTC, which suggests that STR may be more than MTR to provide better-tolerated regimens for PEP (110).

The DORAVIPEP trial reported AEs in 31% of patients, with gastrointestinal, neurological, and musculoskeletal symptoms being the most common. Although the incidence of AEs was lower in the DORAVIPEP trial than in the sexual assault descriptive cohort and the STRIBPEP trial, reflecting different study populations with different drugs and timelines. Discontinuation due to AEs accounted for a small percentage of overall PEP non-completion. These results are consistent with the drive ahead study; the summary of Clinical AE at Week 96 reported at least 30% of AE related to the drug with 3% of discontinuation (223); in our study, lower ratios of adverse event and treatment discontinuation were observed may be due to the short-term treatment (28 days), in contrast with previous studies that reported a higher occurrence of an adverse event in PEP users than HIV positive patients (224,225).

After conducting a meta-analysis of five randomized controlled trials (RCTs), we discovered that EVG/c-based PEP was the best option considering treatment non-completion by day 28 and was more likely to be ranked the best option concerning almost all of the secondary endpoints: PEP switching due to any cause lost to follow-up and adverse events. TDF/FTC + EVG/c STR has better adherence to MTRs; missing doses were reported more with two daily dosing than with Quad dosing. The meta-analysis provides a comparative overview of treatment discontinuations due to AEs among different antiretroviral regimens. Compared to LPV/r, the odds ratios (ORs) for discontinuation with other regimens like ATV, EVG/c, RAL,

and maraviroc MVC were lower, suggesting that these alternative regimens may be better tolerated and potentially lead to improved adherence.

A recent study in which a Fixed-dose combination of TDF/FTC + EVG/c was safe and well tolerated for PEP, with higher regimen completion rates than more frequently dosed PEP regimens (213). MVC, RAL, and ATV-based combinations followed closely behind. On the other hand, the discontinuation rate was highest for the LPV/r regimen.

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MVC, RAL, and ATV-based combinations followed closely behind. On the other hand, the discontinuation rate was highest for the LPV/r regimen.

MVC was the best option concerning discontinuation due to adverse events, and RAL and EVG/c were the second and third best options for this endpoint. All RCTs showed in HIV-positive individuals an excellent safety profile for maraviroc; based on the findings from RCTs, no relevant toxicities and co-morbidities have been described (229). This is especially important in terms of treatment discontinuation, a well-known problem among PEP regimens. No clinical trials or prospective studies have been done after the publication of this article; there is a publication about HCW that tolerated MVC as a PEP regimen (151).

The comparison of PEP regimens across the different studies reveals that LPV/r is associated with higher rates of AEs, particularly gastrointestinal symptoms. Alternative regimens like ATV, EVG/c, RAL, and MVC may be better tolerated, leading to improved adherence and

completion rates. The impact of AEs on PEP adherence should be considered when selecting the most appropriate regimen for different patient populations, as better-tolerated regimens may increase the likelihood of PEP completion and ultimately contribute to better patient outcomes.

These studies' limitations are the lack of external validity because most clinical trials come from the same center; they are not multicenter studies. We had no clinical trials comparing head-to-head STR with II as a third agent. Moreover, the five options under consideration do not include DTG, which is currently considered a first-line treatment, or BIC, which has been scarcely evaluated for PEP, with few studies including very small sample size and a single-arm design that may differ from the study design used in the current meta-analysis (125, 230).

Our study findings demonstrate the superiority of INSTIs compared to other PEP regimens, particularly the EVG/c-containing regimen, which exhibited the highest completion rate by day 28. Therefore, our study concludes that INSTIs are more advantageous for PEP than other regimens.

The next step in PEP research would be a randomized study assessing tolerability profiles, completion rates, and treatment discontinuation with a double-blind design consisting of an STR regimen using II as a third agent. Another consideration, while there is not enough research still, tenofovir alafenamide as a backbone also offers, at least theoretically, higher intracellular levels of the drug, which might protect against infection.

It is still necessary to perform more animal models of PEP efficacy in terms of time from risk. A crucial point in PEP effectivity is determining hazard ratios of HIV infection upon PEP

initiation times in experimentally exposed animals; it has been suggested that a time frame is essential to avoid infection that might differ from each molecule and the ex-vivo model for future models to validate animal models further. The upcoming molecules as long-acting agents that can be used as PrEP and PEP might improve adherence outcomes shortly, one of the most significant handicaps in PEP studies, still under development in phase II clinical trials.

VI.- CONCLUSIONS

"All's well that ends well." - William Shakespeare

"We do not need magic to transform our world. We carry all of the power we need inside ourselves already." - J.K. Rowling

1.- Completion rates for sexual assault PEP were low (<40%). ATV/r was better tolerated than LOP/r, RAL had lower discontinuation rates than LPV/r, and EVG was better tolerated than LPV/r. Appropriate selection of PEP regimens may improve adherence and tolerability in sexual assault victims, with important implications for HIV prevention. In sexual assault PEP, completion rates were low (<40%). LPV/r was less well-tolerated than ATV/r, and LPV/r had higher discontinuation rates than RAL and EVG.

2- PEP regimen with EVG had better adherence rates than a regimen with LPV/r following sexual exposure. The superior tolerability, safety, and adherence of EVG compared to LPV/r supports the recommendation to consider it as the first choice for PEP. These findings have important implications for the prevention of HIV transmission and should be considered when selecting a PEP regimen after sexual exposure.

3.- EVG/c and LPV/r levels in plasma and rectal tissue compartments were correlated, and neither PEP regimen prevented ex vivo infection on human rectal explants after 28 days of treatment. However, further research is needed to validate these findings in larger and more diverse populations.

4.- DOR/3TC/TDF maintained high completion rates and had low adverse events among PEP users. Additionally, DOR/3TC/TDF had high self-reported adherence levels and was well-tolerated as a once-daily PEP regimen.

5.- EVG/c as the third agent had the highest probability of being the most beneficial treatment for the lowest rates of PEP non-completion, loss to follow-up, adverse events, and discontinuations due to adverse events. Additionally, our results showed that MVC as the third agent held the highest probability of being the best treatment for PEP discontinuations due to adverse events

VII.- REFERENCES

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"We are what we repeatedly do. Excellence, then, is not an act, but a habit." - Aristotle

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