

XI CURSO DE ANTIBIOTERAPIA 2017 ACTUALIZACIÓN EN INFECCIÓN POR VIH

Son Espases, 30 de Marzo de 2017

Profilaxis Pre-Exposición (PrEP) y Post-Exposición (PEP)

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Number of HIV diagnoses reported by year of diagnosis and cumulative number of HIV diagnoses in the EU/EEA and the WHO European Region, 1984–2011



European Centre for Disease Prevention and Control/WHO Regional Office for Europe. HIV/AIDS surveillance in Europe 2011. Stockholm: European Centre for Disease Prevention and Control; 2012. http://ecdc.europa.eu/en/publications/Publications/20121130-Annual-HIV-Surveillance-Report.pdf

Tasas de nuevos diagnósticos de VIH anuales totales y según sexo. España*, 2009-2014 Datos corregidos por retraso en la notificación



Tasa de nuevos diagnósticos de VIH anuales según modo de transmisión. España*, 2009-2014 Datos corregidos por retraso en la notificación



4

Tasas de nuevos diagnósticos de VIH en HSH, por año de diagnóstico y grupos de edad España*, 2009-2014. Datos corregidos por retraso en notificación



Número y porcentaje de nuevos diagnósticos de VIH en personas de otros países de origen. España*, 2009-2014. Datos no corregidos por retraso en la notificación



Tasa de nuevos diagnósticos de VIH anuales por modo de transmisión y lugar de origen. España*, 2009-2014. Datos corregidos por retraso en la notificación



HOMBRES

Tasa de nuevos diagnósticos de VIH anuales por modo de transmisión y lugar de origen. España*, 2009-2014. Datos corregidos por retraso en la notificación



MUJERES

Comunidad de Madrid Nuevos diagnósticos VIH (2007-2014)

	Hombres		Mujeres			40,0
	n	%	n	%	Total	35,0 30,0 27,9 35,2 35,2 33,2
2007	821	81,4	188	18,6	1009	25,025,2 25,2 25,2
2008	1086	83,0	223	17,0	1309	20,9 20,3 20,8 19,0
2009	1089	84,1	206	15,9	1295	16,5
2010	1143	85,0	202	15,0	1345	10,0
2011	1040	84,4	192	15,6	1232	5,0
2012	930	86,5	145	13,5	1075	0,0
2013	787	87,6	111	12,4	898	2007 2008 2009 2010 2011 2012 2013 2014
2014	782	88,3	104	11,7	886	Hombre — Mujer — Total
Total	7678	84,8	1371	15,2	9049	*Años 2013/14 no consolidados.

* Años 2013/14 no consolidado

- Fallecidos 270 (3%)
- 1443 (15,9%) han desarrollado alguna enfermedad diagnóstica de sida

Incidencia CM (07-14):

- Total: 17,7 x 100.000
- Hombres: 31,1 x 100.000
- Mujeres: 5,2 x 100.000

HIV Prevention:

Opportunities for biomedical interventions



High levels of coverage with ART and PrEP would be needed for eradication

- A mathematical model was used to predict the effect of public health policies incorporating ART and PrEP on the basic reproductive number (R0) of the HIV epidemic in South Africa
- The HIV eradication threshold was only reached in the scenario:
 - 96% effective ART + 75% effective PrEP (assuming 70% PrEP coverage)
- The eradication threshold was not reached assuming conservative estimates of effectiveness for ART (73%) and PrEP (55%)



HIV prevention pyramid



Fauci A. IAC 2012. Abstract MOPL0101

Antiretrovirals available in 2016



NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PK, pharmacokinetic Adapted from http://www.aidsmeds.com/list.shtml and each product's eMC SPC available at http://www.aidsmeds.com/list.shtml and each product's eMC SPC available at http://www.medicines.org.uk/emc/search

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NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PK, pharmacokinetic Adapted from http://www.aidsmeds.com/list.shtml and each product's eMC SPC available at http://www.aidsmeds.com/list.shtml and each product's eMC SPC available at http://www.medicines.org.uk/emc/search

Profilaxis Pre-Exposición (Prep) Fundamentos

- Datos en primates no humanos
- Estudios farmacocinéticos que muestran que tenofovir y emtricitabina se concentran en secreciones genitales
- Modelos matemáticos que sugieren que, si se encontrara una profilaxis pre-exposición capaz de disminuir el riesgo un 90%, en 10 años se evitarían en África 3,2 millones de infecciones
- Éxitos previos en prevención de transmisión mediante tratamiento (prevención de transmisión vertical)



PrEP Trials Past and Present





ATN - Adolescent Trial Network; CAPRISA - Centre for the AIDS Programme of Research in South Africa; CDC - US Centers for Disease Control and Prevention: FTC - emtricitabine: IAVI - International AIDS Vaccine Initiative; MTN - Microbicide Trials Network; TDF - tenofovir disoproxil fumarate; VOICE - Vaginal and Oral Interventions to Control the Epidemic



Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women

Quarraisha Abdool Karim,^{1,2,4}; Salim S. Abdool Karim,^{1,2,3,4} Janet A. Frohlich,¹ Anneke C. Grobker,¹ Cheryl Barter,¹ Leila E. Mansoor,¹ Ayesha B. M. Kharsany,³ Sengeziwe Söbeko,¹ Koleka P. Mlisana,¹ Zaheen Omar,¹ Tanuja N. Gengiah,¹ Silvia Maarschalk,² Natasha Arulappan,¹ Mukelisiwe Mlotshwa,¹ Lynn Morif,⁵ Douglas Taylor,⁷ on behalf of the CAPIKIS AO4 Trial Groupt

0.20 12hrs 0.18 **Probability of HIV infection** Placebo 0.16 0.14 **p=0.017** 0.12 **Tenofovir** 0.10 0.08 0.06 PRISA 0.04 0.02 0.00

CAPRISA 004: HIV infection rates

Months of follow-up	6	12	18	24	30
Cumulative HIV endpoints	37	65	88	97	98
Cumulative women-years	432	833	1143	1305	1341
HIV incidence rates (Tenofovir vs Placebo)	6.0 vs 11.2	5.2 vs 10.5	5.3 vs 10.2	5.6 vs 9.4	5.6 vs 9.1
Effectiveness (p-value)	47% (0.069)	50% (0.007)	47% (0.004)	40% (0.013)	39% (0.017)

Partners Study: Primary efficacy results







PrEP for HIV prevention in men who have sex with men Efficacy (MITT) 44% (15-63%) Infection Numbers: 64 – 36 = 28 averted



iPrEX: Change in BMD from Baseline





Morbidity and Mortality Weekly Report

January 28, 2011

Interim Guidance: Preexposure Prophylaxis for the Prevention of HIV Infection in Men Who Have Sex with Men

BOX. CDC interim guidance for health-care providers electing to provide preexposure prophylaxis (PrEP) for the prevention of HIV infection in adult men who have sex with men and who are at high risk for sexual acquisition of HIV

Before initiating PrEP

Determine eligibility

- Document negative HIV antibody test(s) immediately before starting PrEP medication.
- Test for acute HIV infection if patient has symptoms consistent with acute HIV infection.
- Confirm that patient is at substantial, ongoing, high risk for acquiring HIV infection.
- Confirm that calculated creatinine clearance is ≥60 mL per minute (via Cockcroft-Gault formula).

Other recommended actions

- Screen for hepatitis B infection; vaccinate against hepatitis B if susceptible, or treat if active infection exists, regardless of decision about prescribing PrEP.
- Screen and treat as needed for STIs.

Beginning PrEP medication regimen

- Prescribe 1 tablet of Truvada* (TDF [300 mg] plus FTC [200 mg]) daily.
- In general, prescribe no more than a 90-day supply, renewable only after HIV testing confirms that patient remains HIV-uninfected.
- If active hepatitis B infection is diagnosed, consider using TDF/FTC for both treatment of active hepatitis B infection and HIV prevention.
- Provide risk-reduction and PrEP medication adherence counseling and condoms.

Follow-up while PrEP medication is being taken

- Every 2–3 months, perform an HIV antibody test; document negative result.
- Evaluate and support PrEP medication adherence at each follow-up visit, more often if inconsistent adherence is identified.
- Every 2–3 months, assess risk behaviors and provide riskreduction counseling and condoms. Assess STI symptoms and, if present, test and treat for STI as needed.
- Every 6 months, test for STI even if patient is asymptomatic, and treat as needed.
- 3 months after initiation, then yearly while on PrEP medication, check blood urea nitrogen and serum creatinine.

On discontinuing PrEP (at patient request, for safety concerns, or if HIV infection is acquired)

- Perform HIV test(s) to confirm whether HIV infection has occurred.
- If HIV positive, order and document results of resistance testing and establish linkage to HIV care.
- If HIV negative, establish linkage to risk-reduction support services as indicated.
- If active hepatitis B is diagnosed at initiation of PrEP, consider appropriate medication for continued treatment of hepatitis B.

PrEP Pre-Exposure Prophylaxis for HIV Prevention

PrEP is when uninfected individuals take HIV treatment medications PRIOR to exposure to protect against HIV infection.

In a recent study funded by the National Institutes of Health, it was determined that HIV negative gay men who took a daily dose of a drug called Viread, alone or in combination with Truvada over a period of 14 months, reduced their chances of contracting HIV by 44%.

Individuals who took their medication as recommended - 100% of the time - had a 92% reduction in their chances of contracting HIV.

It should be noted that the medication needs to be in the body at least 24 hours prior to any potential exposure. PrEP is not as effective if it is taken immediately prior to exposure.

For now, PrEP is a potentially important prevention approach being studied today. But it is important that we continue to promote HIV prevention education, consisently use condoms, regularly test for HIV, and have open dialogue with partners about their HIV status, to help end this epidemic.

For more information, please visit www.gmhc.org or call the GMHC helpline at 1-800-243-7692.





 For couples initiating ART at enrollment, PrEP is offered through 6 months, then stopped:



 For couples in which the infected partner delays or declines ART, PrEP is continued until 6 months after ART initiation:





Participant Characteristics

 Between Nov 2012 and Aug 2014, 1013 couples were enrolled. Characteristics are consistent with elevated HIV risk:

Characteristic	% or median (IQR)
Gender, HIV- partner	33% female / 67% male
Age	Median 30 years (IQR 26-36), with 20% <25 years
No children with study partner	56%
Unprotected sex in the prior month	65%
CD4 count, HIV+ partner	Median 436 (IQR 272-638), with 41% >500 cells/µL
Plasma HIV RNA, HIV+ partner	Median 37,095 (IQR 7058-104,462), with 41% >50,000 copies/mL





HIV Incidence

 The observed incidence is a 96% reduction compared to expected, a result that was highly statistically significant











Main endpoints in Pilot: recruitment and retention From April 2014: HIV infection in first 12 months

Individual incident HIV infections



HIV Incidence

Group	No. of	Follow-	Incidence	90% CI
	infections	up (PY)	(per 100 PY)	
Overall	22	453	4.9	3.4-6.8
Immediate	3	239	1.3	0.4-3.0
Deferred	19	214	8.9	6.0-12.7

Efficacy =86% (90% CI: 58 – 96%) **P value** =0.0002

Rate Difference =7.6 (90% CI: 4.1 – 11.2) **Number Needed to Treat** =13 (90% CI: 9 – 25)



- 3 of 6 individuals who were seroconverting around baseline (immediate group) or month 12 (deferred group) developed M184V/I mutations (as a mixture with wild type)
- K65R was not detected



Reported sexual behaviour (preliminary)

Anal sex partners in last 90 days BASELINE n=539	Immediate Median (IQR)	Deferred Median (IQR)
Total number of partners	10.5 (5-20)	10 (4-20)
Condomless partners, participant receptive	3 (1-5)	2 (1-5)
Condomless partners, participant insertive	2.5 (1-6)	3 (1-7)

Anal sex partners in last 90 days MONTH 12 n=349	Immediate Median (IQR)	Deferred Median (IQR)
Total number of partners	10 (3-24)	8 (3-15)
Condomless partners, participant receptive	3 (1-8)	2 (1-5)
Condomless partners, participant insertive	3 (1-8)	3 (1-6)









Double-Blinded Randomized Placebo-Controlled Trial



* Counseling, condoms and gels, testing and treatment for STIs, vaccination for HBV and HAV, PEP

- End-point driven study : with 64 HIV-1 infections, 80% power to detect a 50% relative decrease in HIV-1 incidence with TDF/FTC (expected incidence: 3/100 PY with placebo)
- Follow-up visits: month 1, 2 and every two months thereafter

Ipergay : Event-Driven iPrEP





Baseline Characteristics



Characteristics (Median, IQR) or (n, %)	TDF/FTC n = 199	Placebo n = 201
Age (years)	35 (29-43)	34 (29-42)
White	190 (95)	184 (92)
Completed secondary education	178 (91)	177 (89)
Employed	167 (85)	167 (84)
Single	144 (77)	149 (81)
History of PEP use	56 (28)	73 (37)
Use of psychoactive drugs*	85 (44)	92 (48)
Circumcised	38 (19)	41 (20)
Infection with NG, CT or TP**	43 (22)	59 (29)
Nb sexual acts in prior 4 weeks	10 (6-18)	10 (5-15)
Nb sexual partners in prior 2 months	8 (5-17)	8 (5-16)

* in last 12 months: ecstasy, crack, cocaine, crystal, speed, GHB/GBL

** NG: Neisseria gonorrhoeae, CT: Chlamydia trachomatis, TP: Treponema pallidum

Sexual Behavior





- 6





Mean follow-up of 13 months: 16 subjects infected **14 in placebo arm** (incidence: 6.6 per 100 PY), **2 in TDF/FTC arm** (incidence: 0.94 per 100 PY)

86% relative reduction in the incidence of HIV-1 (95% CI: 40-99, p=0.002) NNT for one year to prevent one infection : 18 **Four Prevention Opportunities**



- 6

Profilaxis Pre-Exposición: Posicionamiento GeSIDA

PrEP is Changing HIV Prevention



HarlemUnited.org/PrEP

Strategies to Prevent HIV





Recomendaciones sobre Profilaxis Pre-Exposición en adultos para la Prevención de la Infección por VIH en España

Grupo de Estudio de Sida de la SEIMC (GeSIDA)

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

Let me PrEP 11

SKYN

Relias

ROIAF

ROM

How to improve PrEP delivery in clinical settings

- Who should receive PrEP
- What should be prescribed for PrEP
- Who should prescribe PrEP
- Where should PrEP be prescribed

Who should receive PrEP?



Who is Eligible for PrEP? General Considerations

- Adults (18 years or older)
- Negative HIV serologic assay (4th generation ELISA)
- No sign of primary HIV infection
- No recent HIV exposure (< 1 month)
- High risk of sexual HIV acquisition

Who is Eligible for PrEP? High Risk of Sexual HIV Acquisition (I)

Population with a risk ≥2 cases per 100 p-y

- MSM or transgender individuals with condomless anal sex over the last 6 months and, at least, one of the following
 - Two or more different partners
 - Episodes of STIs (syphilis, chlamydiae, gonorrhea, HBV, HCV)
 - PEP prescription
 - Use of drugs during sexual intercourse (cocaine, GHB, MDMA, etc...)

Cost-Effectiveness of PrEP Among MSM in the Netherlands



49

Adherence and Sexual Behavior

 Participants that reported engaging in condomless sex had consistently higher levels of TFV-DP (p=0.005)

- Remained consistent over course of the study.

- Similarly, participants who reported CRAI with last partner demonstrated higher TFV-DP levels over course of the study
 - Trend not statistically significant

Who is Eligible for PrEP? High Risk of Sexual HIV Acquisition (II)

- Other persons at high risk of HIV acquisition on a case by case basis:
 - Sex workers exposed to condomless sex
 - Partners of persons with uncontrolled HIV-infection exposed to condomless sex
 - Vulnerable persons exposed to condomless sex with people from a group with a high prevalence of HIV
 - Person from areas/countries of high HIV prevalence
 - Person with multiple sexual partners
 - IVDU

Who is <u>Not</u> Eligible for PrEP

- HIV Serologic assay positive or unknown
- Signs or symptoms of primary HIV-infection
- Creatinine clearance < 50 ml/mn
- On demand PrEP if chronic HBV infection
- Breast-feeding
- Hypersensitivity to TDF or FTC or excipients

What should be prescribed for PrEP?



What should be prescribed for PrEP? Modalities of Truvada use

Dosing Schedule

- Daily use (1 pill a day)
- On demand use (Ipergay protocol) possible for MSM

Patients follow-up

- Baseline visit: HIV/HBV/HCV, tests for STIs and creatinine
- Month 1: HIV test and creatinine
- Every 3 months: HIV test, creatinine,
- Once a year: tests for STIs

HPTN 067/ADAPT: Harlem Cohort Comparison of PrEP Strategies

- 179 MSM or TGW randomized
 - Daily PrEP, n = 59
 - Time-driven PrEP, n = 60
 - Event-driven PrEP, n = 60
- Baseline characteristics: median age 30 yrs, 98% MSM, 70% black
- HIV seroconversion seen in 2 pts
 - Both pts had low or undetectable TDF in dried blood spots/plasma at study visits

*P = .001 vs daily. †P = .47 vs event driven.

Complete coverage: taking \geq 1 PrEP dose within 4 days before sex and \geq 1 dose within 24 hrs after sex.

Mannheimer S, et al. IAS 2015. Abstract MOAC0305LB.



HPTN 067/ADAPT: Bangkok Cohort Comparison of PrEP Strategies

- 178 MSM or TGW randomized
 - Daily PrEP, n = 60
 - Time-driven PrEP, n = 59
 - Event-driven PrEP, n = 59
- Baseline characteristics: median age 31 yrs, 99% MSM, 100% Asian
- HIV seroconversions observed in 2 pts during prerandomization directly observed dosing phase
 - Both associated with undetectable or low levels of FTC or TFV in plasma/PBMCs

Holtz TH, et al. IAS 2015. Abstract MOAC0306LB.



*P = .02 vs daily arm, P = .04 vs time driven arm. Complete coverage defined as taking \geq 1 PrEP dose within 4 days before sex and \geq 1 dose within 24 hrs after sex.

Who should prescribe PrEP?



Who should prescribe PrEP?

- Prep is a medical intervention, so it must be prescribed and supervised by a physician, with
 - Experience in the management of HIV infection
 - Experience in the use of antiretrovirals
 - Experience in STI

Where should PreP be prescribed?



Where should PreP be prescribed? (I)

 PreP Centers may be single or associated, and must warrant the adequate development of all the phases of the strategy, including initial evaluation and follow-up, as well as the delivery of the medication

Essential requirements

- Physician with expertise in HIV, ART, and STIs
- Lab facilities for the diagnosis of HIV infection, HIV RNA measurements, and genotypic resistance testing
- Lab facilities for the monitoring of drug toxicities
- Facilities for the evaluation of STIs

Where should PreP be prescribed? (II)

- PreP Centers may varied and be adapted to different realities:
 - Hospital HIV Units
 - STI Centers
 - Community Centers
- Since ARVs are hospital-based drugs, a delivery system must be designed in case PrEP is prescribed in centers other than the hospital

PrEP Implementation

- Truvada can be prescribed only by hospital-based HIV specialists
- Truvada can be obtained only at hospital pharmacies
- PrEP awareness is still low and physicians and nurses need to be trained
- Community-based peer-counseling needs to be available
- PrEP scale-up needs to be encouraged
 - Public health benefit only if a large number of high risk individuals receive PrEP
 - Combine PrEP with up-scaled testing and rapid treatment of HIV-infection

The commitment of the City of Paris in HIV Prevention



Paris City Hall, February 2016

Major Challenges with PrEP

- Address remaining skepticism from physicians, the Gay community, the Payers and the general population
- ✓ Avoid stigmatization of PrEP users in the community
- Address the issue of cost and explain the public health benefit of combined prevention
- Increase awareness for PrEP and increase the number of sites to deliver and monitor PrEP
- "No new HIV-infection" becomes a real prospect, we need to become "HIV prevention advocates"

Share the Night, Not HIV



is preventive medication that can help you stay negative, even if he might be positive.



Condoms provide additional protection. For more information on PrEP, talk to your doctor, call 311 or visit nyc.gov and search "HIV PrEP and PEP"



Profilaxis Post-Exposición: Fundamentos

PEP: Fundamentos

- Concepto
- Base científica
- Valoración del riesgo
 - Fluidos infectantes
 - Tipo de Exposición
 - Fuente
- Fármacos

PEP: Hospital Ramón y Cajal



Muchas Gracias