Les antirétroviraux dans leur contexte de prescription…

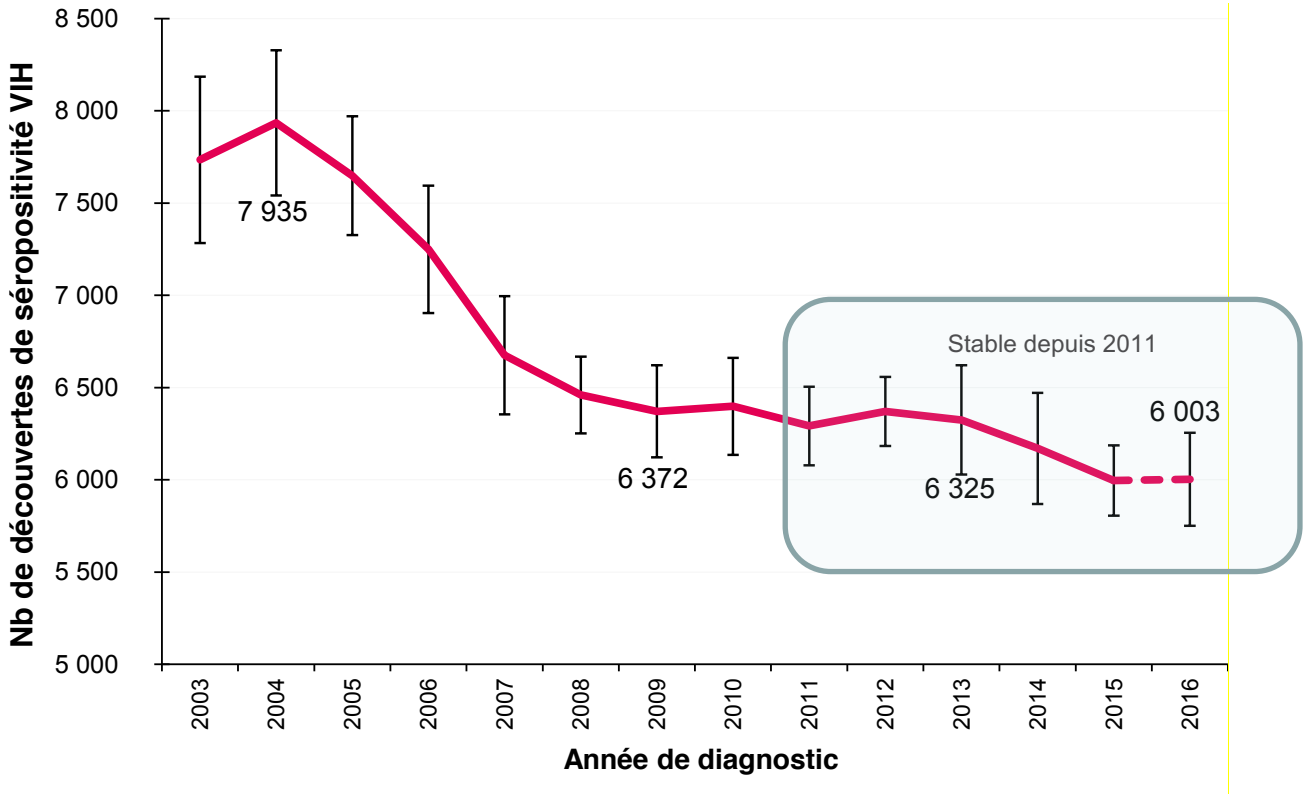
Cours pour les IDE/AS de maladies infectieuses

CHU de Rennes – Mars 2018

Dr Cédric Arvieux – CHU de Rennes – COREVIH Bretagne

LE CONTEXTE

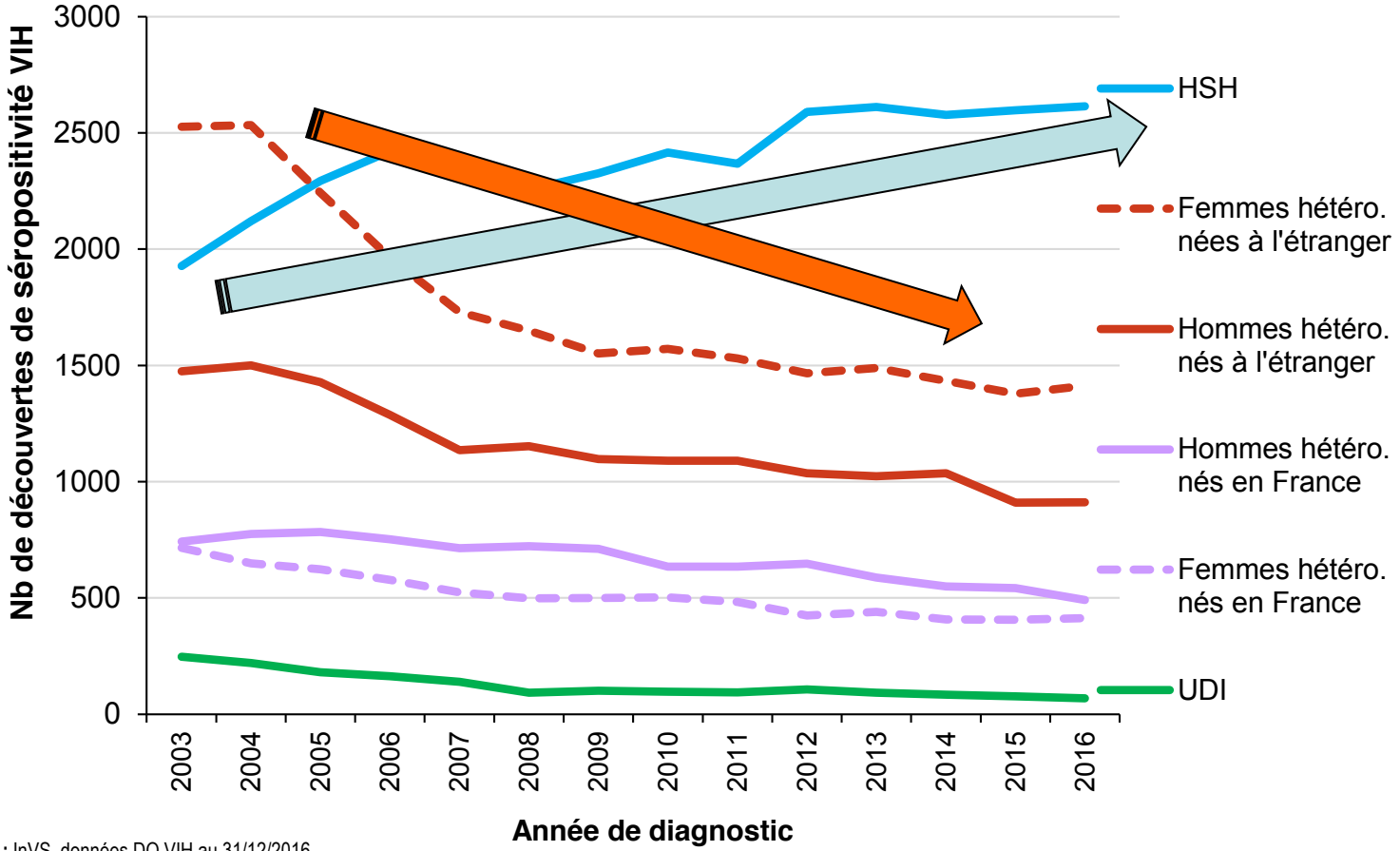
Autour de 6 000 personnes ont découvert leur séropositivité VIH en 2016



L'incertitude est plus importante sur le dernier point, en raison des délais de déclaration.

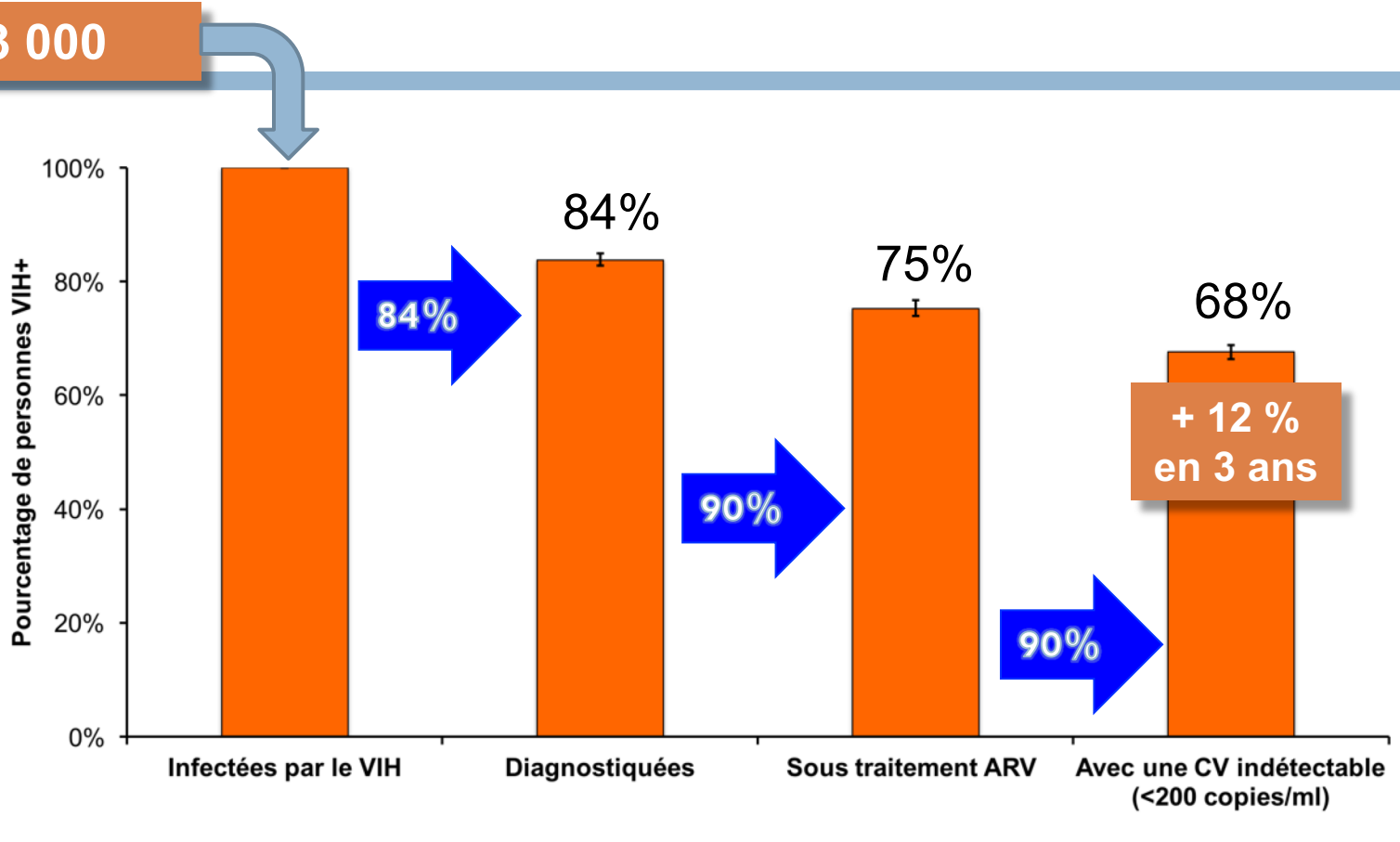
Source : Santé publique France, DO VIH au 31/12/2016 corrigées pour les délais, la sous déclaration et les valeurs manquantes

Découvertes de séropositivité par mode de contamination



Source : InVS, données DO VIH au 31/12/2016

Cascade de la prise en charge en France en 2013*



* Résultats provisoires

Antirétroviraux en 2018

Quizz – Quels sont les deux intrus… qui ne sont pas des antirétroviraux ?

- Zidovudine
- Lamivudine
- Didanosine
- Emtricitabine
- Pomedapine
- Doravirine
- Zalcitabine
- Etravirine
- Rilpivirine
- Nevirapine
- Stavudine

- Tenofovir
- Fosamprenavir
- Saquinavir
- Amprenavir
- Indinavir
- Petinavir
- Raltegravir
- Atazanavir
- Dolutegravir
- Elvitegravir
- Cabotegravir

- Efavirenz
- Maraviroc
- Enfuvirtide

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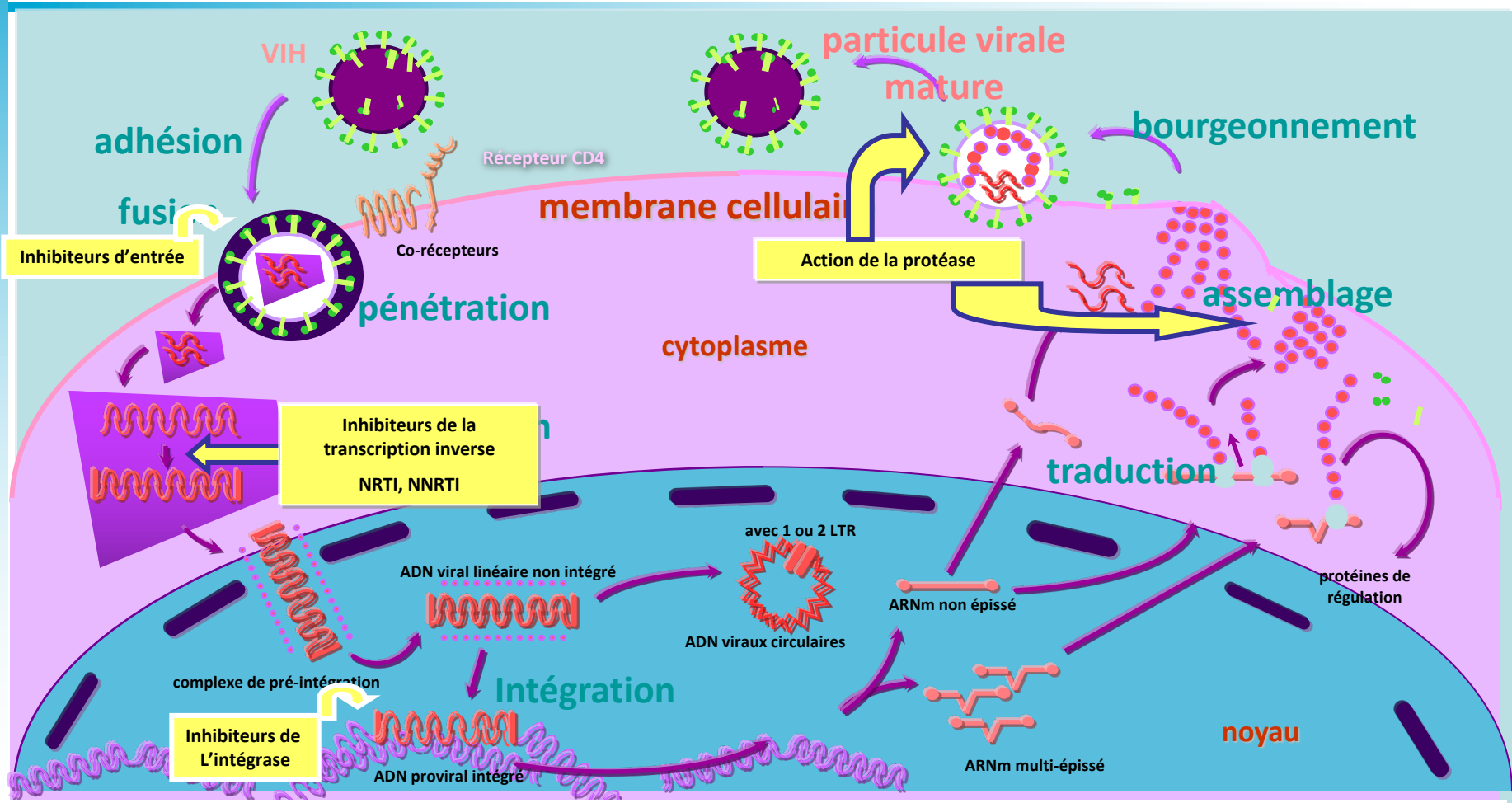
- Elvitegravir
- Cabotegravir

- Efavirenz
- Maraviroc
- Enfuvirtide

Cycle de réplication du VIH et cibles des ARV



D'après Furtado M. N Engl J Med. 1999, 340(21) : 1614-22

LES TRAITEMENTS DE 1ÈRE INTENTION

Les indications des traitement

- Toute personne infectée par le VIH
  - Quel que soit le niveau de CD4
  - Quel que soit les symptômes cliniques

Associations d'antirétroviraux recommandées 2016

Associations recommandées - Noms commerciaux (DCI)	Coût mensuel (€)	Coût annuel (€)
Eviplera® (ténofovirDF/emtricitabine + rilpivirine)	681,90	8 183
Truvada®+Prezista®/Norvir® (ténofovirDF/emtricitabine+darunavir/r)	869,66	10 423
Triumeq® (abacavir/lamivudine + dolutégravir)	928,43	11 141
Stribild® (ténofovirDF/emtricitabine/elvitégravir/cobicistat)	977,09	11 725
Truvada® + Isentress® (ténofovirDF/emtricitabine + raltégravir)	1020,33	12 240
Truvada® + Tivicay® (ténofovirDF/emtricitabine + dolutégravir)	1060,30	12 724

Associations d'antirétroviraux recommandées 2017

(prix public ville TTC sur http://www.codage.ext.cnamts.fr/codif/bdm_it/index.php ; consulté le 12 octobre 2017)

Associations recommandées - Noms commerciaux (DCI)	Cout mensuel (€)	Coût annuel (€)
TénofovirDF/emtricitabine (Gé) + Edurant® (rilpivirine)	446,43	5 357
TénofovirDF/emtricitabine (Gé) + Prezista®/Norvir® (darunavir/r)	627,29	7 527
Eviplera® (ténofovirDF/emtricitabine/rilpivirine)	681,90	8 183
TénofovirDF/emtricitabine (Gé) + Isentress® (raltégravir)	736,65	8 840
Abacavir/lamivudine (Gé) + Tivicay® (dolutégravir)	769,92	9 239
TénofovirDF/emtricitabine (Gé) + Tivicay® (dolutégravir)	788,93	9 467
Truvada® + Prezista®/Norvir® (ténofovirDF/emtricitabine + darunavir/r)	854,26	10 251
Genvoya® (ténofovir AF/emtricitabine/elvitégravir//cobicistat)	882,16	10 586
Triumeq® (abacavir/lamivudine/dolutégravir)	928,43	11 141
Truvada® + Isentress® (ténofovirDF/emtricitabine + raltégravir)	963,62	11 563
Truvada® + Tivicay® (ténofovirDF/emtricitabine + dolutégravir)	1015,90	12 191

La grande révolution (inaperçue) de 2017

- L'arrivée des génériques
  - De Truvada
  - De Kivexa
  - De Viramune, de sustiva…

Deux exemples

EVIPLERA (Rilpivirine + emtricitabine + ténofovir disoproxil)	1/J	**626,28** euros (30 comprimés).	
Emtricitabine + tenofovir disoproxil Gé	1/J	176,02 euros (Fl/30).	**441,86**
EDURANT (Rilpivirine)	1/J	265,84 euros (Fl/30).	
TRIUMEQ (abacavir + lamivudine + dolutégravir)	1/J	**927,74** euros (flacon de 30 comprimés).	
Abacavir Lamivudine Gé +	1/J	156,42 euros (Plq/30).	**764,77**
TIVICAY (dolutégravir)	1/J	608,35 euros (30 comprimés à 50 mg).	

- Eviplera versus Edurant + Emtricitabine/ténofovir générique
  - 184,42 € de différence par mois = 2 213 € par an
  - 21 patients passés sous générique = un poste d'infirmière
- Un patient qui passe du Triumeq® à Edurant + Emtricitabine/ténofovir générique
  - 5 830€ par an
  - 8 patients changés de traitement = un poste d'infirmière

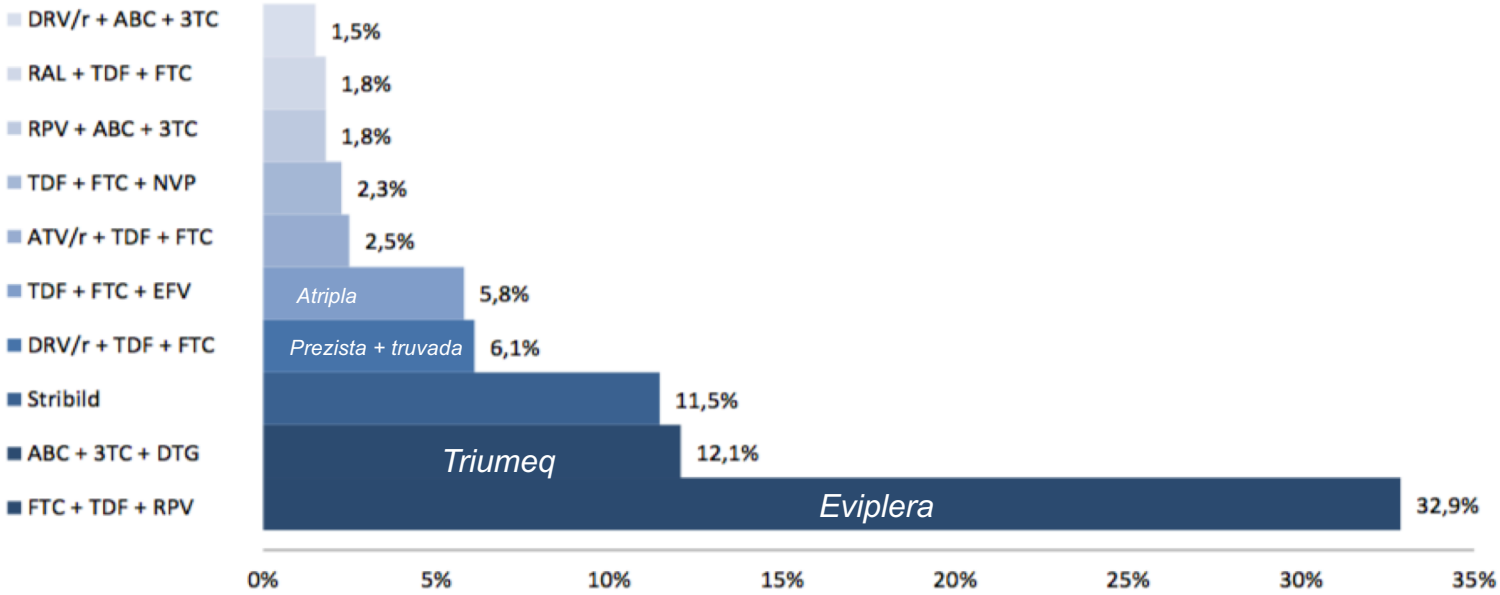
Les « nouveautés » récentes

- Le remplacement du tenofovir-disoproxyl par le ténofovir fumarate
  - Une opération commerciale de Gilead
    - Permet de « contourner » le générique du Ténofovir…
  - Mais un petit avantage au niveau tolérance osseuse et rénale
  - Concerne
    - EVIPLERA ® → ODEFSEY®
    - STRIBILD® → GENVOYA®

Les traitements utilisés à Rennes en 2016

→ 144 lignes de traitements différentes

- Les 10 associations de traitements les plus prescrites :
  - 1056 patients
  - 79,6% de la file active traitée



L’espérance de vie et les traitements (1)

- Plus de 20 molécules disponibles
- En Bretagne
  - Sur les 3005 patients dont l’info est disponible
    - 56% reçoivent un traitement antiviral en un seul comprimé/j
    - Le traitement le plus utilisé est l’eviplera®
    - 28 schémas thérapeutiques sont pris par plus de 10 patients
    - Près de 200 combinaisons utilisées !!

L'espérance de vie et les traitements (2)

- L'espérance de vie dépend
  - De la précocité du traitement antirétroviral
    - Importance du « nadir » de CD4
  - **DU TABAC +++**
- L'espérance de vie est proche de celle de la population générale
  - Si le traitement a été débuté tôt
  - Si l'on ne fume pas
  - Si l'on ne s'est jamais injecté de drogue
- **2017**
  - Europe : 73 ans pour les hommes et 76 pour les femmes (début de traitement entre 2008 et 2010)

→ Paradoxe : dans certaines zones des USA, le fait d'être séropositif AUGMENTE l'espérance de vie !!

LES SITUATIONS PARTICULIÈRES

La Primo-infection

Tout patient diagnostiqué en primo-infection VIH relève d'un **traitement antirétroviral rapide** (au mieux 24-48h) associant

- 2 INTI
  - **TDF/FTC**
- 3ème agent
  - IP/r (**darunavir/ritonavir**, 800/100 mg)
  - INI (**dolutégravir**)
- Ce choix est fait en l'absence des résultats du typage HLA-B*5701 et du test génotypique de résistance aux ARV
- Le traitement sera adapté selon ces résultats

La co-infection hépatite B

- Sont actifs sur le VIH et le VHB
  - Ténofovir (Viread®)
  - Transitoirement efficace en monothérapie
    - Emtricitabine
    - Lamivudine (Epivir®)
- Actif sur le VHB mais pas le VIH
  - Entecavir
- Principe
  - Pas de lamivudine ou emtricitabine « seule » si VIH+VHB
  - Attention +++ aux changements de traitements pour le VIH en oubliant le VHB…

Les interactions

- La tuberculose
  - Interactions +++ entre la rifampicine et
    - Les non-analogues nucléosidiques
    - Les antiprotéases
    - Certaines anti-intégrases
      - Raltegravir et dolutegravir sont utilisables en adaptatn les doses
      - Associé à une bithérapie d'INTI : en général truvada ou kivexa
- Les cancers/chimiothérapie
  - Utilisation de principe : Raltegravir + 2 INTI (attention au truvada en cas de chimio néphrotoxique).

PrEP : prophylaxie pré exposition

TPE ou « PEP »: traitement post-exposition

TasP : traitement comme prévention

LES « AUTRES » MODALITÉS DE TRAITEMENT

TASP

Essai Partner

Original Investigation

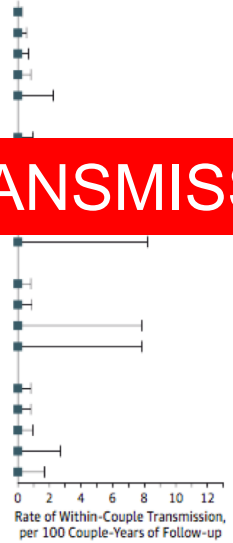
JAMA July 12, 2016 Volume 316, Number 2

Sexual Activity Without Condoms and Risk of HIV Transmission in Serodifferent Couples When the HIV-Positive Partner Is Using Suppressive Antiretroviral Therapy

Alison J. Rodger, MD; Valentina Cambiano, PhD; Tina Bruun, RN; Pietro Vernazza, MD; Simon Collins; Jan van Lunzen, PhD; Giulio Maria Corbelli; Vicente Estrada, MD; Anna Maria Geretti, MD; Apostolos Beloukas, PhD; David Asboe, FRCP; Pompeyo Viciana, MD; Félix Gutiérrez, MD; Bonaventura Clotet, PhD; Christian Pradier, MD; Jan Gerstoft, MD; Rainer Weber, MD; Katarina Westling, MD; Gilles Wandeler, MD; Jan M. Prins, PhD; Armin Rieger, MD; Marcel Stoeckle, MD; Tim Kümmerle, PhD; Teresa Bini, MD; Adriana Ammassari, MD; Richard Gilson, MD; Ivanka Krznaric, PhD; Matti Ristola, PhD; Robert Zangerle, MD; Pia Handberg, RN; Antonio Antela, PhD; Sris Allan, FRCP; Andrew N. Phillips, PhD; Jens Lundgren, MD; for the PARTNER Study Group

Figure 1. Rate of HIV Transmission According to Sexual Behavior Reported by the HIV-Negative Partner

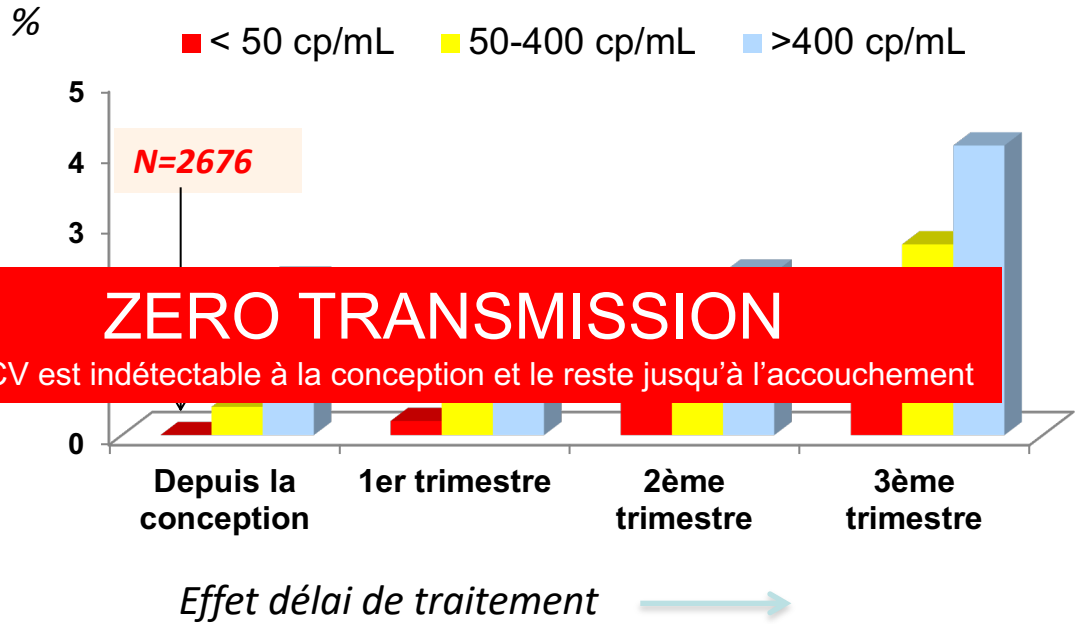
	HIV-Negative Members of Eligible Couples Reporting Specific Sex Act, No./Total (%)	Couple-Years of Follow-up	Upper 95% Confidence Limit
All			
Any sex	863/866 (99.7)	1238	0.30
Vaginal sex	532/878 (60.6)	629	0.59
Anal sex	449/849 (52.9)	522	0.71
Insertive anal sex	363/862 (42.1)	417	0.88
Receptive anal sex with ejaculation	185/864 (21.4)	166	2.23
Heterosexual women			
Receptive anal sex without ejaculation	55/253 (21.7)	45	8.14
Heterosexual men			
Any sex	272/274 (99.3)	418	0.88
Vaginal sex	271/275 (98.5)	383	0.96
Anal sex	60/264 (22.7)	47	7.85
Insertive anal sex	60/264 (22.7)	47	7.85
Men who have sex with men			
Any sex	330/330 (100)	439	0.84
Anal sex	328/329 (99.7)	415	0.89
Insertive anal sex	303/329 (92.1)	370	1.00
Receptive anal sex with ejaculation	148/329 (45.0)	137	2.70
Receptive anal sex without ejaculation	217/324 (67.0)	220	1.68



Denominators are the group-specific number of HIV-negative participants who contributed eligible couple-years of follow-up. The upper limit of the 95% confidence interval was estimated using the exact Poisson method.

ZERO TRANSMISSION

Un des meilleurs exemples de TasP : la prévention de la transmission mère enfant



ZERO TRANSMISSION

Si la CV est indétectable à la conception et le reste jusqu'à l'accouchement

EPF anRS INSERM CESP 1018

ARV débutés avant conception et CV <50 : TME = 0% [0.0 - 0.1]

Mandelbrot et al.CID 2015

PREP

Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial

Sheena McCormack*, David T Dunn*, Monica Desai, David I Dolling, Mitzy Gafos, Richard Gilson, Ann K Sullivan, Amanda Clarke, Iain Reeves, Gabriel Schembri, Nicola Mackie, Christine Bowman, Charles J Lacey, Vanessa Apea, Michael Brady, Julie Fox, Stephen Taylor, Simone Antonucci, Saye H Khoo, James Rooney, Anthony Nardone, Martin Fisher, Alan McOwan, Andrew N Phillips, Anne M Johnson, Brian Gazzard, Owen N Gill

Summary

Background Randomised placebo-controlled trials have shown that daily oral pre-exposure prophylaxis (PrEP) with tenofovir–emtricitabine reduces the risk of HIV infection. However, this benefit could be counteracted by risk compensation in users of PrEP. We did the PROUD study to assess this effect.

Methods PROUD is an open-label randomised trial done at 13 sexual health clinics in England. We enrolled HIV-negative gay and other men who have sex with men who had had anal intercourse without a condom in the previous 90 days. Participants were randomly assigned (1:1) to receive daily combined tenofovir disoproxil fumarate (245 mg) and emtricitabine (200 mg) either immediately or after a deferral period of 1 year. Randomisation was done via web-based access to a central computer-generated list with variable block sizes (stratified by clinical site). Follow-up was quarterly. The primary outcomes for the pilot phase were time to accrue 500 participants and retention; secondary outcomes included incident HIV infection during the deferral period, safety, adherence, and risk compensation. The trial is registered with ISRCTN (number ISRCTN94465371) and ClinicalTrials.gov (NCT02065986).

Findings We enrolled 544 participants (275 in the immediate group, 269 in the deferred group) between Nov 29, 2012, and April 30, 2014. Based on early evidence of effectiveness, the trial steering committee recommended on Oct 13, 2014, that all deferred participants be offered PrEP. Follow-up for HIV incidence was complete for 243 (94%) of 259 patient-years in the immediate group versus 222 (90%) of 245 patient-years in the deferred group. Three HIV infections occurred in the immediate group (1·2/100 person-years) versus 20 in the deferred group (9·0/100 person-years) despite 174 prescriptions of post-exposure prophylaxis in the deferred group (relative reduction 86%, 90% CI 64–96, p=0·0001; absolute difference 7·8/100 person-years, 90% CI 4·3–11·3). 13 men (90% CI 9–23) in a similar population would need access to 1 year of PrEP to avert one HIV infection. We recorded no serious adverse drug reactions; 28 adverse events, most commonly nausea, headache, and arthralgia, resulted in interruption of PrEp. We detected no difference in the occurrence of sexually transmitted infections, including rectal gonorrhoea and chlamydia, between groups, despite a suggestion of risk compensation among some PrEP recipients.

Interpretation In this high incidence population, daily tenofovir–emtricitabine conferred even higher protection against HIV than in placebo-controlled trials, refuting concerns that effectiveness would be less in a real-world setting. There was no evidence of an increase in other sexually transmitted infections. Our findings strongly support the addition of PrEP to the standard of prevention for men who have sex with men at risk of HIV infection.

Funding MRC Clinical Trials Unit at UCL, Public Health England, and Gilead Sciences.

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See Online/Comment http://dx.doi.org/10.1016/S0140-6736(15)00153-1

*Equal contribution

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Introduction

HIV is a disease of major importance in the UK, with an estimated 107 800 individuals with HIV at the end of 2013.[1] Prognosis is excellent, but treatment is lifelong with an inexorable increase in costs to the National Health Service.[2] Gay, bisexual, and other men who have sex with men are the most at risk of acquiring HIV in the UK.[3] There has been no decrease in the numbers of new diagnoses reported each year for the past decade (3250 in 2013), and estimates suggest that HIV incidence has increased in this population.[3] These trends have occurred despite increased HIV testing and a move towards earlier initiation of antiretroviral therapy, which renders most patients non-infectious.[4,5] Although HIV testing and promotion of condom use will always be core strategies for reducing risk, a more radical approach is needed for people who do not have HIV and whose condom use is inconsistent. One such approach is pre-exposure prophylaxis (PrEP), the provision of antiretroviral drugs before HIV exposure to prevent infection.

The biological efficacy of daily oral tenofovir-based regimens used as PrEP to reduce HIV acquisition has been established through randomised placebo-controlled trials including men who have sex with men,[6]

PROUD

ORIGINAL ARTICLE

On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection

J.-M. Molina, C. Capitant, B. Spire, G. Pialoux, L. Cotte, I. Charreau, C. Tremblay, J.-M. Le Gall, E. Cua, A. Pasquet, F. Raffi, C. Pintado, C. Chidiac, J. Chas, P. Charbonneau, C. Delaugerre, M. Suzan-Monti, B. Loze, J. Fonsart, G. Peytavin, A. Cheret, J. Timsit, G. Girard, N. Lorente, M. Préau, J.F. Rooney, M.A. Wainberg, D. Thompson, W. Rozenbaum, V. Doré, L. Marchand, M.-C. Simon, N. Etien, J.-P. Aboulker, L. Meyer, and J.-F. Delfraissy, for the ANRS IPERGAY Study Group*

ABSTRACT

BACKGROUND

Antiretroviral preexposure prophylaxis has been shown to reduce the risk of human immunodeficiency virus type 1 (HIV-1) infection in some studies, but conflicting results have been reported among studies, probably due to challenges of adherence to a daily regimen.

METHODS

We conducted a double-blind, randomized trial of antiretroviral therapy for preexposure HIV-1 prophylaxis among men who have unprotected anal sex with men. Participants were randomly assigned to take a combination of tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) or placebo before and after sexual activity. All participants received risk-reduction counseling and condoms and were regularly tested for HIV-1 and HIV-2 and other sexually transmitted infections.

RESULTS

Of the 414 participants who underwent randomization, 400 who did not have HIV infection were enrolled (199 in the TDF-FTC group and 201 in the placebo group). All participants were followed for a median of 9.3 months (interquartile range, 4.9 to 20.6). A total of 16 HIV-1 infections occurred during follow-up, 2 in the TDF-FTC group (incidence, 0.91 per 100 person-years) and 14 in the placebo group (incidence, 6.60 per 100 person-years), a relative reduction in the TDF-FTC group of 86% (95% confidence interval, 40 to 98; P=0.002). Participants took a median of 15 pills of TDF-FTC or placebo per month (P=0.57). The rates of serious adverse events were similar in the two study groups. In the TDF-FTC group, as compared with the placebo group, there were higher rates of gastrointestinal adverse events (14% vs. 5%, P=0.002) and renal adverse events (18% vs. 10%, P=0.03).

CONCLUSIONS

The use of TDF-FTC before and after sexual activity provided protection against HIV-1 infection in men who have sex with men. The treatment was associated with increased rates of gastrointestinal and renal adverse events. (Funded by the National Agency of Research on AIDS and Viral Hepatitis [ANRS] and others; ClinicalTrials.gov number, NCT01473472.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Molina at the Department of Infectious Diseases, Hôpital Saint-Louis, 1 Ave. Claude Vellefaux, 75475 Paris, France, or at jean-michel.molina@aphp.fr.

*A complete list of investigators in the France Recherche Nord et Sud Sida-HIV et Hépatites (ANRS) Intervention Prévention de l'Exposition aux Risques avec et pour les Gays (IPERGAY) study group is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on December 1, 2015, at NEJM.org.

DOI: 10.1056/NEJMoa1506273

IPERGAY

PrEP : deux essais essentiels

IPERGAY

- Tenofovir/emtricitabine
- Randomisée
- Placebo
- France/Québec
- **PrEP au « coup par coup »**

- **Ça marche très bien !**
  - - 86% d'infection VIH
  - NPT = 18

PROUD

- Tenofovir/emtricitabine
- Randomisée
- PrEP immédiate versus retardée
- UK
- **PrEP continue**

- **Ça marche très bien !**
  - - 86% d'infection VIH
  - NPT = 13

Mc Cormack S et al. Lancet 10 septembre 2015 - Molina JM et al. NEJM 1er décembre 2015

Les évolutions attendues (1)

- Les traitements en injectables
  - Cabotegravir LP et Rilpivirine LP
  - Tous les deux mois
  - Pour qui ?

Les évolutions attendues (2) : allégements

- La diminution des posologies
  - Traitement 4 ou 5 jours sur 7
    - Essai quatuor en cours
- Le passage aux monothérapies et monothérapies
  - Pourquoi ?
  - Comment ?
    - Darunavir/ritonavir monothérapie (Prezista®/Norvir®)
    - Dolutegravir/lamivudine (Tivicay®/Lamivudine)
    - Dolutegravir/Rilpivirine (Tivicay®/Edurant®)
    - Raltegravir/Etravirine (Isentress®/Intelence®)
    - …
- Paradoxe
  - Allégement = augmentation du nombre de comprimés

Quelques molécules très proches de la commercialisation

- Bictégravir
  - Nouvelle anti-intégrase
  - A priori bien tolérée, durée d'action assez longue
  - Commercialisée en monocomprimé avec ténofovir-F et emtricitabine
- Doravirine
  - Nouvel inhibiteur non nucléosidique (INNTI)
  - Efficace sur souche résistantes aux autres INNTI
- Darunavir/cobi/tenofovir-F et emtricitabine
  - 1er monocomprimé avec une antiprotéase (Symtuza®)

LE SITE DU COREVIH BRETAGNE

http://www.corevih-bretagne.fr