Le VIH… quoi de neuf en 2016

EN 25 MINUTES TOP CHRONO…

Les axes essentiels

- L’épidémiologie
- La PrEP
- (Le tabac)
- Les drogues « récréatives »
- L’initiation précoce du traitement
- La transmission mère-enfant

RESEARCH ARTICLE

HIV EPIDEMIOLOGY

The early spread and epidemic ignition of HIV-1 in human populations

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Thirty years after the discovery of HIV-1, the early transmission, dissemination, and establishment of the virus in human populations remain unclear. Using statistical approaches applied to HIV-1 sequence data from central Africa, we show that from the 1920s Kinshasa (in what is now the Democratic Republic of Congo) was the focus of early transmission and the source of pre-1960 pandemic viruses elsewhere. Location and dating estimates were validated using the earliest HIV-1 archival sample, also from Kinshasa. The epidemic histories of HIV-1 group M and nonpandemic group O were similar until ~1960, after which group M underwent an epidemiological transition and outpaced regional population growth. Our results reconstruct the early dynamics of HIV-1 and emphasize the role of social changes and transport networks in the establishment of this virus in human populations.

AIDS is one of the most devastating infectious diseases in human history, and its cause, HIV, has been responsible for nearly 75 million infections (*1*). Shortly after the first reports of AIDS in the United States in 1981 (*2*) and the isolation of HIV-1 2 years later (*3*, *4*), the disease was discovered to be established in heterosexual populations of central and east Africa (*5*, *6*), suggesting a much older—and, to that point, hidden—history of the pandemic in Africa.

Surveys of African apes identified chimpanzee [*Pan troglodytes troglodytes* (*Ptt*)] populations in southern Cameroon harboring simian immunodeficiency viruses (SIVs) most closely related to the pandemic lineage of HIV-1, group M (*7*, *8*). HIV-1 group M comprises numerous genetically distinct virus subtypes (A, B, C, etc.) and recombinant forms. Although only group M viruses established pandemic spread, other separate cross-species transmissions of SIV to humans in the Congo River basin led to nonpandemic transmission of HIV-1 groups O, N, and P, which are still largely confined to Cameroon and its surrounding countries (*9*–*11*).

By the end of 1980s, the genetic diversity of HIV-1 group M in the Democratic Republic of Congo (DRC), then known as Zaire, was greater and more complex than that in the rest of the world (*12*, *13*). HIV-1 strains collected in central Africa form phylogenetic outgroups to the subtypes of group M (*14*), suggesting that the latter are the products of incomplete sampling and exportation events (*15*). Two HIV-1 sequences substantially predate the discovery of AIDS and were retrospectively recovered from blood and tissue samples (*16*, *17*) collected in Kinshasa, capital of the DRC, in 1959–1960. Other countries in the Congo River basin—notably the Republic of Congo (RC) (*18*, *19*), as well as Cameroon and Gabon (*20*, *21*)—also harbor very high diversities of HIV-1 comparable to that observed in the DRC. Nevertheless, hypotheses concerning the geographic source of the pandemic and its early dissemination in humans remain controversial and have yet to be formally tested.

Although critical to our understanding of the establishment and evolution of human pathogens, a substantial period of HIV pandemic history is unclear. Despite our increased understanding of the cross-species transmissions of SIV to humans, we know very little about the early dissemination routes of HIV-1 and how group M became established as a continental epidemic in the decades immediately following its spillover from chimpanzees. Further, the genesis of major HIV-1 lineages, such as subtypes B and C, remains obscure. The lack of direct evidence about the early transmission of HIV-1 group M has led to several competing hypotheses for the emergence of AIDS (*22*). The two most widely accepted hypotheses for the establishment of the group M pandemic argue that urbanization and/or viral genetic factors, such as adaptation of the HIV-1 *vpu* gene (*23*), were decisive in the epidemiological success of group M compared with other SIV cross-species transmissions, such as group O, that did not cause pandemics.

By probing information contained in sampled viral sequences, evolutionary analyses can reveal the epidemic history of fast-evolving pathogens (*24*). Molecular clocks agree that a common ancestor of HIV-1 group M existed in the first half of the 20th century (*16*, *25*–*27*), and models that link viral phylogenies to past transmission rates have been used to infer the epidemic history of group M (*16*, *27*). However, several aspects of the evolutionary models used remain vulnerable to criticism (*28*), and the impact of recombination [a driver of HIV-1 genetic diversity (*29*)] on estimates of the time scale of group M spread has not been fully addressed. Using alternative methods of evolutionary analysis applied to a compilation of HIV-1 sequences from central Africa, we have uncovered the dynamics of the establishment of HIV-1 in humans, which explain how just one of many cross-species transmission events gave rise to the global pandemic we see today.

The spatiotemporal origins of pandemic HIV-1

A preliminary analysis of all available *env* C2V3 HIV-1 sequence data (*30*) from countries in the Congo River basin, as well as the range of *Ptt* chimpanzees, indicated that group M spread from the DRC to other countries (figs. S1 and S3); hence, we focused on this area in subsequent analyses. A very high genetic diversity of HIV-1 has been reported, not only in Kinshasa and the north and south of the DRC (*12*, *13*, *31*, *32*), but also in Brazzaville in the RC and, to a lesser extent, in the Mayombe area of RC near Pointe-Noire, all of which have been suggested as potential source locations of the pandemic (*22*, *33*, *34*). We therefore performed phylogeographic analyses of viruses collected in both the DRC and RC (table S1) and compared sequence sampling locations with phylogenetic history to formally test hypotheses concerning the location of ancestral viral lineages (*30*). Our analyses robustly place

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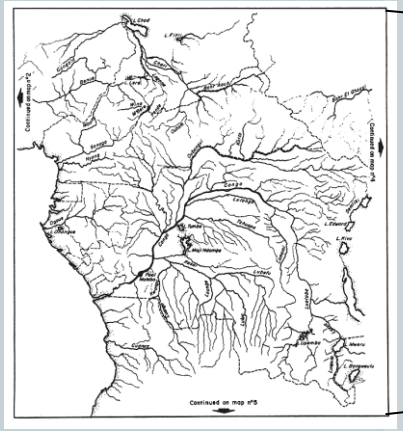
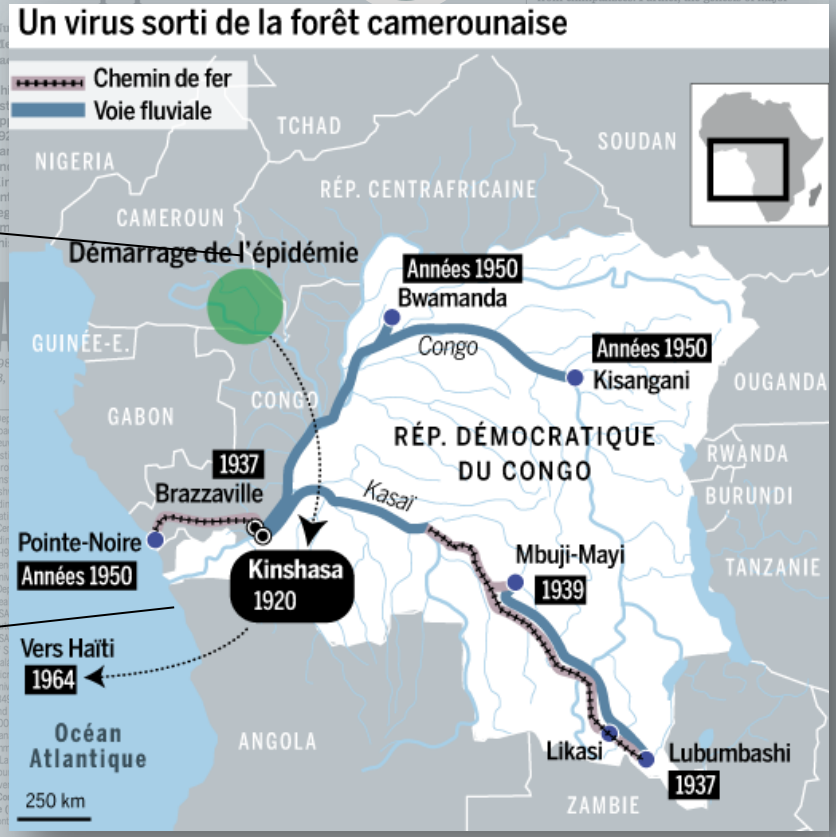
Un voyage en pirogue, puis en train, puis en bateau, puis en avion…





Faria et al. Science 2014

Infographie « le Monde »

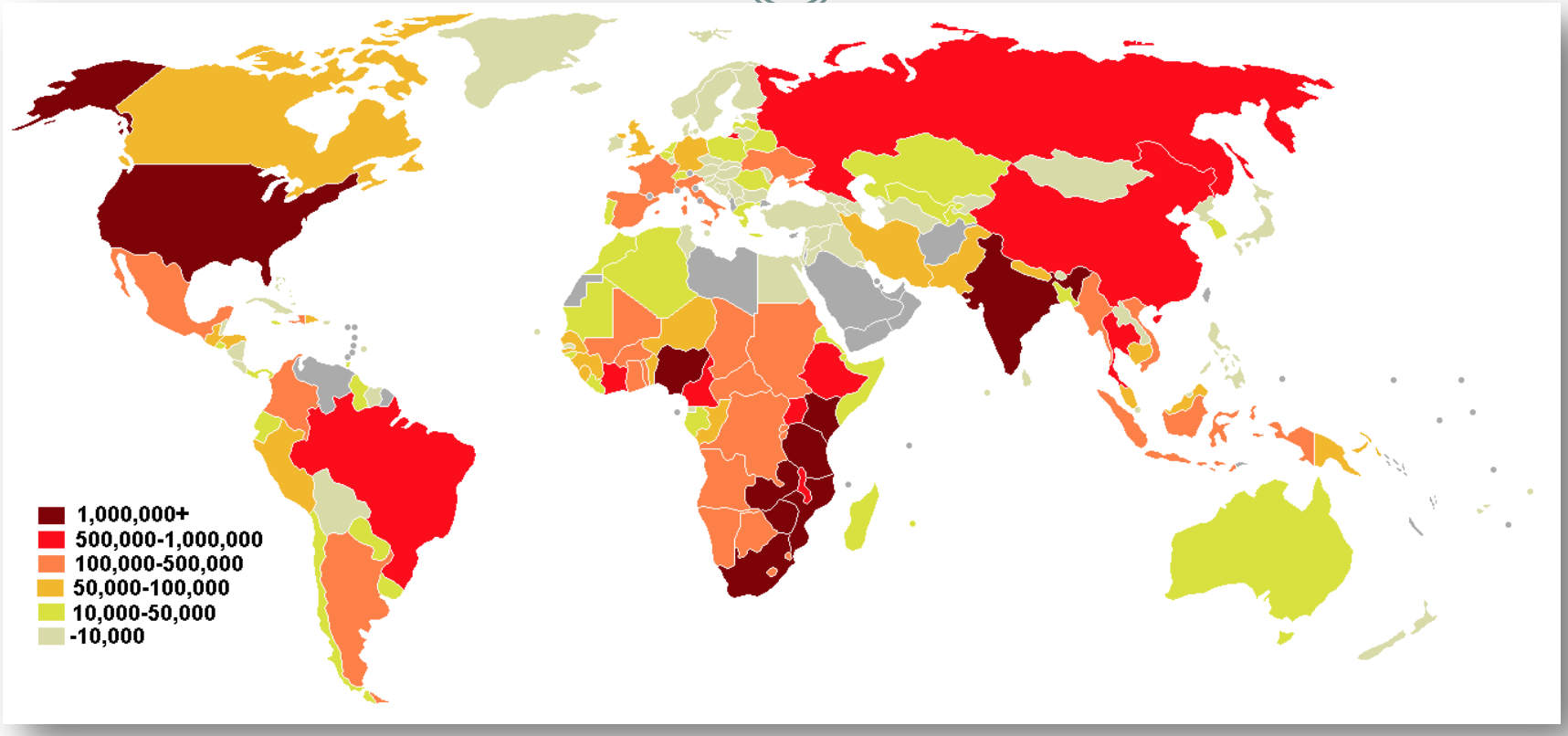
5 600 nouvelles infections par jour en 2014

7 000 en 2011, 5 750 en 2013

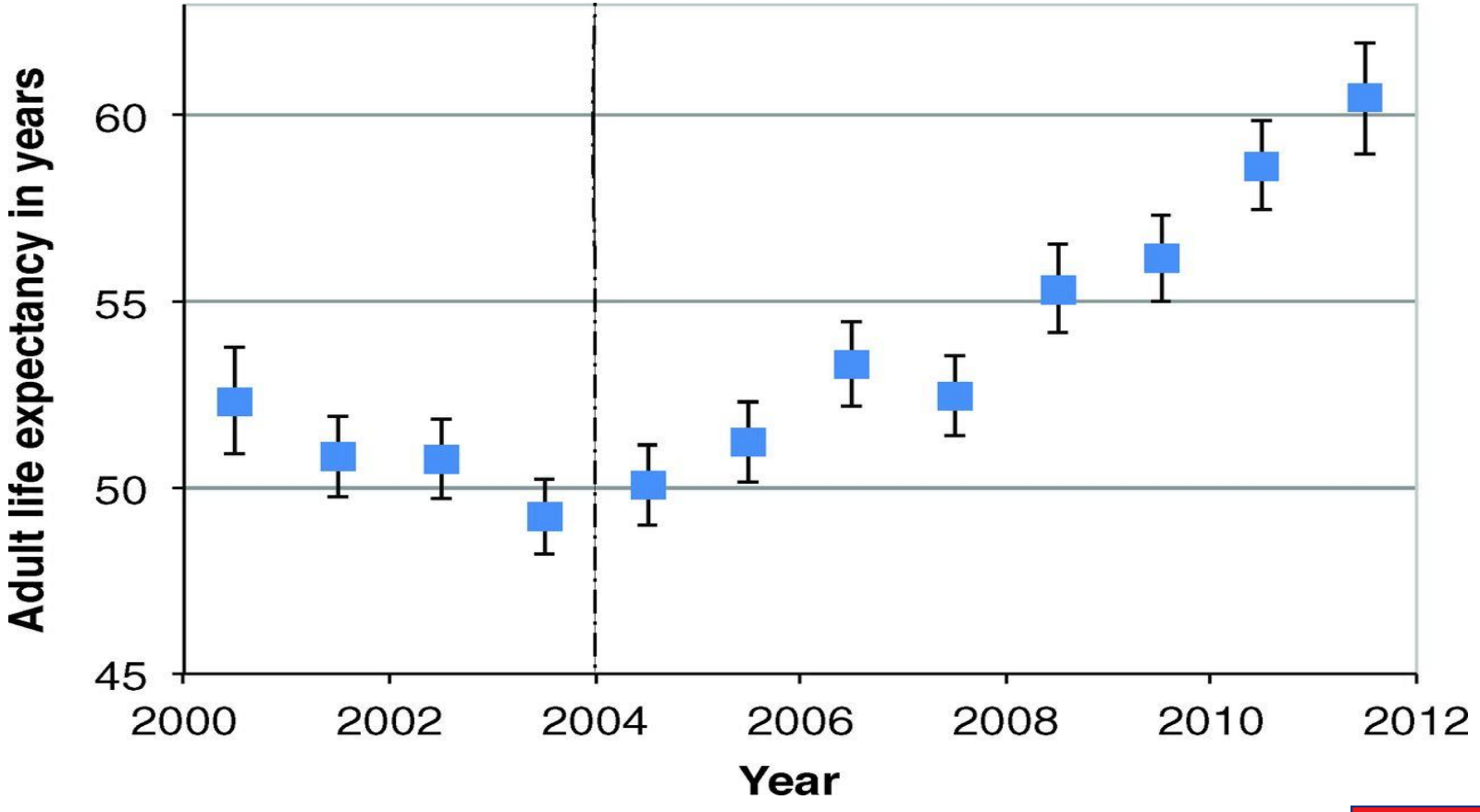
- Dont 66% en Afrique sub-saharienne
- Dont 600/j chez des enfants de moins de 15 ans
- Dont 5 000/j chez les adultes
  - Dont 48% de femmes
  - Dont 30% de jeunes de 15-24 ans

Répartition mondiale de la prévalence du VIH

Vue « Populationnelle »



Remontée de l'espérance de vie au Kwazulu Natal.



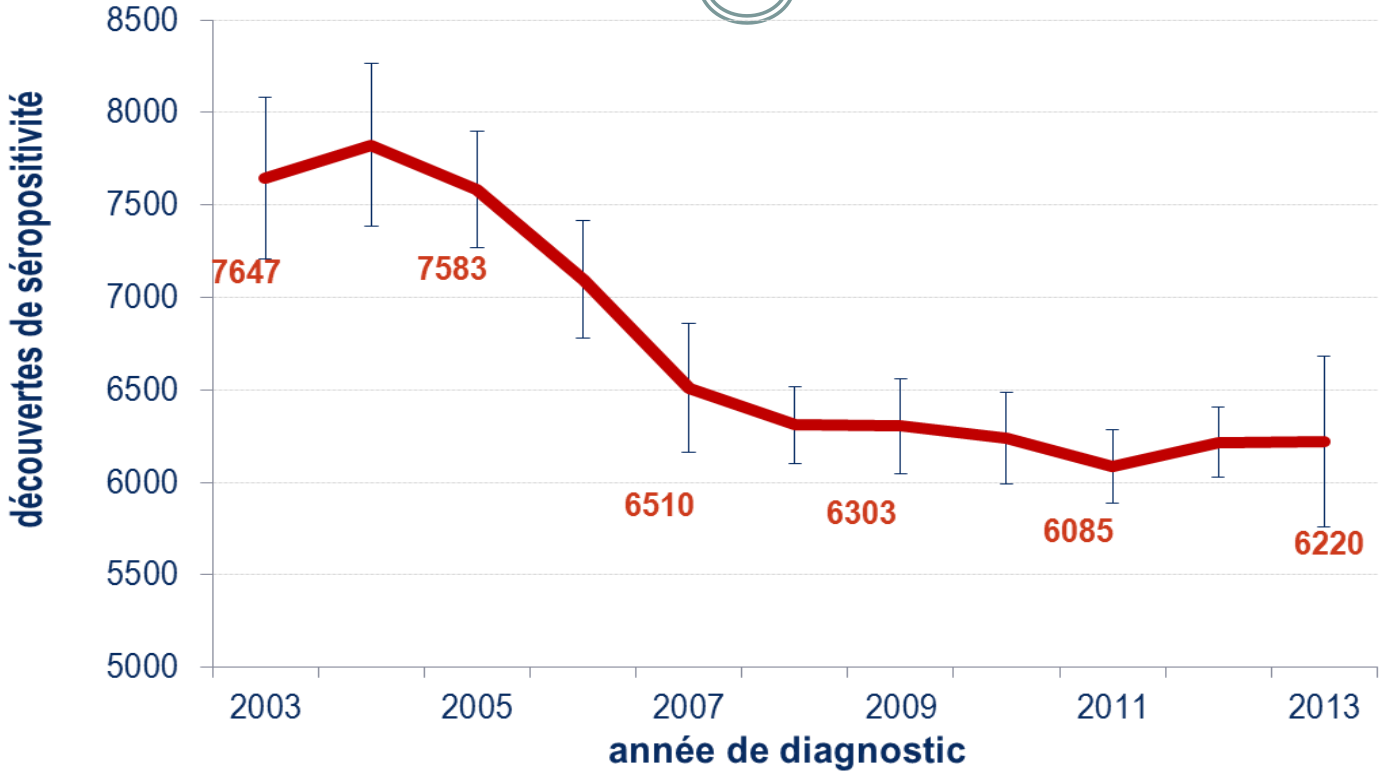
J Bor et al. Science 2013;339:961-965

Science
AAAS

En France aujourd'hui

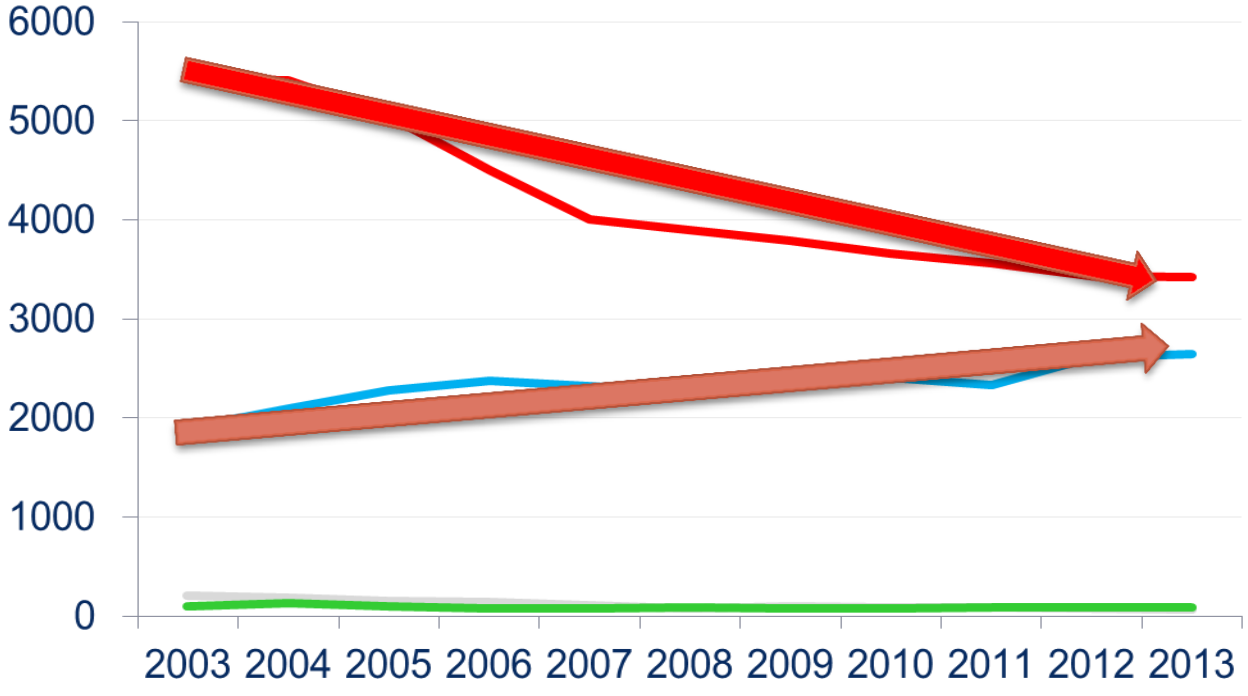
Environ 6 200 personnes [5 800-6 700] ont découvert leur séropositivité en 2013

9



Source : InVS, données DO VIH au 31/12/2013 corrigées pour les délais, la sous déclaration et les valeurs manquantes

Découvertes de séropositivité par mode de contamination



En 2013 :

55% Hétérosexuels

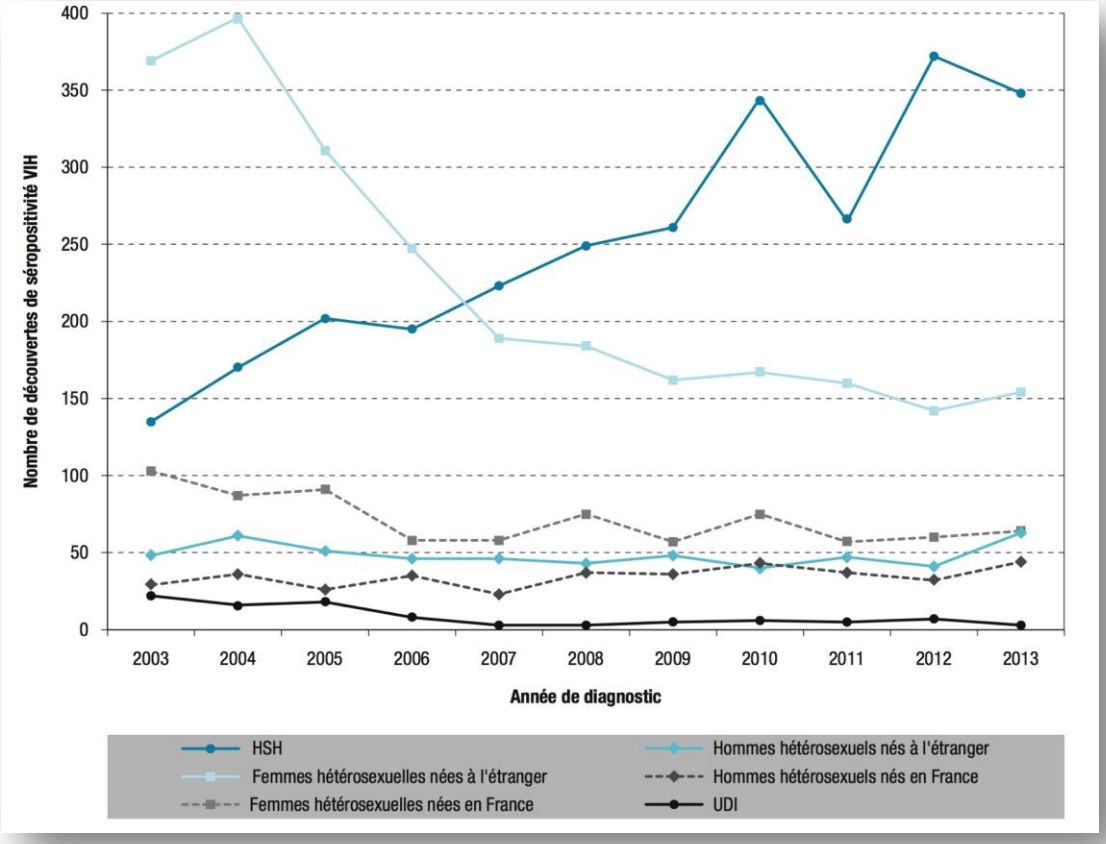
43% Hommes homosexuels (HSH)

1% Usagers de drogue injectable (UDI)

1% Autre

Source : InVS, données DO VIH au 31/12/2013 corrigées pour les délais, la sous déclaration et les valeurs manquantes

Evolution des modes de contaminations chez les 18-24 ans en France

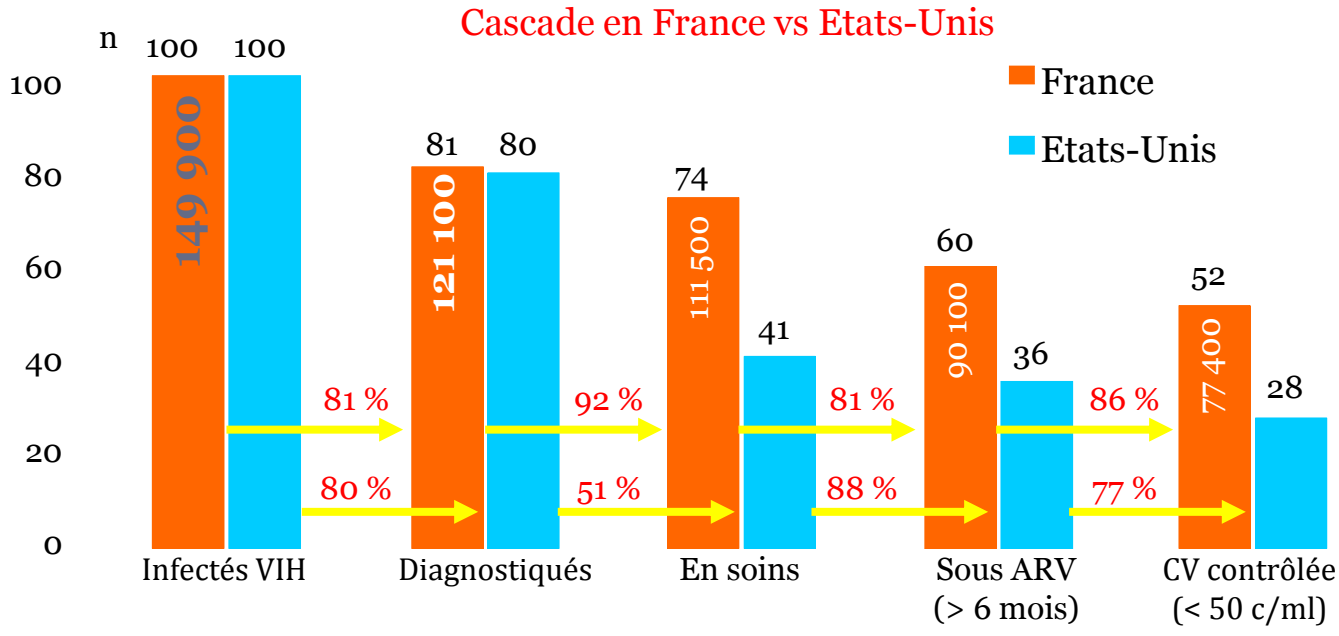


Prévalence du VIH en 2010

	Nb de PVVIH	Taille pop. 18-64 ans	Taux de prévalence(%)
Total	149 500 (143000-155800)	39 566 800	**0,37** (0,36-0,39)
Total Hommes	100 600	19 517 600	0,51
Total Femmes	48 800	20 049 200	0,24
HSH	53 100 (51200-55600)	312 300	**17,00** (16,39-17,80)
UDI	14 200 (12900-16700)	81 000	**17,53** (15,93-20,62)
Femmes hétérosexuelles étrangères	20 300 (18600-22600)	1 296 400	1,57 (1,43-1,74)
Hommes hétérosexuels étrangers	13 700 (11400-16400)	1 312 900	1,04 (0,87-1,25)
Femmes hétérosexuelles françaises	22 300 (19700-24600)	18 752 800	0,12 (0,11-0,13)
Hommes hétérosexuels français	22 000 (18400-26500)	17 811 400	0,12 (0,10-0,15)
Autres (transfusion sanguine, hémophilie, transmission périnatale)	3 800 (3000-4700)	-	-

En France: 150 000 personnes infectées et une cascade de la prise en charge du VIH

- Estimation du nombre et du pourcentage des personnes VIH+ engagées dans les différentes étapes des soins
- Comparaison avec données Etats-Unis *(Cohen SM, MMWR 2011,60:1618-23)*



Sources pour estimation:

- Déclarations de nouvelles séroposivités (INVS)
- Données de l'assurance maladie (CNAMTS)
- Cohorte hospitalière française (FHDH – ANRS CO4)

- Données 2010

Les nouvelles contaminations

Clinical Infectious Diseases Advance Access published September 19, 2015

HIV-1 Transmission During Recent Infection and During Treatment Interruptions as Major Drivers of New Infections in the Swiss HIV Cohort Study

Alex Marzel,[1,2] Mohaned Shilaih,[1,2] Wan-Lin Yang,[1,2] Jürg Böni,[2] Sabine Yerly,[3] Thomas Klimkait,[5] Vincent Aubert,[7] Dominique L. Braun,[1,2] Alexandra Calmy,[4] Hansjakob Furrer,[9] Matthias Cavassini,[8] Manuel Battegay,[6] Pietro L. Vernazza,[10] Enos Bernasconi,[11] Huldrych F. Günthard,[1,2] Roger D. Kouyos,[1,2] and the Swiss HIV Cohort Study[a]

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Background. Reducing the fraction of transmissions during recent human immunodeficiency virus (HIV) infection is essential for the population-level success of "treatment as prevention".

Methods. A phylogenetic tree was constructed with 19 604 Swiss sequences and 90 994 non-Swiss background sequences. Swiss transmission pairs were identified using 104 combinations of genetic distance (1%–2.5%) and bootstrap (50%–100%) thresholds, to examine the effect of those criteria. Monophyletic pairs were classified as recent or chronic transmission based on the time interval between estimated seroconversion dates. Logistic regression with adjustment for clinical and demographic characteristics was used to identify risk factors associated with transmission during recent or chronic infection.

Findings. Seroconversion dates were estimated for 4079 patients on the phylogeny, and comprised between 71 (distance, 1%; bootstrap, 100%) to 378 transmission pairs (distance, 2.5%; bootstrap, 50%). We found that 43.7% (range, 41%–56%) of the transmissions occurred during the first year of infection. Stricter phylogenetic definition of transmission pairs was associated with higher recent-phase transmission fraction. Chronic-phase viral load area under the curve (adjusted odds ratio, 3; 95% confidence interval, 1.64–5.48) and time to antiretroviral therapy (ART) start (adjusted odds ratio 1.4/y; 1.11–1.77) were associated with chronic-phase transmission as opposed to recent transmission. Importantly, at least 14% of the chronic-phase transmission events occurred after the transmitter had interrupted ART.

Conclusions. We demonstrate a high fraction of transmission during recent HIV infection but also chronic transmissions after interruption of ART in Switzerland. Both represent key issues for treatment as prevention and underline the importance of early diagnosis and of early and continuous treatment.

Keywords. HIV recent (early) infection; treatment as prevention; treatment interruptions; HIV transmission; endgame.

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[a]Members of the Swiss HIV Cohort Study are listed in the Acknowledgments.

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Clinical Infectious Diseases®

DOI: 10.1093/cid/civ732

Human immunodeficiency virus (HIV) remains an immense public health threat, with a global prevalence of 35.3 million infected individuals in 2013 [1]. Whereas in most high-income countries the incidence of male-female transmission has been stable or decreasing, the incidence of male-male transmission is rising or remains high [2]. In this context, one pivotal question is

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MAJOR ARTICLE HIV/AIDS

HIV-1 Transmission During Recent Infection and During Treatment Interruptions as Major Drivers of New Infections in the Swiss HIV Cohort Study

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- Un peu plus de 4 000 patients avec séquence virale
- Fort taux de transmission au cours de la 1ère année d'infection (42%)
- Nombre non négligeable d'infection en rapport avec des arrêts de traitement (14%)

transmission. Importantly, at least 14% of the chronic-phase transmission events occurred after the transmitter had interrupted ART.

Conclusions. We demonstrate a high fraction of transmission during recent HIV infection but also chronic transmissions after interruption of ART in Switzerland. Both represent key issues for treatment as prevention and underline the importance of early diagnosis and of early and continuous treatment.

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La « PrEP »

PRÉVENTION PRÉ-EXPOSITION

PROUD

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.

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]

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*Equal contribution

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IPERGAY

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.

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PrEP : deux essais essentiels

IPERGAY

- Truvada®
- Randomisée
- Placebo
- France/Québec
- **PrEP au « coup par coup »**
  - **Ça marche très bien !**
    - **- 86%** d'infection VIH
    - NPT = 18

PROUD

- Truvada®
- 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

No New HIV Infections With Increasing Use of HIV Preexposure Prophylaxis in a Clinical Practice Setting

Jonathan E. Volk,[1] Julia L. Marcus,[2] Tony Phengrasamy,[1] Derek Blechinger,[1] Dong Phuong Nguyen,[1] Stephen Follansbee,[1] and C. Bradley Hare[1]

[1]Department of Adult and Family Medicine, Kaiser Permanente San Francisco Medical Center, and [2]Division of Research, Kaiser Permanente Northern California, Oakland, California

(See the Editorial Commentary by Koester and Grant on pages 1604–5.)

Referrals for and initiation of preexposure prophylaxis (PrEP) for human immunodeficiency virus (HIV) infection increased dramatically in a large clinical practice setting since 2012. Despite high rates of sexually transmitted infections among PrEP users and reported decreases in condom use in a subset, there were no new HIV infections in this population.

Keywords. preexposure prophylaxis; men who have sex with men; HIV; sexually transmitted infections; behavioral disinhibition.

The effectiveness of once-daily oral preexposure prophylaxis (PrEP) using tenofovir/emtricitabine for prevention of sexually acquired human immunodeficiency virus (HIV) infection has been demonstrated in trials and open-label studies [1, 2]; however, data on PrEP use outside of the research context are limited. Interest in PrEP was high among men who have sex with men (MSM) in a demonstration project in the United States [3], yet initial pharmacy data indicated that many at-risk individuals were not accessing PrEP [4]. In addition, despite reassuring data suggesting that sexual risk behavior and the incidence of sexually transmitted infections (STIs) did not increase in PrEP trials [5, 6], few data on sexual behavior or STIs have been reported among PrEP users outside of research settings.

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DOI: 10.1093/cid/civ778

We aimed to characterize patterns of PrEP use among members of the Kaiser Permanente Medical Center in San Francisco (KPSF). We describe characteristics of individuals evaluated for and initiating PrEP, trends in PrEP referrals and initiation, incidence of HIV and other STIs among PrEP users, and self-reported changes in condom use and number of sexual partners after PrEP initiation.

METHODS

Kaiser Permanente is a large integrated healthcare system that provides comprehensive medical services to >170 000 adult residents in San Francisco. Our study population included all adult KPSF members evaluated for PrEP from July 2012 (the date of approval by the US Food and Drug Administration) through February 2015. At KPSF, primary care or other providers refer patients to a specialized PrEP program after assessment of risk or patient-initiated request. This program, created to meet the growing demand for PrEP, provides adherence support and clinical monitoring by infectious disease physicians, pharmacists, nurses, and administrative staff.

As part of the PrEP program, patients were screened for medical contraindications to the use of tenofovir/emtricitabine and for HIV antibody and viral load. Demographic data and reasons for starting or not starting PrEP were assessed during an in-person intake visit. Similar to PrEP trials [1], safety assessments and HIV/STI screening were repeated every 1–3 months after PrEP initiation. Testing for chlamydia and gonorrhea was done using nucleic acid amplification tests of urine and self-collected swabs of the throat and rectum. Beginning in July 2014, patients were surveyed by secure email after 6 months of PrEP use about changes in sexual behavior since starting PrEP.

We used descriptive statistics to compare PrEP initiators and noninitiators and those who did and did not report increases in risk behavior, with χ^2 tests for categorical variables and t tests for continuous variables. We used Kaplan–Meier analysis to compute the cumulative incidence of STIs and HIV after 6 and 12 months of PrEP use. Concurrent diagnosis of an STI at multiple anatomic sites (ie, pharyngeal, urethral, and/or rectal) was considered 1 infection, whereas diagnoses of gonorrhea and chlamydia in 1 anatomic site were considered multiple infections. Analyses were conducted using SAS software version 9.1 (SAS Institute, Cary, North Carolina). Statistical tests were 2-sided except where otherwise indicated, and statistical significance was defined as $P < .05$.

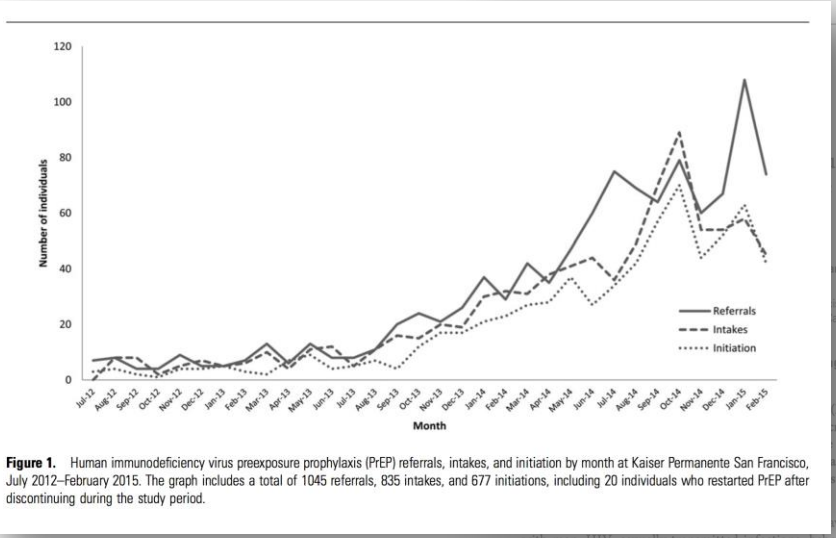

Figure 1. Human immunodeficiency virus preexposure prophylaxis (PrEP) referrals, intakes, and initiation by month at Kaiser Permanente San Francisco, July 2012–February 2015. The graph includes a total of 1045 referrals, 835 intakes, and 677 initiations, including 20 individuals who restarted PrEP after discontinuing during the study period.

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DOI: 10.1093/cid/civ778

- <u>Aucune infection VIH parmi les initiateurs de PrEP</u>
  - Malgré
    - Une diminution d'utilisation de préservatif de 41%
    - Une incidence importante des IST, notamment rectales

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 5, 2015 VOL. 372 NO. 6

Tenofovir-Based Preexposure Prophylaxis for HIV Infection among African Women

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ABSTRACT

BACKGROUND

Reproductive-age women need effective interventions to prevent the acquisition of human immunodeficiency virus type 1 (HIV-1) infection.

METHODS

We conducted a randomized, placebo-controlled trial to assess daily treatment with oral tenofovir disoproxil fumarate (TDF), oral tenofovir–emtricitabine (TDF-FTC), or 1% tenofovir (TFV) vaginal gel as preexposure prophylaxis against HIV-1 infection in women in South Africa, Uganda, and Zimbabwe. HIV-1 testing was performed monthly, and plasma TFV levels were assessed quarterly.

RESULTS

Of 12,320 women who were screened, 5029 were enrolled in the study. The rate of retention in the study was 91% during 5509 person-years of follow-up. A total of 312 HIV-1 infections occurred; the incidence of HIV-1 infection was 5.7 per 100 person-years. In the modified intention-to-treat analysis, the effectiveness was −49.0% with TDF (hazard ratio for infection, 1.49; 95% confidence interval [CI], 0.97 to 2.29), −4.4% with TDF-FTC (hazard ratio, 1.04; 95% CI, 0.73 to 1.49), and 14.5% with TFV gel (hazard ratio, 0.85; 95% CI, 0.61 to 1.21). In a random sample, TFV was detected in 30%, 29%, and 25% of available plasma samples from participants randomly assigned to receive TDF, TDF-FTC, and TFV gel, respectively. Independent predictors of TFV detection included being married, being older than 25 years of age, and being multiparous. Detection of TFV in plasma was negatively associated with characteristics predictive of HIV-1 acquisition. Elevations of serum creatinine levels were seen more frequently among participants randomly assigned to receive oral TDF-FTC than among those assigned to receive oral placebo (1.3% vs. 0.2%, P=0.004). We observed no significant differences in the frequencies of other adverse events.

CONCLUSIONS

None of the drug regimens we evaluated reduced the rates of HIV-1 acquisition in an intention-to-treat analysis. Adherence to study drugs was low. (Funded by the National Institutes of Health; VOICE ClinicalTrials.gov number, NCT00705679.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Marrazzo at the Division of Infectious Diseases, Harborview Medical Center, 325 9th Ave., Mailbox 359932, Seattle, WA 98104, or at jmm2@uw.edu.

*A complete list of members of the Vaginal and Oral Interventions to Control the Epidemic (VOICE) Study Team is provided in the Supplementary Appendix, available at NEJM.org.

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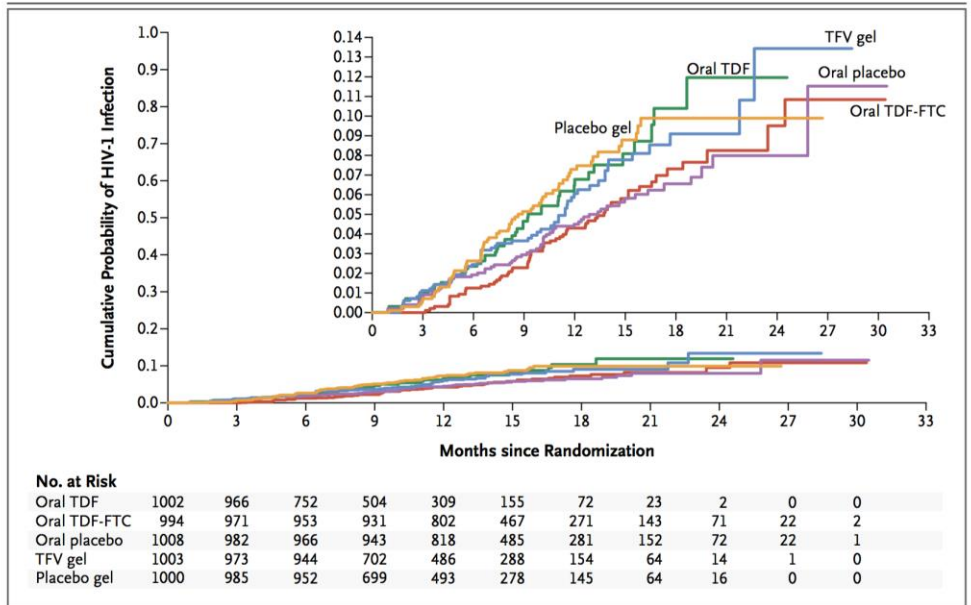

No. at Risk

Oral TDF	1002	966	752	504	309	155	72	23	2	0	0
Oral TDF-FTC	994	971	953	931	802	467	271	143	71	22	2
Oral placebo	1008	982	966	943	818	485	281	152	72	22	1
TFV gel	1003	973	944	702	486	288	154	64	14	1	0
Placebo gel	1000	985	952	699	493	278	145	64	16	0	0

Figure 2. Cumulative Probability of HIV-1 Infection, According to Study Group.

The numbers shown below the graph are the numbers of participants who were at risk at the start of each quarterly interval. The inset shows the same data on an enlarged y axis.

Le traitement précoce
Un bénéfice individuel et collectif !

LE 30 SEPTEMBRE 2015, L'OMS RECOMMANDE POUR LA PREMIÈRE FOIS L'INTRODUCTION DU TRAITEMENT POUR TOUS LES SÉROPOSITIFS, QUEL QUE SOIT LEUR STATUT CLINIQUE OU IMMUNITAIRE

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 27, 2015 VOL. 373 NO. 9

Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection

The INSIGHT START Study Group*

ABSTRACT

BACKGROUND

Data from randomized trials are lacking on the benefits and risks of initiating antiretroviral therapy in patients with asymptomatic human immunodeficiency virus (HIV) infection who have a CD4+ count of more than 350 cells per cubic millimeter.

METHODS

We randomly assigned HIV-positive adults who had a CD4+ count of more than 500 cells per cubic millimeter to start antiretroviral therapy immediately (immediate-initiation group) or to defer it until the CD4+ count decreased to 350 cells per cubic millimeter or until the development of the acquired immunodeficiency syndrome (AIDS) or another condition that dictated the use of antiretroviral therapy (deferred-initiation group). The primary composite end point was any serious AIDS-related event, serious non–AIDS-related event, or death from any cause.

RESULTS

A total of 4685 patients were followed for a mean of 3.0 years. At study entry, the median HIV viral load was 12,759 copies per milliliter, and the median CD4+ count was 651 cells per cubic millimeter. On May 15, 2015, on the basis of an interim analysis, the data and safety monitoring board determined that the study question had been answered and recommended that patients in the deferred-initiation group be offered antiretroviral therapy. The primary end point occurred in 42 patients in the immediate-initiation group (1.8%; 0.60 events per 100 person-years), as compared with 96 patients in the deferred-initiation group (4.1%; 1.38 events per 100 person-years), for a hazard ratio of 0.43 (95% confidence interval [CI], 0.30 to 0.62; P<0.001). Hazard ratios for serious AIDS-related and serious non–AIDS-related events were 0.28 (95% CI, 0.15 to 0.50; P<0.001) and 0.61 (95% CI, 0.38 to 0.97; P=0.04), respectively. More than two thirds of the primary end points (68%) occurred in patients with a CD4+ count of more than 500 cells per cubic millimeter. The risks of a grade 4 event were similar in the two groups, as were the risks of unscheduled hospital admissions.

CONCLUSIONS

The initiation of antiretroviral therapy in HIV-positive adults with a CD4+ count of more than 500 cells per cubic millimeter provided net benefits over starting such therapy in patients after the CD4+ count had declined to 350 cells per cubic millimeter. (Funded by the National Institute of Allergy and Infectious Diseases and others; START ClinicalTrials.gov number, NCT00867048.)

The members of the writing group (Jens D. Lundgren, M.D. [cochair], Abdel G. Babiker, Ph.D. [cochair], Fred Gordin, M.D. [cochair], Sean Emery, Ph.D., Birgit Grund, Ph.D., Shweta Sharma, M.S., Anchalee Avihingsanon, M.D., David A. Cooper, M.D., Gerd Fätkenheuer, M.D., Josep M. Llibre, M.D., Jean-Michel Molina, M.D., Paula Munderi, M.D., Mauro Schechter, M.D., Robin Wood, M.D., Karin L. Klingman, M.D., Simon Collins, H. Clifford Lane, M.D., Andrew N. Phillips, Ph.D., and James D. Neaton, Ph.D. [INSIGHT PI]) of the INSIGHT START Study Group assume responsibility for the overall content and integrity of this article. The affiliations of the members of the writing group are listed in the Appendix. Address reprint requests to Dr. Lundgren at the Department of Infectious Diseases, Rigshospitalet, University of Copenhagen, Blegdamsvej 9, 2100 Copenhagen Ø, Denmark, or at jens.lundgren@regionh.dk.

*A complete list of members in the Strategic Timing of Antiretroviral Treatment (START) Study Group is provided in the Supplementary Appendix, available at NEJM.org.

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ORIGINAL ARTICLE

A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa

The TEMPRANO ANRS 12136 Study Group*

ABSTRACT

BACKGROUND

In sub-Saharan Africa, the burden of human immunodeficiency virus (HIV)–associated tuberculosis is high. We conducted a trial with a 2-by-2 factorial design to assess the benefits of early antiretroviral therapy (ART), 6-month isoniazid preventive therapy (IPT), or both among HIV-infected adults with high CD4+ cell counts in Ivory Coast.

METHODS

We included participants who had HIV type 1 infection and a CD4+ count of less than 800 cells per cubic millimeter and who met no criteria for starting ART according to World Health Organization (WHO) guidelines. Participants were randomly assigned to one of four treatment groups: deferred ART (ART initiation according to WHO criteria), deferred ART plus IPT, early ART (immediate ART initiation), or early ART plus IPT. The primary end point was a composite of diseases included in the case definition of the acquired immunodeficiency syndrome (AIDS), non–AIDS-defining cancer, non–AIDS-defining invasive bacterial disease, or death from any cause at 30 months. We used Cox proportional models to compare outcomes between the deferred-ART and early-ART strategies and between the IPT and no-IPT strategies.

RESULTS

A total of 2056 patients (41% with a baseline CD4+ count of ≥500 cells per cubic millimeter) were followed for 4757 patient-years. A total of 204 primary end-point events were observed (3.8 events per 100 person-years; 95% confidence interval [CI], 3.3 to 4.4), including 68 in patients with a baseline CD4+ count of at least 500 cells per cubic millimeter (3.2 events per 100 person-years; 95% CI, 2.4 to 4.0). Tuberculosis and invasive bacterial diseases accounted for 42% and 27% of primary end-point events, respectively. The risk of death or severe HIV-related illness was lower with early ART than with deferred ART (adjusted hazard ratio, 0.56; 95% CI, 0.41 to 0.76; adjusted hazard ratio among patients with a baseline CD4+ count of ≥500 cells per cubic millimeter, 0.56; 95% CI, 0.33 to 0.94) and lower with IPT than with no IPT (adjusted hazard ratio, 0.65; 95% CI, 0.48 to 0.88; adjusted hazard ratio among patients with a baseline CD4+ count of ≥500 cells per cubic millimeter, 0.61; 95% CI, 0.36 to 1.01). The 30-month probability of grade 3 or 4 adverse events did not differ significantly among the strategies.

CONCLUSIONS

In this African country, immediate ART and 6 months of IPT independently led to lower rates of severe illness than did deferred ART and no IPT, both overall and among patients with CD4+ counts of at least 500 cells per cubic millimeter. (Funded by the French National Agency for Research on AIDS and Viral Hepatitis; TEMPRANO ANRS 12136 ClinicalTrials.gov number, NCT00495651.)

The members of the writing group, who are listed in the Appendix, assume responsibility for the content and integrity of this article. Address reprint requests to Dr. Anglaret at INSERM Unité 897, Université de Bordeaux, 146 rue Léo Saignat, 33076 Bordeaux, France, or at xavier.anglaret@isped.u-bordeaux2.fr.

*A list of additional members of the TEMPRANO ANRS 12136 Study Group is provided in the Supplementary Appendix, available at NEJM.org.

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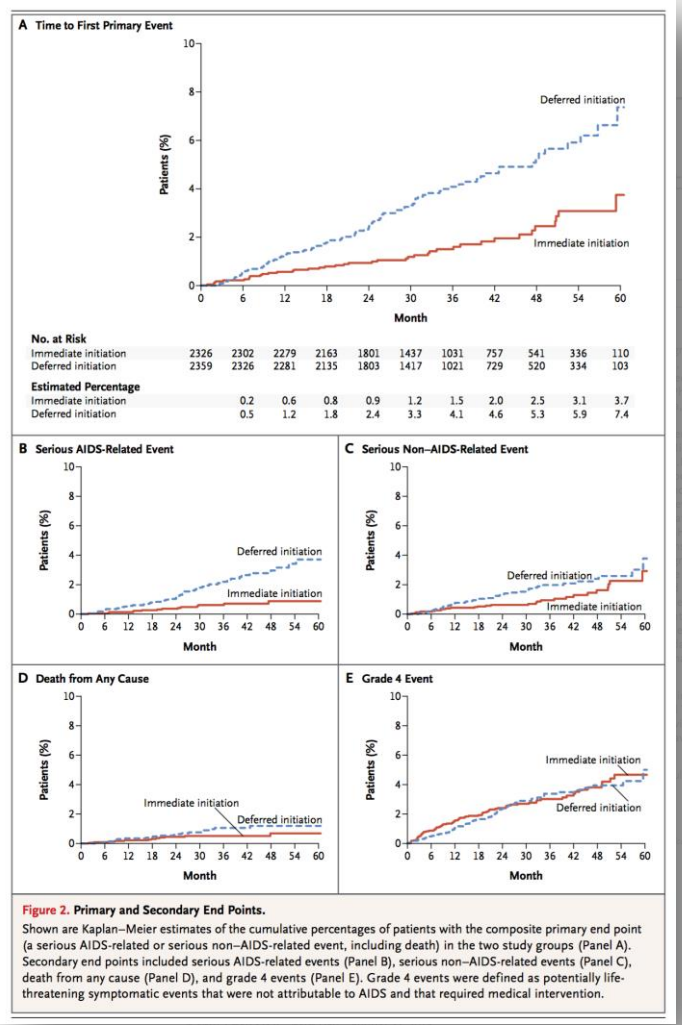

Figure 2. Primary and Secondary End Points.

Shown are Kaplan–Meier estimates of the cumulative percentages of patients with the composite primary end point (a serious AIDS-related or serious non–AIDS-related event, including death) in the two study groups (Panel A). Secondary end points included serious AIDS-related events (Panel B), serious non–AIDS-related events (Panel C), death from any cause (Panel D), and grade 4 events (Panel E). Grade 4 events were defined as potentially life-threatening symptomatic events that were not attributable to AIDS and that required medical intervention.

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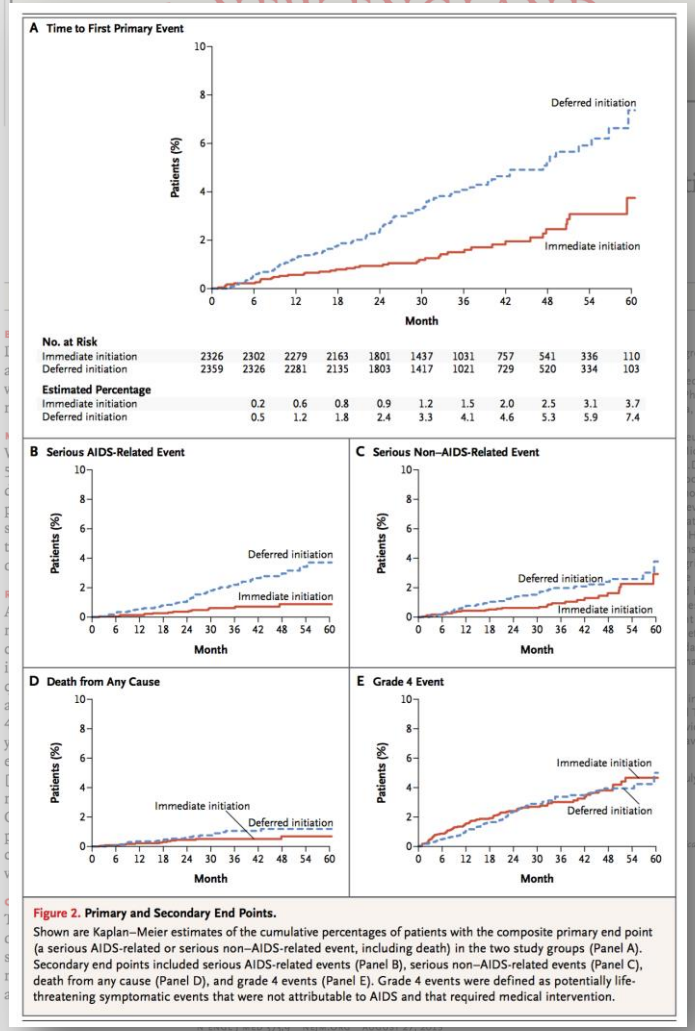

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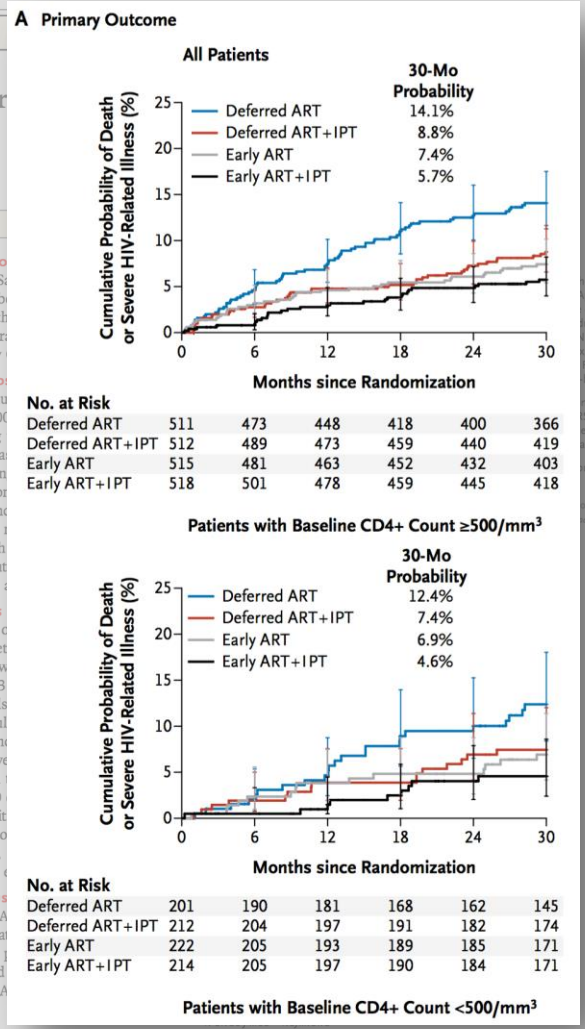

Increasing use of 'party drugs' in people living with HIV on antiretrovirals: a concern for patient safety

Margherita Bracchi[a], David Stuart[b], Richard Castles[c], Saye Khoo[d], David Back[d] and Marta Boffito[a,b,e]

Use of 'party drugs', a particular set of recreational drugs used in the context of 'ChemSex', is frequent among MSM living with HIV. A recently published observational study showed that more than half of HIV-infected MSM interviewed reported use of illicit substances in the previous 3 months, with frequent concomitant use of three or more drugs. These substances are a combination of 'club drugs' (methylenedioxymethamphetamine, gamma-hydroxybutyrate, ketamine, benzodiazepine) and drugs that are more specifically used in a sexualized context (methamphetamine, mephedrone, poppers and erectile dysfunction agents). Although formal data on pharmacokinetic or pharmacodynamic interactions between recreational drugs and antiretroviral agents are lacking, information regarding potentially toxic interactions can be theorized or sometimes conclusions may be drawn from case studies and cohort observational studies. However, the risk of coadministering party drugs and antiretrovirals should not be overestimated. The major risk for a drug–drug interaction is when using ritonavir-boosting or cobicistat-boosting agents, and maybe some nonnucleoside reverse transcriptase inhibitors. Knowledge of the metabolic pathways of 'party drugs' may help in advising patients on which illicit substances have a high potential for drug–drug interactions, as this is not the case for all.

AIDS 2015, **29**:1585–1592

Keywords: antiretroviral agents, drug interactions, HIV infection, MSM, recreational drugs, street drugs

Introduction

Recreational drug abuse and addiction have been linked with HIV/AIDS since the beginning of the epidemic, with the commonest substances in the early days being 'street drugs' such as opiates, crack and cocaine [1]. In the last two decades and even more so in the past few years, different recreational drugs have become more frequently used among MSM and bisexual men, especially within HIV-positive patients [2,3]. These recreational drugs, commonly called 'party drugs' or 'club drugs', are consumed in club or house parties, and they are often used to have sex, which can last for entire weekends [4–6]. They consist of a mix of agents such as methylenedioxymethamphetamine (MDMA), gamma-hydroxybutyrate (GHB), ketamine, benzodiazepine (e.g. diazepam) [7] – and of substances that are more specifically used in a sexualized context. The latter are methamphetamine, mephedrone, poppers and erectile dysfunction agents (EDA). According to the recently published Antiretrovirals, Sexual Transmission Risk and Attitudes (ASTRA) study [3], of 2248 HIV MSM surveyed for HIV-related, sociodemographic and lifestyle factors, half of the individuals (1138, 50.6%) reported use of recreational drugs in the previous 3 months. About a

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Table 1. 'Party drugs' pharmacological characteristics.

Drug name (alternative/street names)	Route of administration	Bioavailability when orally administered	Metabolism	Half-life	Interaction potential
Crystal methamphetamine (Crystal, Tina, Meth)	Oral ingestion, smoke, insufflation, rectal insertion, IV	67–80%	CYP2D6; Other non-CYP pathways (minor)	~12 h	Moderate (COBI/RTV inhibition of CYP2D6)
MDMA (Ecstasy, X, Mandy)	Oral ingestion, insufflation (capsules/ tablets/powder)	40–60%	CYP2D6; CYP1A2, CYP2B6 and CYP3A4 (minor)	~7 h	Moderate (COBI /RTV inhibition of CYP2D6)
Mephedrone (Miaw Miaw, plant food, bath salts)	Oral ingestion, insufflation (most common), rectal insertion (dissolved or as gel forms), IV	10%	CYP2D6; NADPH-dependent enzymes (minor)	30 min–1.5 h	Moderate (COBI /RTV inhibition of CYP2D6)
Cocaine (Charlie, C, Coke)	Oral ingestion, insufflation (most common), smoke, IV	30–60%	Plasma/liver cholinesterases	0.5–2 h	Low to moderate
Ketamine (K, vitamin K, special K)	Oral ingestion, insufflation, IV or IM	20–45%	CYP3A4; CYPB6 and CYP2C9 (minor)	1.8–2.8 h	High (COBI /RTV inhibition of CYP3A4)
GHB/GBL/1,4 GD (G, Gina, liquid E)	Oral ingestion (liquid), (rarely IV)	GHB: 59–65% GBL: 85%	GHB: GHB-DH and SSA-DH GBL: Lactonase 1,4 BD: alcohol DH and aldehyde DH	GHB: 20–60 min (GLB and 1,4 BD are rapidly converted to GHB)	Unknown
Benzodiazepines (alprazolam, diazepam)	Oral ingestion (tablets), rectal (gel forms), IV (crushed tablets)	Diazepam: 100% Alprazolam: 90%	Diazepam: CYP3A4; CYP2C19 (minor) Alprazolam: CYP3A4	Alprazolam: 12–15 h Diazepam: 43–56 h	High (COBI /RTV inhibition of CYP3A4)
EDAs (sildenafil, tadalafil, vardenafil)	Oral ingestion (tablets)	Sildenafil: 41% Tadalafil: 80% Vardenafil: 15%	CYP3A4	Sildenafil: 4 h Tadalafil: 17.5 h Vardenafil: 4.5 h	High (COBI /RTV inhibition of CYP3A4)

1,4 BD, 1,4 butanediol; COBI, cobicistat; DH, dehydrogenase; EDA, erectile dysfunction agents; GBL, gamma-butyrolactone; GHB-DH, gamma-hydroxybutyrate dehydrogenase; IM, intramuscular; IV, intravenous; NADPH, nicotinamide adenine dinucleotide phosphate (reduced form); RTV, ritonavir; SSA-DH, succinic semialdehyde dehydrogenase.

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Transmission mère-enfant

OBJECTIF OMS « ZÉRO TRANSMISSION MÈRE-ENFANT EN 2020 » EN VUE…

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No Perinatal HIV-1 Transmission From Women With Effective Antiretroviral Therapy Starting Before Conception

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Background. The efficacy of preventing perinatal transmission (PT) of human immunodeficiency virus type 1 (HIV-1) depends on both viral load (VL) and treatment duration. The objective of this study was to determine whether initiating highly active antiretroviral therapy (ART) before conception has the potential to eliminate PT.

Methods. A total of 8075 HIV-infected mother/infant pairs included from 2000 to 2011 in the national prospective multicenter French Perinatal Cohort (ANRS-EPF) received ART, delivered live-born children with determined HIV infection status, and did not breastfeed. PT was analyzed according to maternal VL at delivery and timing of ART initiation.

Results. The overall rate of PT was 0.7% (56 of 8075). No transmission occurred among 2651 infants born to women who were receiving ART before conception, continued ART throughout the pregnancy, and delivered with a plasma VL <50 copies/mL (upper 95% confidence interval [CI], 0.1%). VL and timing of ART initiation were independently associated with PT in logistic regression. Regardless of VL, the PT rate increased from 0.2% (6 of 3505) for women starting ART before conception to 0.4% (3 of 709), 0.9% (24 of 2810), and 2.2% (23 of 1051) for those starting during the first, second, or third trimester ($P < .001$). Regardless of when ART was initiated, the PT rate was higher for women with VLs of 50–400 copies/mL near delivery than for those with <50 copies/mL (adjusted odds ratio, 4.0; 95% CI, 1.9–8.2).

Conclusions. Perinatal HIV-1 transmission is virtually zero in mothers who start ART before conception and maintain suppression of plasma VL.

Keywords. HIV; pregnancy; antiretroviral therapy; treatment as prevention; mother-to-child transmission.

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[a]Members of the ANRS-EPF Study Group are listed in the Acknowledgments.

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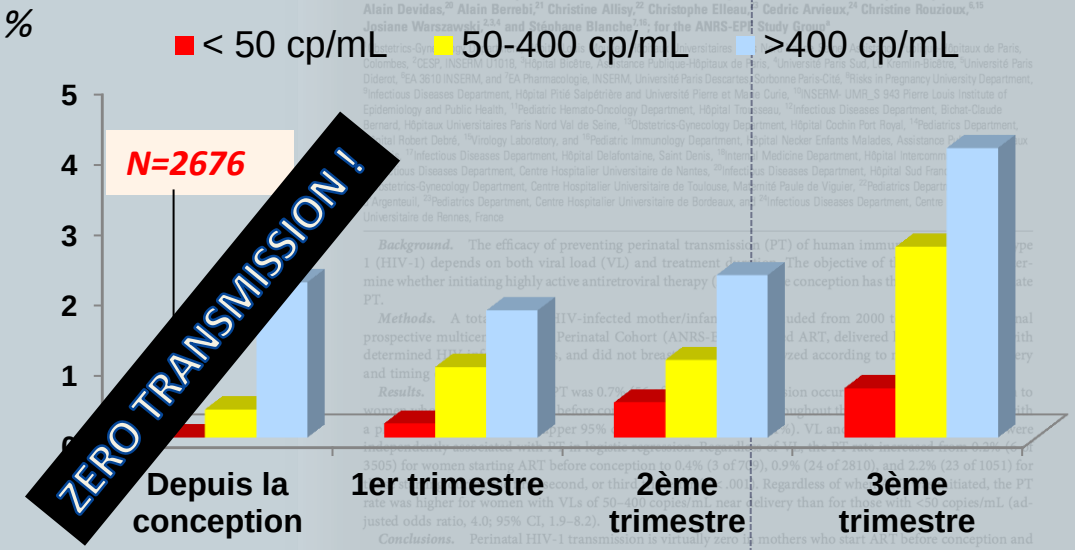
Transmission mère-enfant sous multithérapieselon le moment de début de traitement et la charge virale à l'accouchement, 2000-2010



EPF anRS
INSERM
CESP 1018

Effet charge virale

Effet délai de traitement

Traitement débuté avant conception et charge virale < 50 cop/mL

TME = 0% [0.0 - 0.1]

Conclusions

- Une évolution épidémique mondiale à la baisse
  - Mais pas partout
  - D'importants succès (TME)
- Une évolution en France inquiétante chez les HSH
  - Notamment chez les jeunes
  - Associé à une consommation variée de produits…
- De nouveaux outils de prévention
  - TasP et PrEP