JNI 19es Journées Nationales d'Infectiologie
du mercredi 13 au vendredi 15 juin 2018
Cité des Congrès de Nantes
Nantes
et la région Pays de la Loire

Best of en Infectiologie
Infection VIH/SIDA

François Raffi
SMIT, CHU de NANTES

UNIVERSITÉ DE NANTES
CIC Nantes
CENTRE HOSPITALIER UNIVERSITAIRE DE NANTES
SMIT CHU NANTES

- **Liens d'intérêts**

  - Soutien recherche : MSD
  - Advisory boards et/ou consultant : Gilead Sciences, Janssen, MSD, ViiV Healthcare

VIH et Résistance

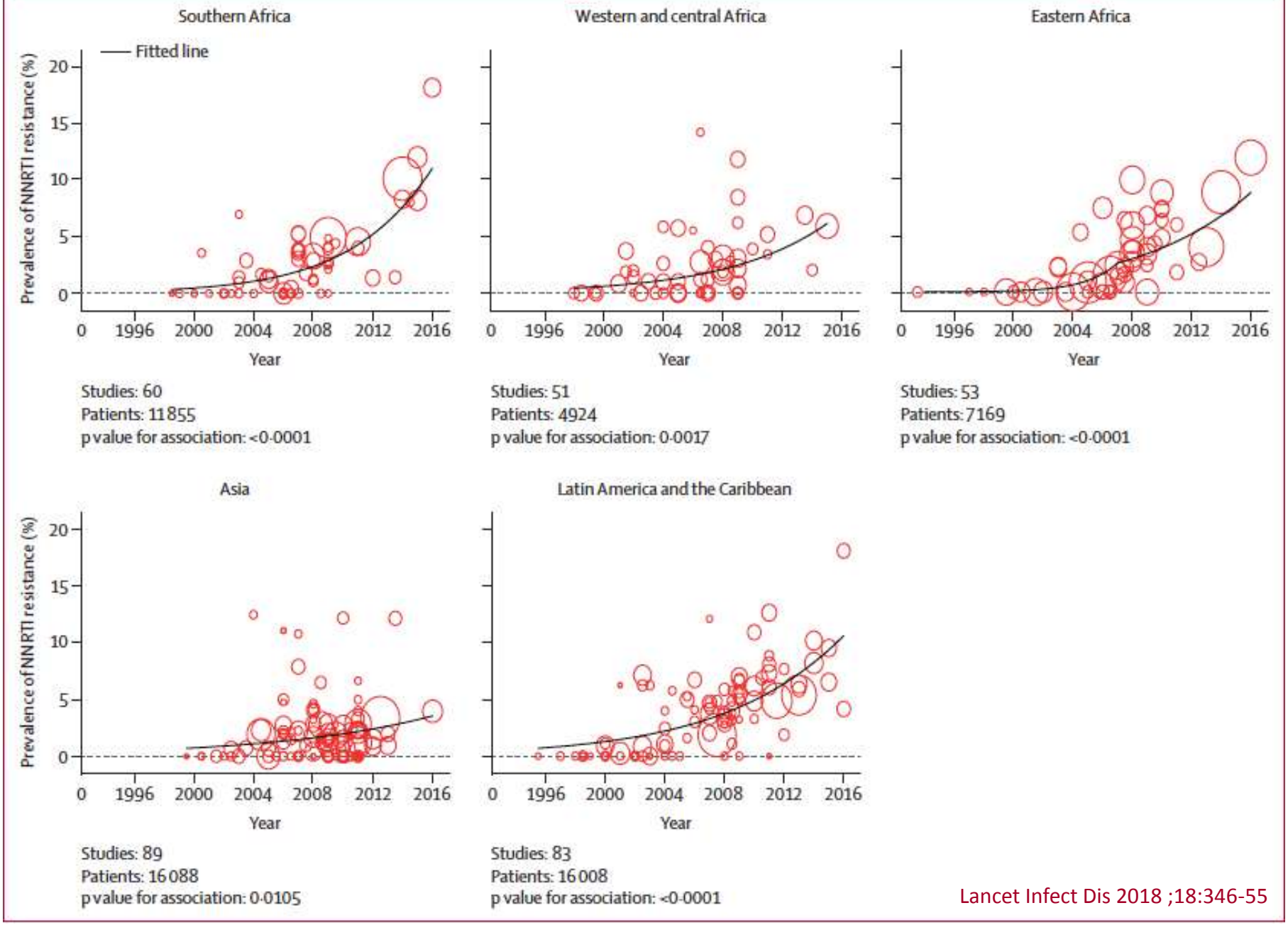
HIV-1 drug resistance before initiation or re-initiation of first-line antiretroviral therapy in low-income and middle-income countries: a systematic review and meta-regression analysis

Ravindra K Gupta, John Gregson, Neil Parkin, Hiwot Haile-Selassie, Amilcar Tanuri, Liliana Andrade Forero, Pontiano Kaleebu, Christine Watera, Avelin Aghokeng, Nicholus Mutenda, Janet Dzangare, San Hone, Zaw Zaw Hang, Judith Garcia, Zully Garcia, Paola Marchorro, Enrique Beteta, Amalia Giron, Raph Hamers, Seth Inzaule, Lisa M Frenkel, Michael H Chung, Tulio de Oliveira, Deenan Pillay, Kogie Naidoo, Ayesha Kharsany, Ruthiran Kugathasan, Teresa Cutino, Gillian Hunt, Santiago Avila Rios, Meg Doherty, Michael R Jordan, Silvia Bertagnolio

Interpretation Pretreatment drug resistance is increasing at substantial rate in LMICs, especially in sub-Saharan Africa. In 2016, the prevalence of pretreatment NNRTI resistance was near WHO's 10% threshold for changing first-line ART in southern and eastern Africa and Latin America, underscoring the need for routine national HIV drug-resistance surveillance and review of national policies for first-line ART regimen composition.

Lancet Infect Dis 2018 ;18:346-55

: Prevalence of pretreatment HIV resistance to NNRTI inhibitors by year of sampling



Lancet Infect Dis 2018 ;18:346-55

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

HIV Drug Resistance — An Emerging Threat to Epidemic Control

Chris Beyrer, M.D., M.P.H., and Anton Pozniak, M.D.

October 26, 2017
N Engl J Med 2017; 377:1605-1607

The fourth HIV epidemic

G Laborde-Balen, B Taverne, C T Ndour, C Kouanfack, M Peeters, I Ndoye, E Delaporte

This fourth epidemic… emergence of viral resistance to ARV drugs, could affect 3–5 million people between 2020 and 2030

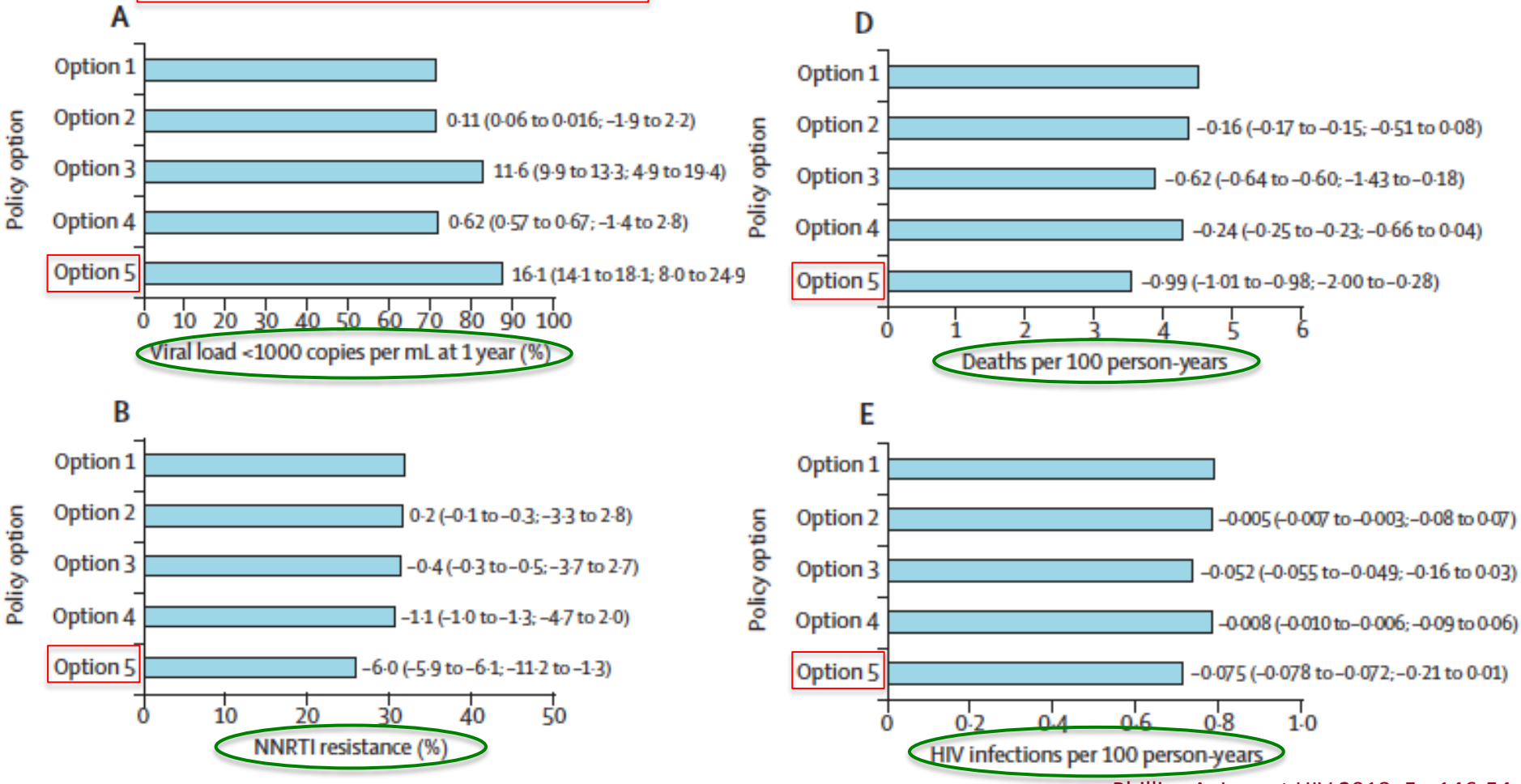
Cost-effectiveness of public-health policy options in the presence of pretreatment NNRTI drug resistance in sub-Saharan Africa: a modelling study

Andrew N Phillips, Valentina Cambiano, Fumiyo Nakagawa, Paul Revill, Michael R Jordan, Timothy B Hallett, Meg Doherty, Andrea De Luca, Jens D Lundgren, Mutsa Mhangara, Tsitsi Apollo, John Mellors, Brooke Nichols, Urvi Parikh, Deenan Pillay, Tobias Rinke de Wit, Kim Sigaloff, Diane Havlir, Daniel R Kuritzkes, Anton Pozniak, David van de Vijver, Marco Vitoria, Mark A Wainberg, Elliot Raizes, Silvia Bertagnolio, Working Group on Modelling Potential Responses to High Levels of Pre-ART Drug Resistance in Sub-Saharan Africa*

Lancet HIV 2018: 5:e146-54

Figure 1: **Predicted mean outcomes for 2018–38 according to policy option for setting scenarios where more than 10% of initiators have NNRTI resistance in 2017 (mean over all 3 month periods in 20 years; n=2915)**

- Option 1 : maintien stratégie actuelle (1ère ligne 2 INTI + EFV)
- Option 2 : génotype de R pour pré-exposés à ARV (PMTCT) avant début 2 INTI + EFV ; si R-INNTI : DTG
- Option 3 : génotype de R avant toute 1ère ligne d'ARV ; si R-INNTI : DTG
- Option 4 : DTG en 1ère ligne pour les patients pré-exposés à ARV
- Option 5 : DTG en 1ère ligne pour tous



Phillips A. Lancet HIV 2018: 5:e146-54

Option 1 : maintien stratégie actuelle (1ère ligne 2 INTI + EFV)
Option 2 : génotype de R pour pré-exposés à ARV (PMTCT) avant début 2 INTI + EFV ; si R : DTG
Option 3 : génotype de R avant toute 1ère ligne d'ARV ; si R : DTG
Option 4 : DTG en 1ère ligne pour les patients pré-exposés à ARV
Option 5 : DTG en 1ère ligne pour tous

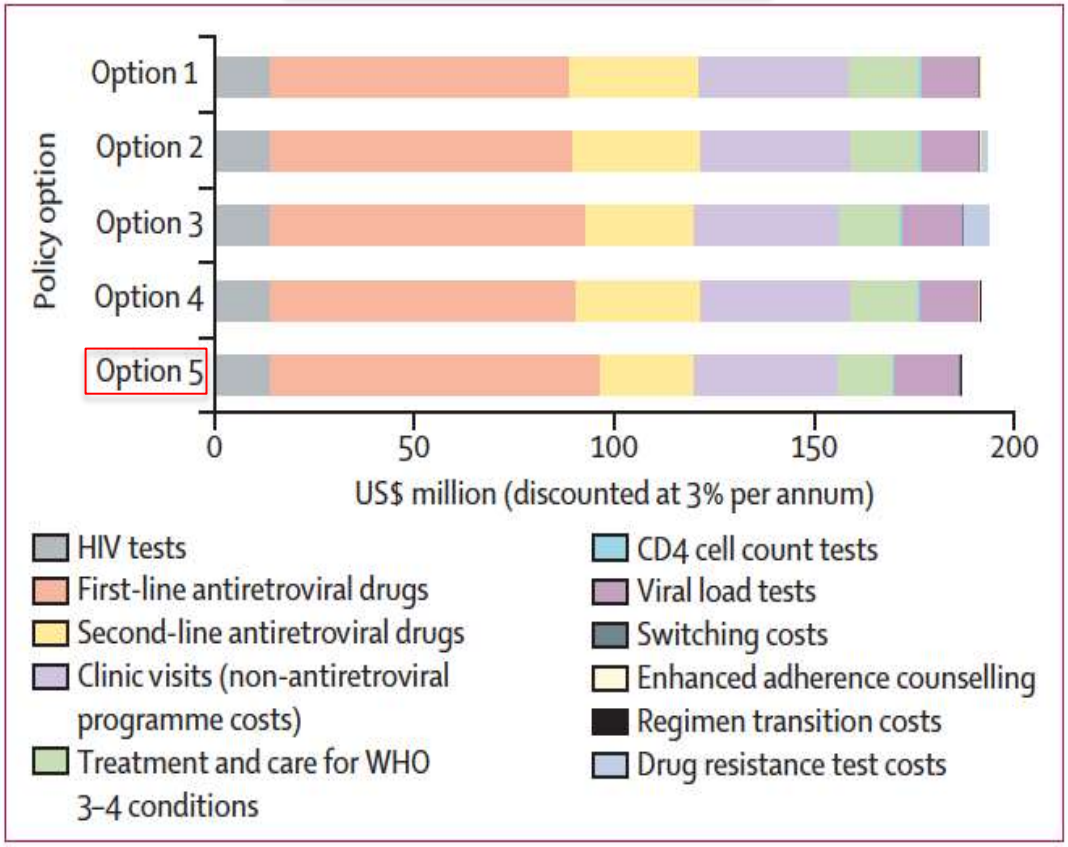
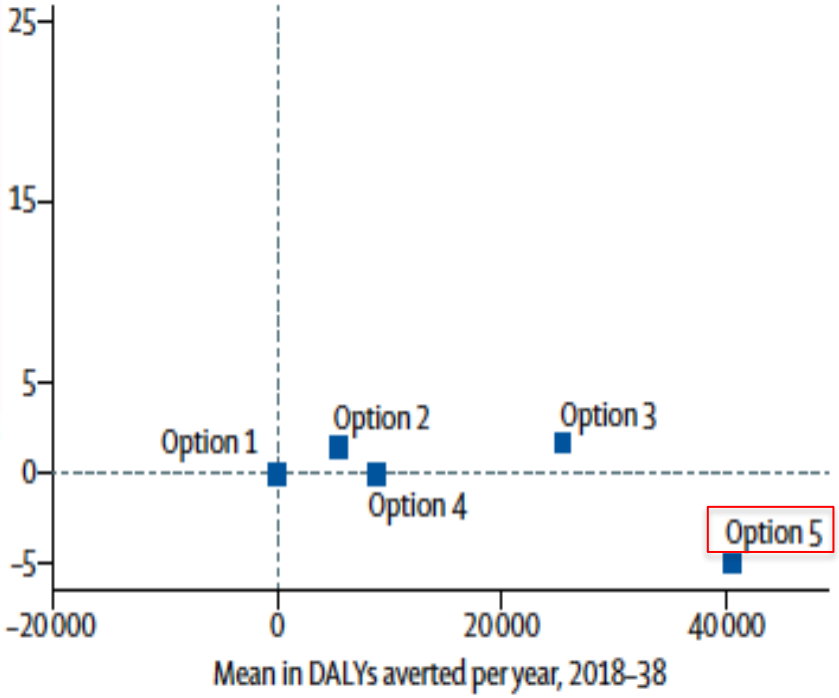


Figure 2: **Mean annual cost for 2018–38 according to policy option for setting scenarios where more than 10% of ART initiators have NNRTI resistance in 2017**

Modification moyenne coût annuel (2018-2038) en Millions USD



Phillips A. Lancet HIV 2018: 5:e146-54

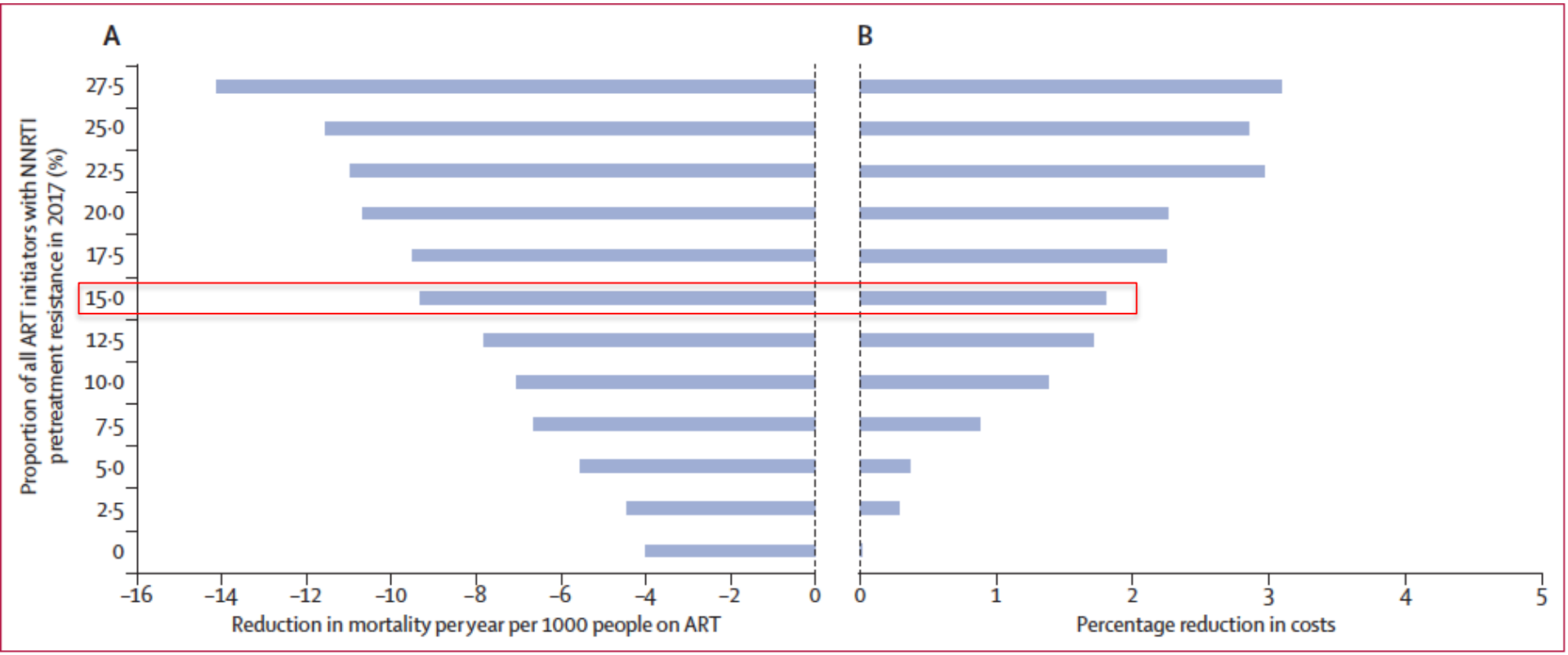


Figure 4: **Reductions in mortality and cost associated with use of dolutegravir in ART initiators rather than efavirenz**
(A) Difference in mortality (per 1000 people on ART per year) for 2018–38 when using dolutegravir in ART initiators versus continuing with efavirenz-based ART, according to proportion of all ART initiators with NNRTI resistance in 2017. 95% CIs are narrower than +/– 0·1. (B) Percentage reduction in annual costs for the policy of using dolutegravir in ART initiators versus continuing with efavirenz-based ART, according to proportion of all ART initiators with NNRTI resistance in 2017.

Phillips A. Lancet HIV 2018: 5:e146-54

18 May 2018
EMA/295960/2018

New study suggests risk of birth defects in babies born to women on HIV medicine dolutegravir

FDA Drug Safety Communication

FDA to evaluate potential risk of neural tube birth defects with HIV medicine dolutegravir (Juluca, Tivicay, Triumeq)

Dolutegravir for HIV: a lesson in pregnancy safety research Lancet 2018 June 9; 391: 2296

Preliminary results prompted WHO, the European Medicines Agency, and the US Food and Drug Administration to issue warnings on May 18 about the use of dolutegravir, a first-line antiretroviral drug, by women at the time of conception. In an unplanned preliminary analysis of an ongoing 4-year observational study in Botswana, 0·9% (4/426) of babies whose mothers became pregnant while taking dolutegravir had a neural tube defect compared with 0·1% (14/11173) of babies whose mothers took other HIV medicines. An analysis

In-utero ART exposure and the need for pharmacovigilance Mofenson LM Lancet Global Health 2018 June 4

18 May 2018
EMA/295960/2018

New study suggests risk of birth defects in babies born to women on HIV medicine dolutegravir

While EMA review is ongoing, dolutegravir should not be used in women seeking to become pregnant

FDA Drug Safety Communication

FDA to evaluate potential risk of neural tube birth defects with HIV medicine dolutegravir (Juluca, Tivicay, Triumeq)

Health care professionals should inform women of childbearing age about the potential risk of neural tube defects when a dolutegravir-containing regimen is used at the time of conception and early in pregnancy. In addition:

- Health care professionals should weigh the benefits and the risks of dolutegravir when prescribing antiretroviral medicines to women of childbearing age. Alternative antiretroviral medicines should be considered. Discuss the relative risks and benefits of appropriate alternative antiretroviral therapies.

Comparative safety of dolutegravir-based or efavirenz-based antiretroviral treatment started during pregnancy in Botswana: an observational study

Rebecca Zash, Denise L Jacobson, Modiegi Diseko, Gloria Mayondi, Mompati Mmalane, Max Essex, Tendani Gaolethe, Chipo Petlo, Shahin Lockman, Lewis B Holmes, Joseph Makhema, Roger L Shapiro

Lancet Global Health 2018 June 4

Dolutegravir as maintenance monotherapy for HIV (DOMONO): a phase 2, randomised non-inferiority trial

Ingeborg Wijting, Casper Rokx, Charles Boucher, Jeroen van Kampen, Suzan Pas, Theodora de Vries-Sluijs, Carolina Schurink, Hannelore Bax, Maarten Derksen, Eleni-Rosalina Andrinopoulou, Marchina van der Ende, Eric van Gorp, Jan Nouwen, Annelies Verbon, Wouter Bierman, Bart Rijnders

Génotype intégrase amplifié : 6/8 échecs
- Mutation INI = 3/6
  - N155H
  - S230R
  - R263K

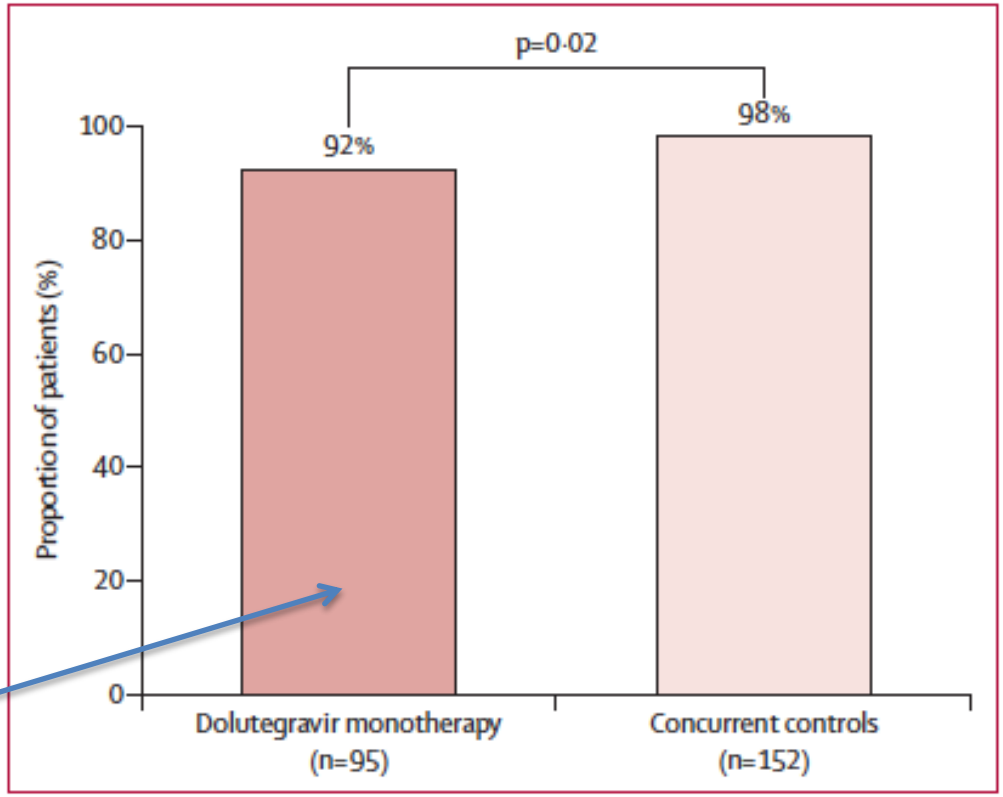


Figure 3: **Proportion of patients with virological suppression in the entire on-treatment population on dolutegravir monotherapy compared with concurrent controls**

Virological suppression was defined as an HIV RNA viral load of less than 200 copies per mL.

Lancet HIV 2017; 4: e547–54

Mutations région 3'-PPT du gène *nef* associées à résistance à DTG (sans mutation gène intégrase)

In vitro : sélection sous très forte concentration de DTG

↓

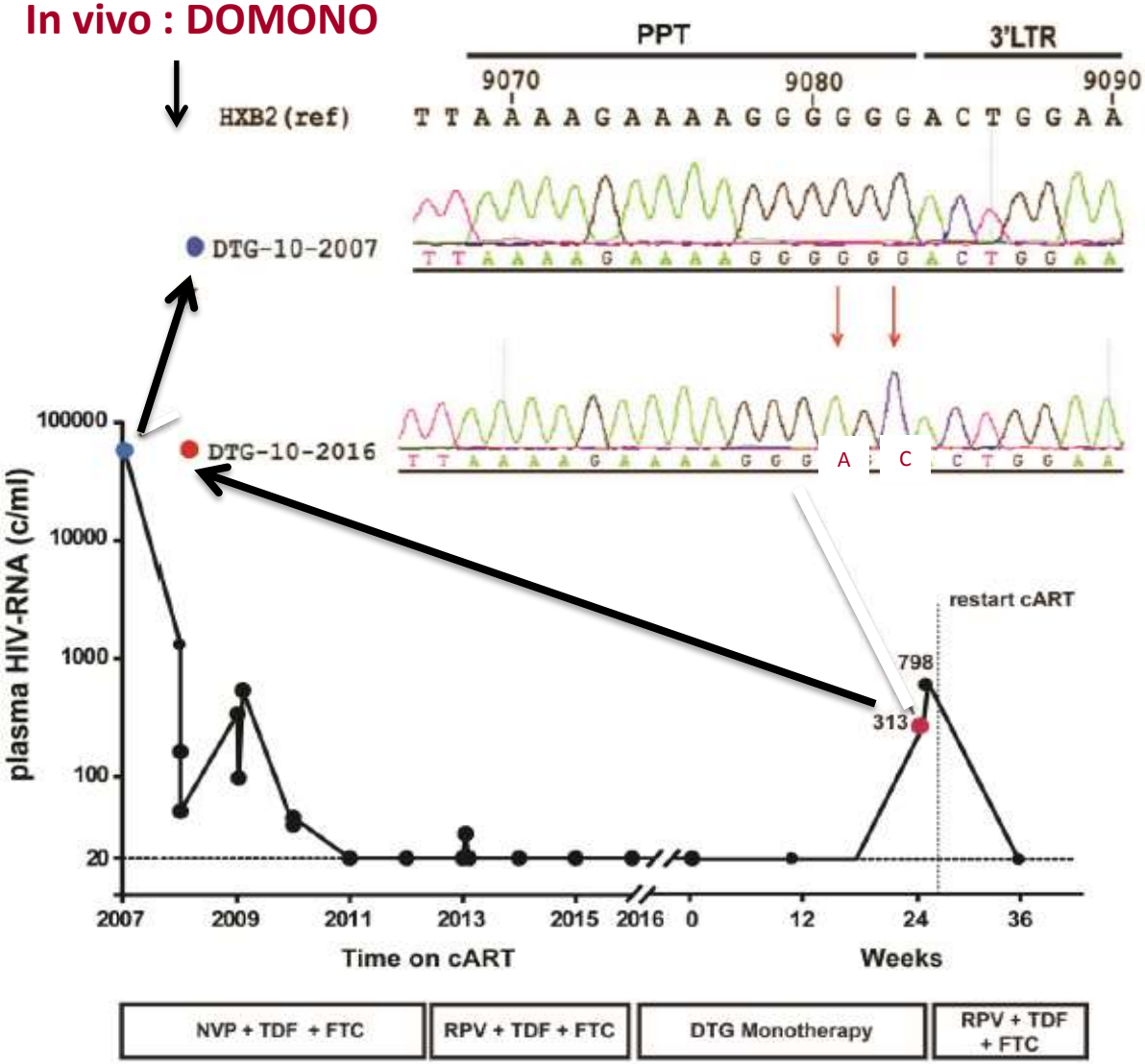
Mutations Located outside the Integrase Gene Can Confer Resistance to HIV-1 Integrase Strand Transfer Inhibitors

Isabelle Malet,[a,b] Frédéric Subra,[c] Charlotte Charpentier,[d,e,f] Gilles Collin,[d,e,f] Diane Descamps,[d,e,f] Vincent Calvez,[a,b] Anne-Geneviève Marcelin,[a,b] Olivier Delelis[c]

Séquence de la région 3'PPT

- **Virus sauvage GGGGGG**
- **Virus Muté GCAGTdél**

In vivo : DOMONO



MBio. 2017 Sep 26;8(5). pii: e00922-17

Wijting I. JID 2018, Mar 29

Tolérance ARV

Weight Gain in Persons With HIV Switched From Efavirenz-Based to Integrase Strand Transfer Inhibitor–Based Regimens

Jamison Norwood, MD, Megan Turner, MS,† Carmen Bofill, MPH,† Peter Rebeiro, PhD,† Bryan Shepherd, PhD,‡ Sally Bebawy,† Todd Hulgan, MD, MPH,*† Stephen Raffanti, MD,*† David W. Haas, MD,*†§ Timothy R. Sterling, MD,*† and John R. Koethe, MD, MS*†*

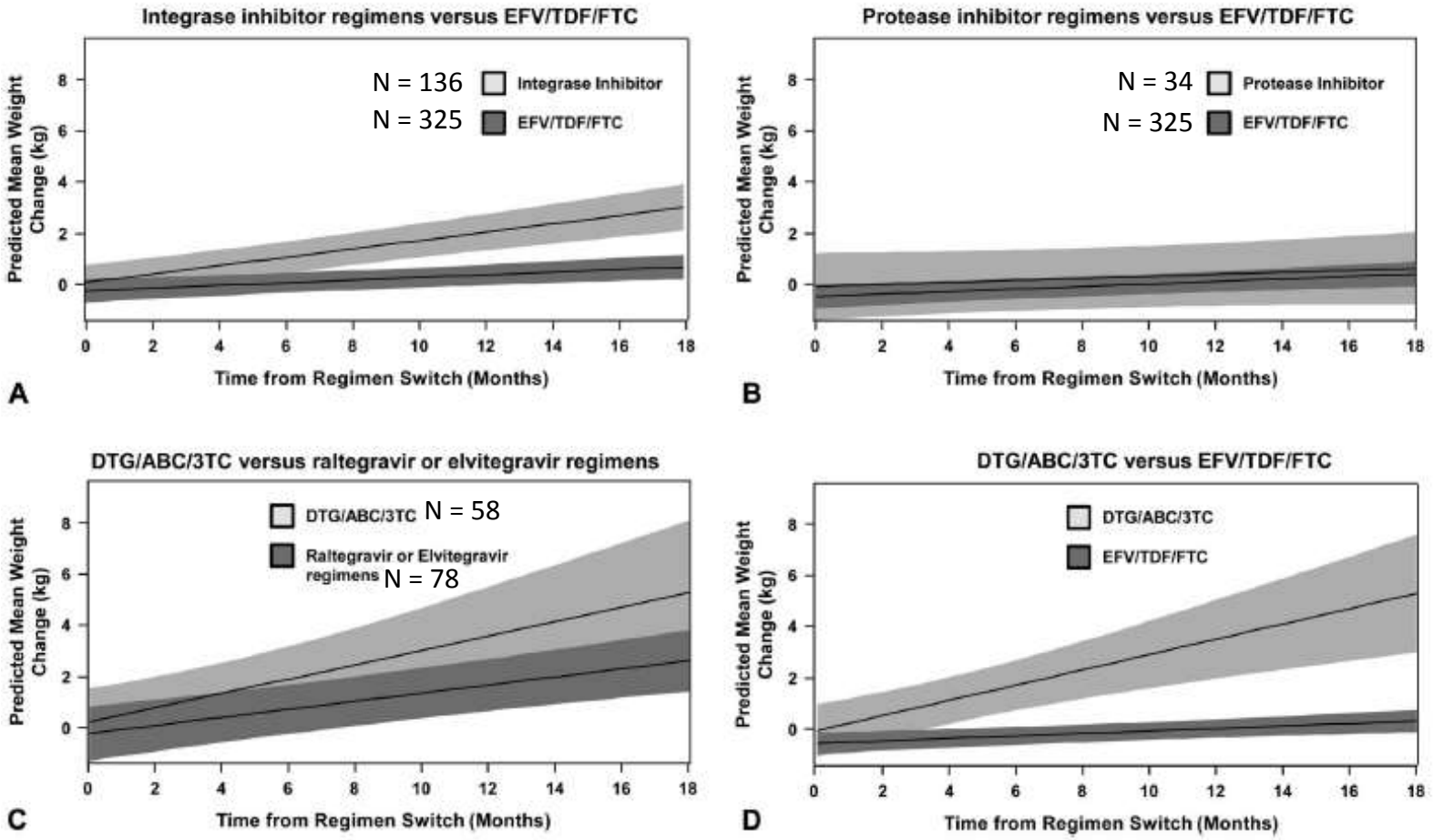


FIGURE 1. Weight change at 18 months among patients switching to an integrase inhibitor-based regimen versus remaining on EFV/TDF/FTC (panel A), switching to a protease inhibitor-based regimen versus remaining on EFV/TDF/FTC (panel B), switching to DTG/ABC/3TC versus a raltegravir or elvitegravir-based regimen (panel C), or switching to DTG/ABC/3TC versus remaining on EFV/TDF/FTC (panel D). Models adjusted for age, sex, race, total duration of ART, and baseline CD4+ T-cell count and weight.

(*J Acquir Immune Defic Syndr* 2017;76:527–531)

Amélie Menard, Line Meddeb, Herve Tissot-Dupont, Isabelle Ravaux, Catherine Dhiver, Saadia Mokhtari, Christelle Tomei, Philippe Brouqui, Philippe Colson and Andreas Stein, URMITE, Aix Marseille Université,

AIDS 2017, 31:1499–1502

Dolutegravir and weight gain: an unexpected bothering side effect?

Obesity following ART initiation is common and influenced by both traditional and HIV-/ART-specific risk factors

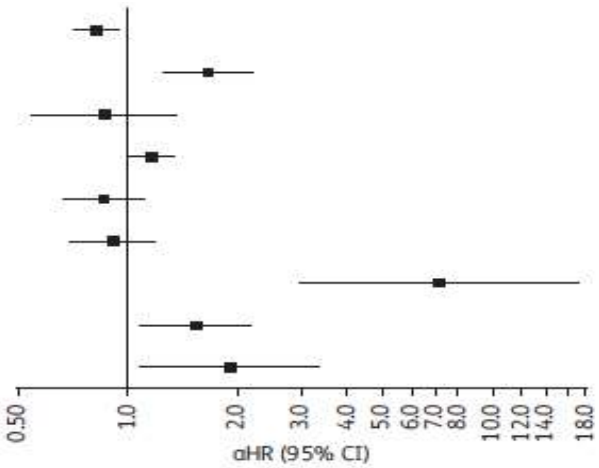
JAC 2018, May 2

David R. Bakal [1]*, Lara E. Coelho[2], Paula M. Luz[2], Jesse L. Clark[1], Raquel B. De Boni[2], Sandra W. Cardoso[2], Valdilea G. Veloso[2], Jordan E. Lake[1,3]† and Beatriz Grinsztejn[2]†

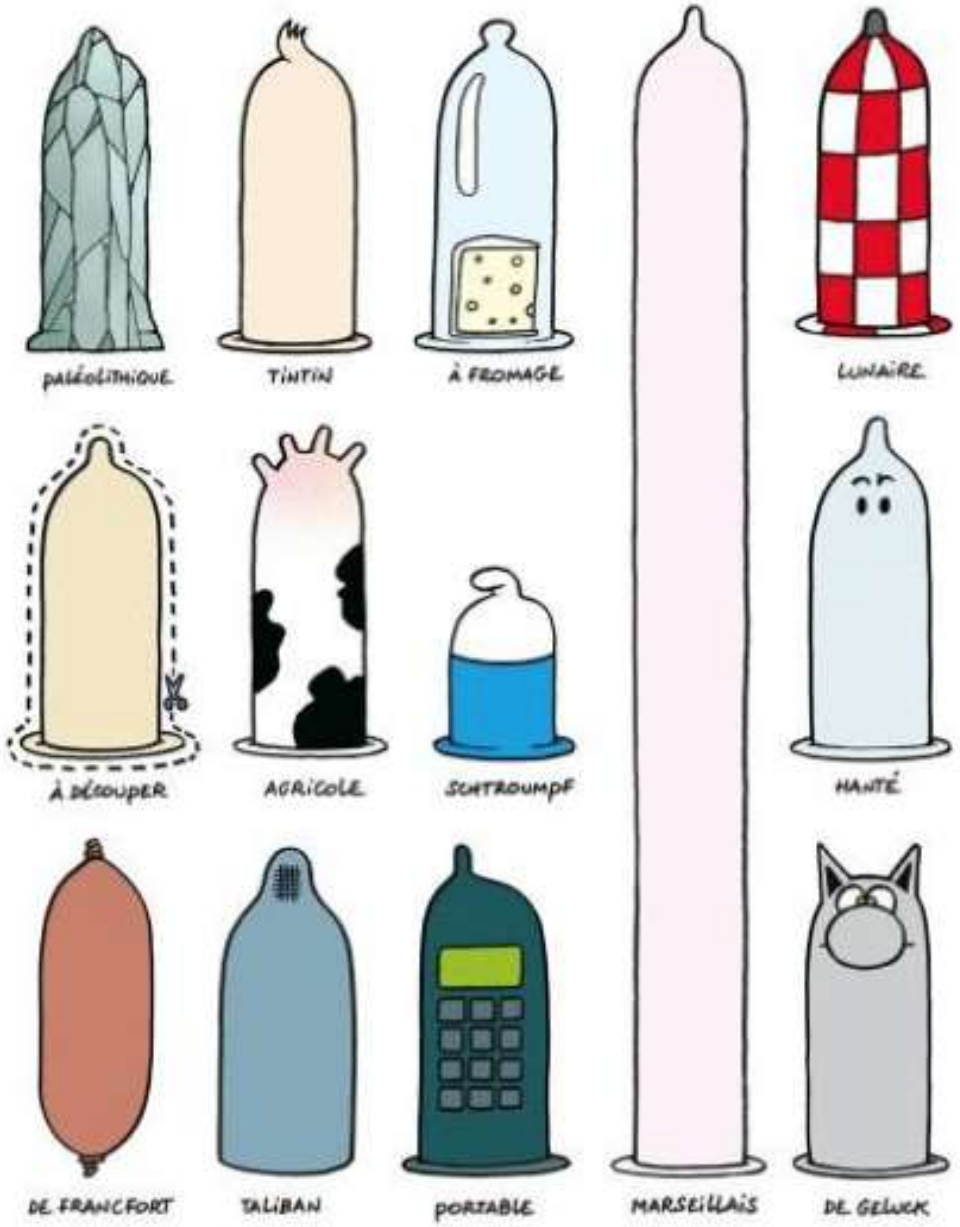
Conclusions: Obesity following ART initiation is frequent among HIV-infected adults. Key risk factors include female sex, HIV disease severity and INSTI use. Further research regarding the association between INSTIs and the development of obesity is needed.

Retrospective,
n = 1567
- 66% NNRTI
- 33% PI
- 1% INSTI

Age at ART Initiation (per 10 year increase)	0.82	0.72	0.94
Sex: Female (reference male)	1.66	1.26	2.20
Sex: TW	0.87	0.55	1.36
Baseline Viral Load (copies/mL) Log_{10}*	1.16	1.02	1.33
NRTI: AZT (reference TDF)	0.86	0.67	1.10
ART Core Drug: PI (reference NNRTI)	0.91	0.70	1.18
ART Core Drug: INSTI	7.12	2.97	17.09
Baseline Diagnosis of Hypertension	1.54	1.09	2.16
Baseline Diagnosis of Diabetes Mellitus	1.92	1.09	3.36



PrEP-VIH + PEP-IST, la totale ?

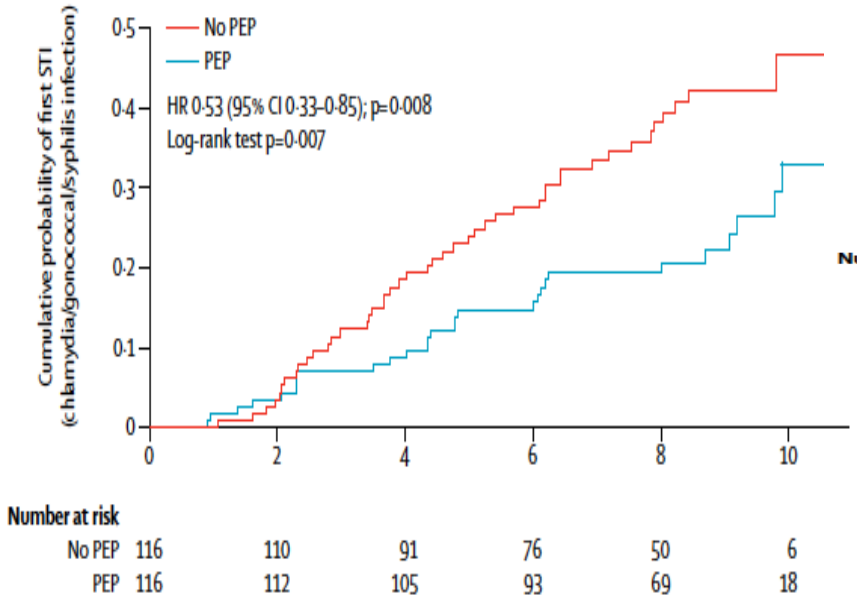


Post-exposure prophylaxis with doxycycline to prevent sexually transmitted infections in men who have sex with men: an open-label randomised substudy of the ANRS IPERGAY trial

*Jean-Michel Molina, Isabelle Charreau, Christian Chidiac, Gilles Pialoux, Eric Cua, Constance Delaugerre, Catherine Capitant, Daniela Rojas-Castro, Julien Fonsart, Béatrice Bercot, Cécile Bébéar, Laurent Cotte, Olivier Robineau, François Raffi, Pierre Charbonneau, Alexandre Aslan, Julie Chas, Laurence Niedbalski, Bruno Spire, Luis Sagaon-Teyssier, Diane Carette, Soizic Le Mestre, Veronique Doré, Laurence Meyer, for the ANRS IPERGAY Study Group**

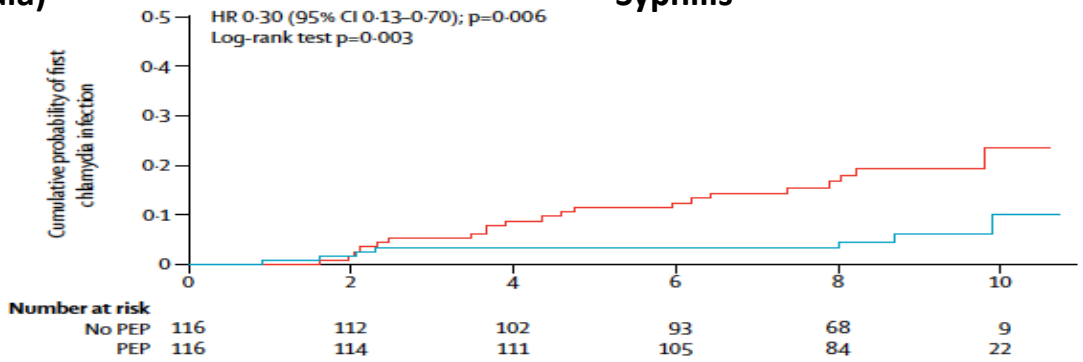
Doxycycine 200 mg x 1 dans les 24 h après rapport sexuel à risque (max : 600 mg/semaine)

Probabilité cumulée 1ère IST (syphilis, gono, Chlamydia)

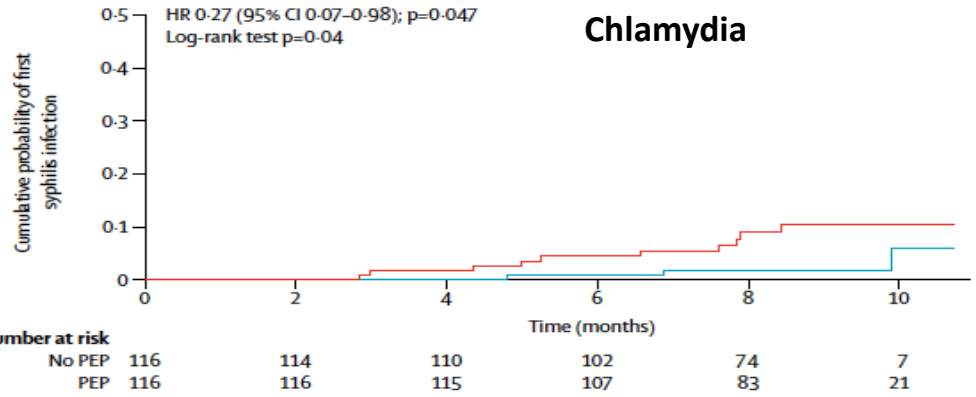


Gonocoque : HR = 0,83 (0,47-1,47), p = 0,52

Syphilis



Chlamydia



Lancet Infect Dis 2018; 18:308-17

Volume 18, Issue 3, March 2018, Pages 233-234

Comment

Doxycycline post-exposure prophylaxis: let the debate begin

Christopher K Fairley [a, b] ✉, Eric P F Chow [a, b]

Given the absence of data on population-wide benefits and antibiotic resistance, we agree with Molina and colleagues that any recommendation in favour of doxycycline prophylaxis is premature. The absence of a

Same day
Test and Treat

Effect of Offering Same-Day ART vs Usual Health Facility Referral During Home-Based HIV Testing on Linkage to Care and Viral Suppression Among Adults With HIV in Lesotho

The CASCADE Randomized Clinical Trial

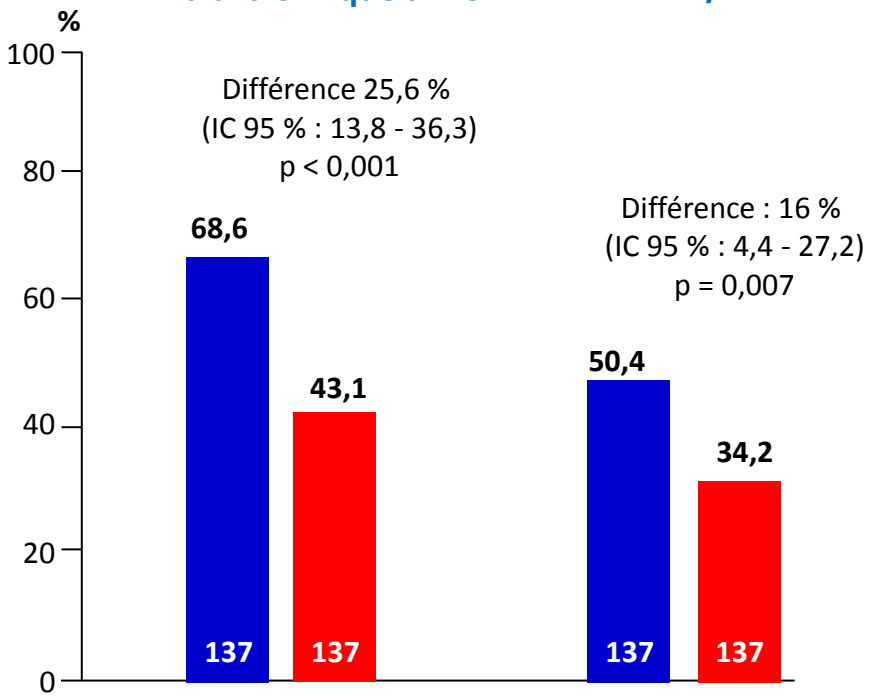
Niklaus D. Labhardt, MD; Isaac Ringera, RN; Thabo I. Lejone, MIH; Thomas Klimkait, PhD; Josephine Muhairwe, MD; Alain Amstutz, MD; Tracy R. Glass, PhD

Test &Treat même jour

Standard of care

Critères principaux de jugement

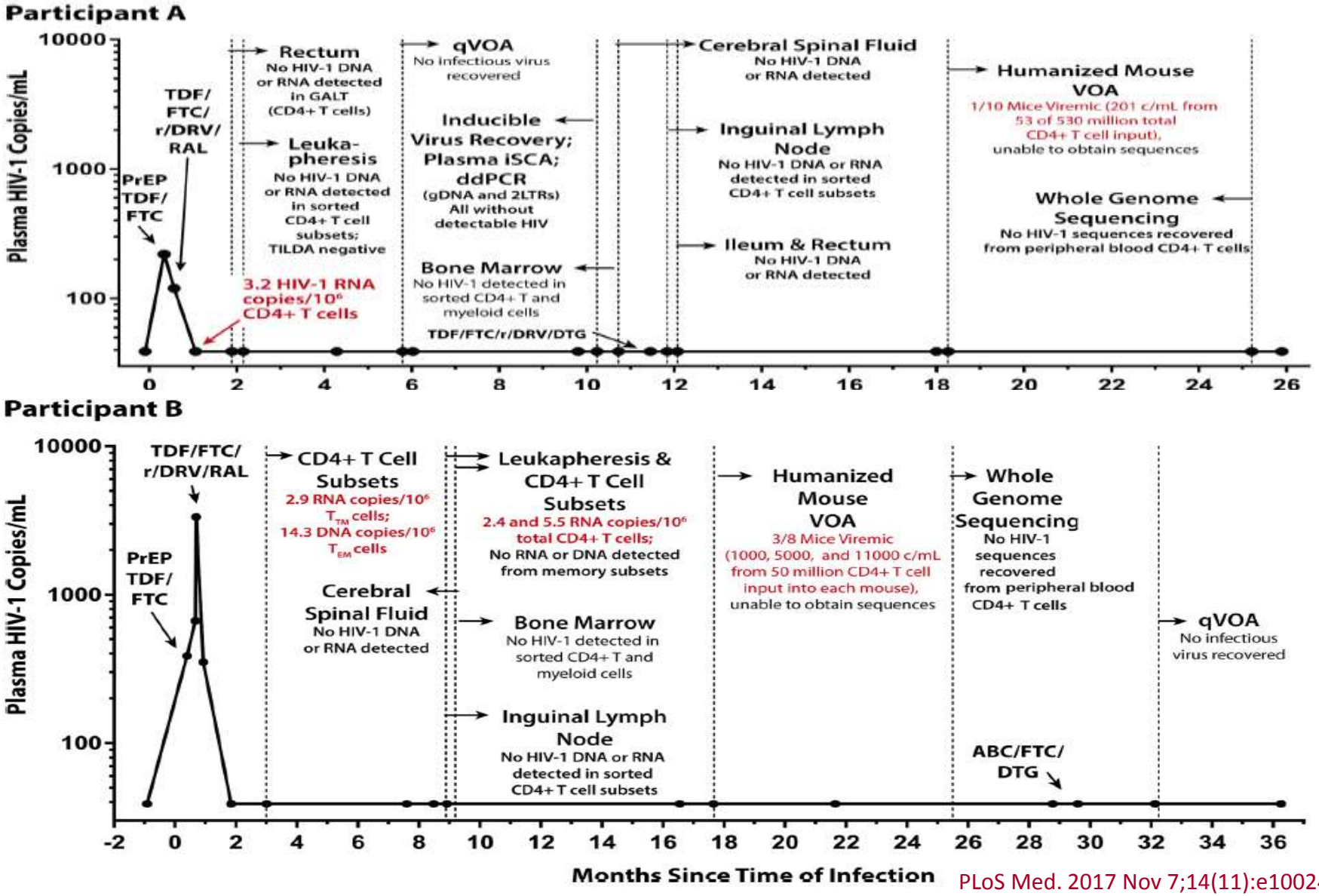
Vu à la clinique à M3 **CV < 100 c/ml à M12**



JAMA 2018; 319:1103-12

- HIV Cure
- Réservoirs

HIV-1 persistence following extremely early initiation of antiretroviral therapy (ART) during acute HIV-1 infection: An observational studv



PLoS Med. 2017 Nov 7;14(11):e1002417

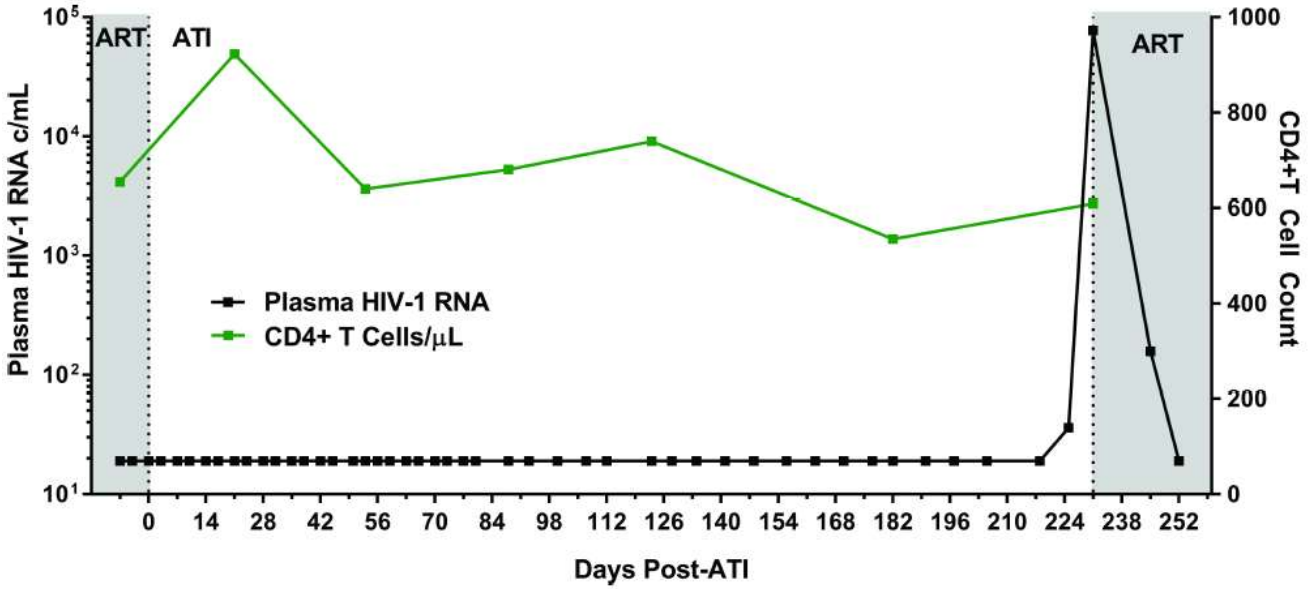
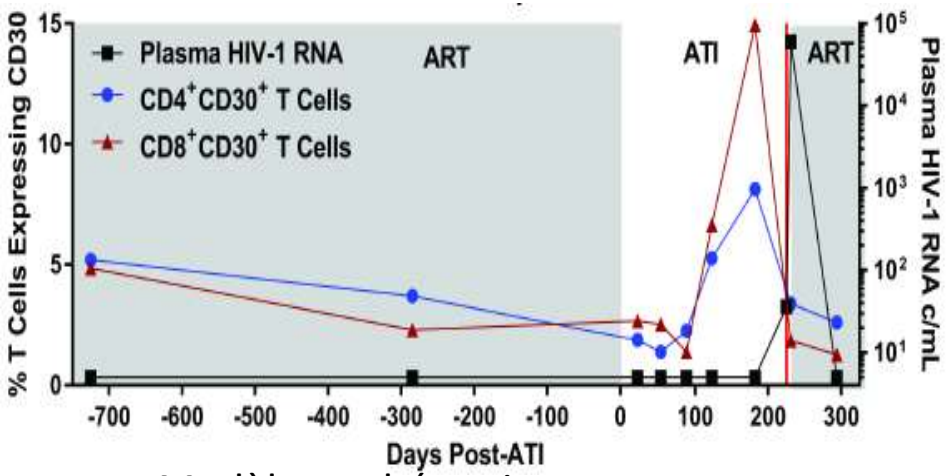
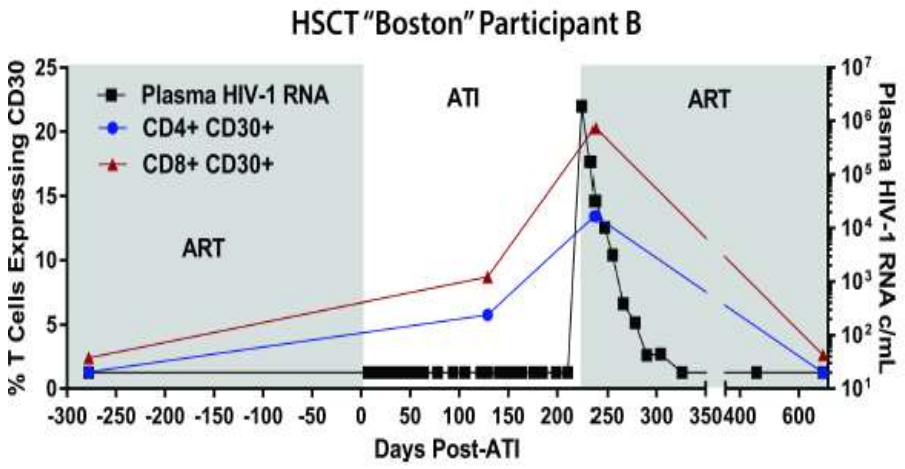


Fig 2. Summary timeline of plasma viral load and CD4+ T cell counts following analytical ART treatment interruption in Participant A.

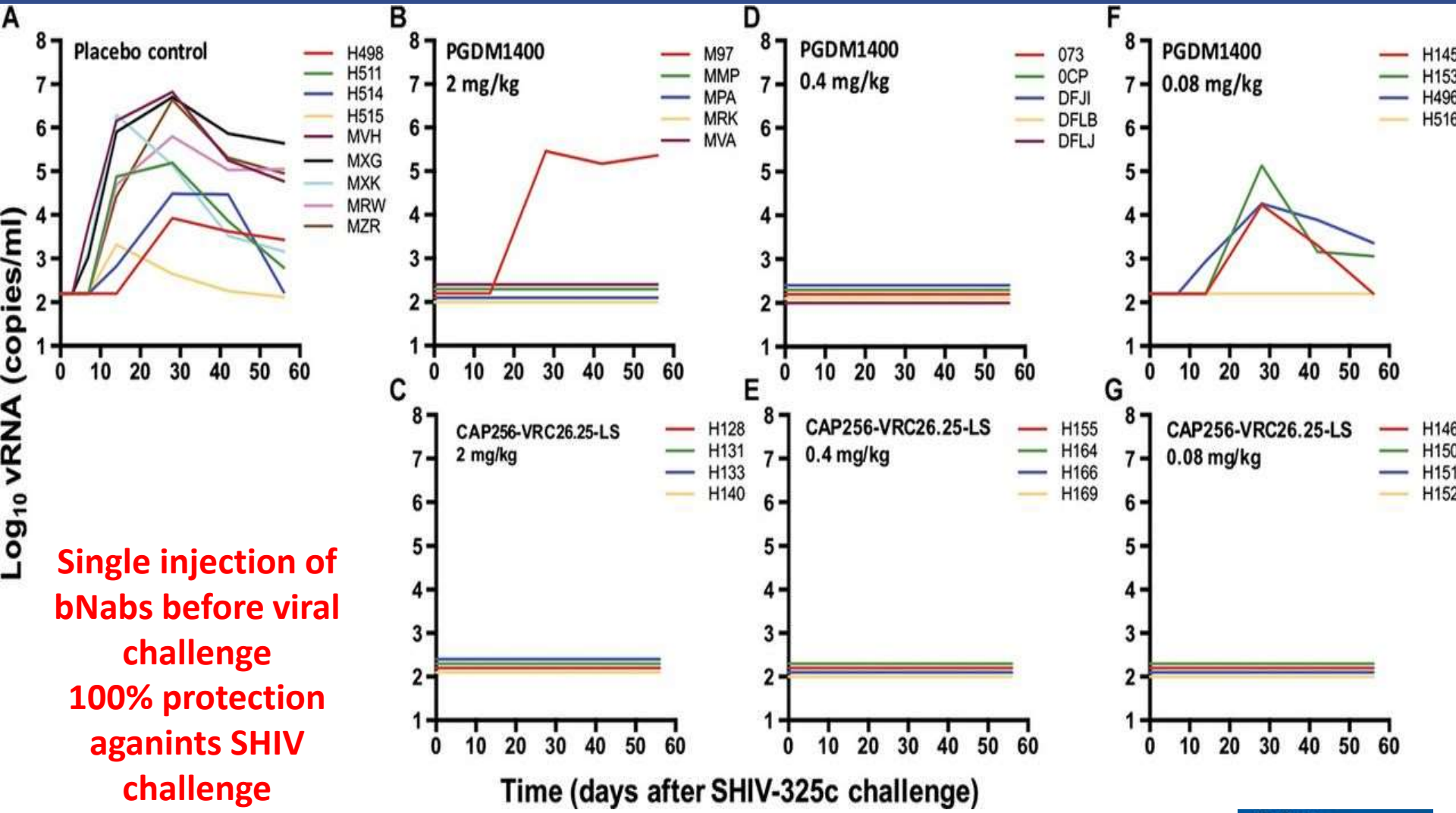




- Modèle mathématique
  - Taille réservoir avant ATI = 0,0020 unité infectieuse/10^6 cellules, correspondant à un nombre total de CD4 infectés d'environ 200
  - La probabilité d'obtenir une rémission complète à vie (> 70 ans) sans rebond, avec un tel réservoir, est < 1%
  - NB : rebond VIH précédé (semaines-mois) de ↗proportion CD8 ET CD4 exprimant CD30

PLoS Med. 2017 Nov 7;14(11):e1002417

Protective efficacy of V2 env specific antibodies (PGDM1400 and CAP256-VRC26.25-LS) against SHIV-325c in rhesus macaques.



Single injection of bNabs before viral challenge
100% protection aganints SHIV challenge

Crédit : F. Barré-Sinoussi

Julg B et al.,Sci Transl Med 2017;9:eaal1321

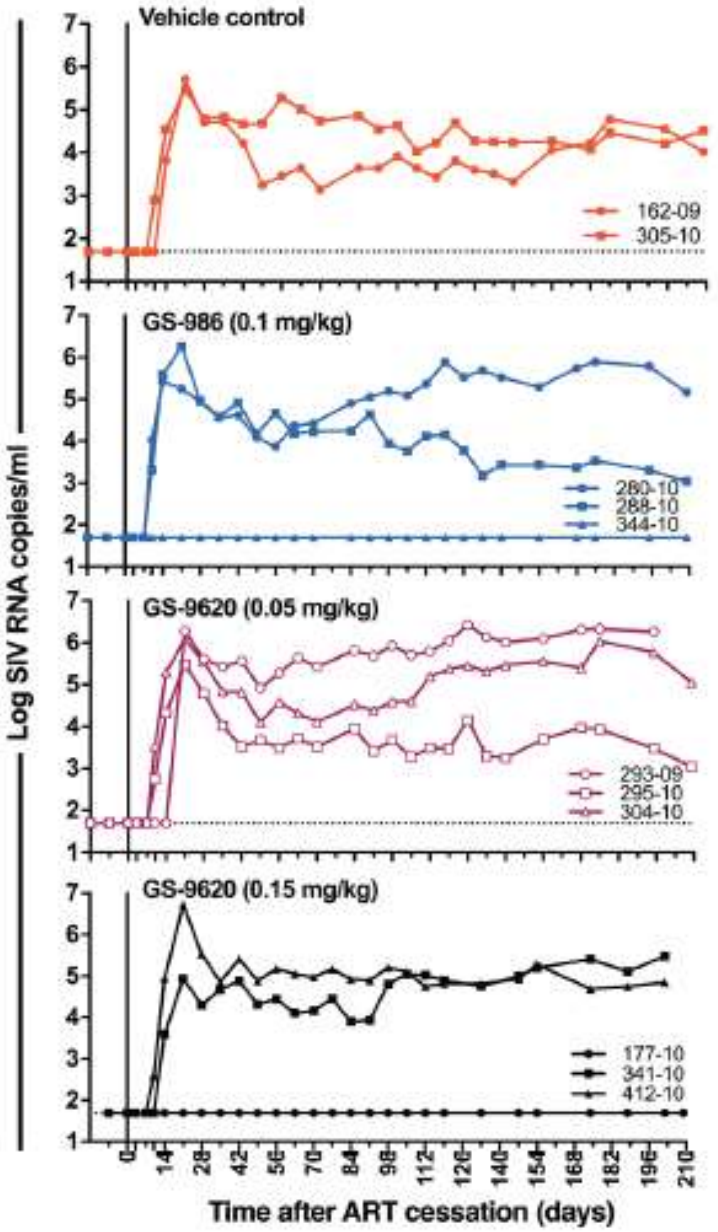
TLR7 agonists induce transient viremia and reduce the viral reservoir in SIV-infected rhesus macaques on antiretroviral therapy

Lim *et al.*, *Sci. Transl. Med.* **10**, eaao4521 (2018) 2 May 2018

SIV-infected rhesus **macaques on ART** received **up to 19 doses of the Toll-like receptor 7 agonists** GS-986 or GS-9620.

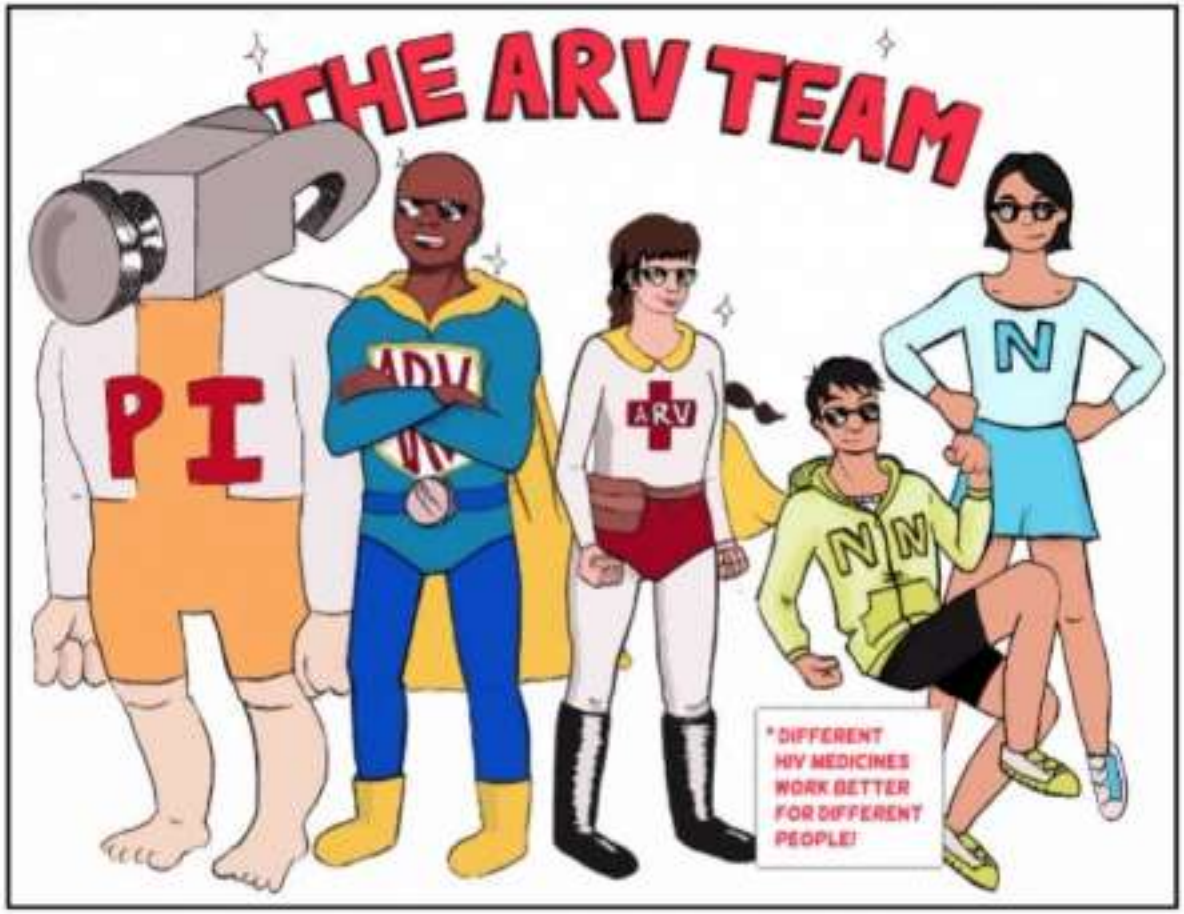
By the 3rddose, all macaques experienced **transient SIV plasma viremia** within 48 hours after dosing. Dosing was also associated with **activation of lymphocytes** (T, NK, and B cells) and **reductions in SIV DNA** in cells from the peripheral blood, lymph nodes, and GI tract.

When ART ceased, 2 of 13 treated macaques did not show rebound of virus and remained **virus-free for more than 2 years**



ARV

- Nouvelles molécules
- Nouvelles stratégies



Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial

Joel Gallant, Adriano Lazzarin, Anthony Mills, Chloe Orkin, Daniel Podzamczer, Pablo Tebas, Pierre-Marie Girard, Indira Brar, Eric S Daar, David Wohl, Jürgen Rockstroh, Xuelian Wei, Joseph Custodio, Kirsten White, Hal Martin, Andrew Cheng, Erin Quirk

Lancet 2017; 390: 2063–72

Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380–1490): a randomised, double-blind, multicentre, phase 3, non-inferiority trial

Paul E Sax, Anton Pozniak, M Luisa Montes, Ellen Koenig, Edwin DeJesus, Hans-Jürgen Stellbrink, Andrea Antinori, Kimberly Workowski, Jihad Slim, Jacques Reynes, Will Garner, Joseph Custodio, Kirsten White, Devi SenGupta, Andrew Cheng, Erin Quirk

Lancet 2017; 390: 2073–82

Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 48-week results of a randomised, double-blind, phase 3, non-inferiority trial

Lancet HIV 2018 May;5(5):e211-e220

Jean-Michel Molina, Kathleen Squires, Paul E Sax, Pedro Cahn, Johan Lombaard, Edwin Dejesus, Ming-Tain Lai, Xia Xu, Anthony Rodgers, Lisa Lupinacci, Sushma Kumar, Peter Sklar, Bach-Yen Nguyen, George J Hanna, Carey Hwang, for the DRIVE-FORWARD Study Group

Efficacy and safety of switching from boosted protease inhibitors plus emtricitabine and tenofovir disoproxil fumarate regimens to single-tablet darunavir, cobicistat, emtricitabine, and tenofovir alafenamide at 48 weeks in adults with virologically suppressed HIV-1 (EMERALD): a phase 3, randomised, non-inferiority trial

Chloe Orkin, Jean-Michel Molina, Eugenia Negredo, José R Arribas, Joseph Gathe, Joseph J Eron, Erika Van Landuyt, Erkki Lathouwers, Veerle Hufkens, Romana Petrovic, Simon Vanveggel, Magda Opsomer, on behalf of the EMERALD study group

Lancet HIV 2018; 5: e23–34

Efficacy, safety, and tolerability of dolutegravir-rilpivirine for the maintenance of virological suppression in adults with HIV-1: phase 3, randomised, non-inferiority SWORD-1 and SWORD-2 studies

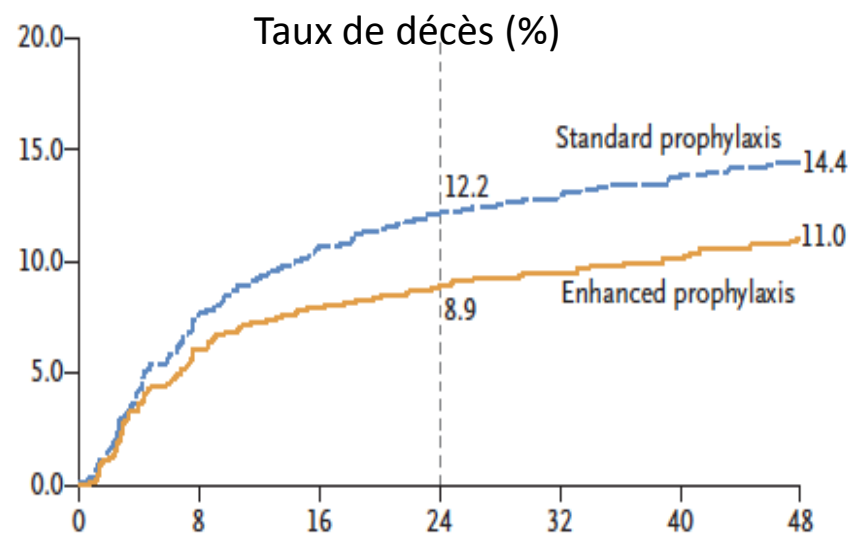
Josep M Llibre, Chien-Ching Hung, Cynthia Brinson, Francesco Castelli, Pierre-Marie Girard, Lesley P Kahl, Elizabeth A Blair, Kostas Angelis, Brian Wynne, Kati Vandermeulen, Mark Underwood, Kim Smith, Martin Gartland, Michael Aboud

Lancet 2018; 391:839-49

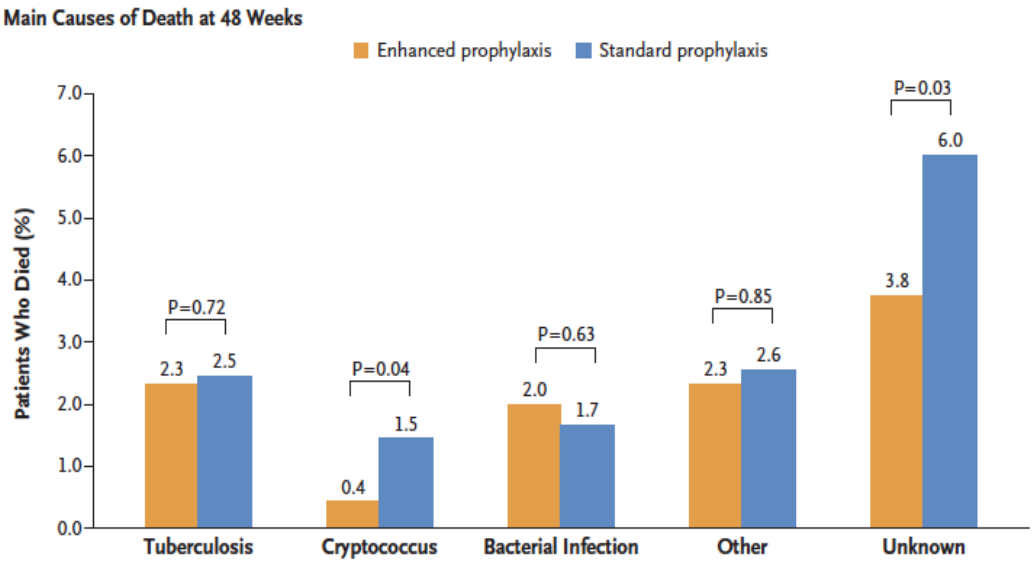
Enhanced Prophylaxis plus Antiretroviral Therapy for Advanced HIV Infection in Africa

J. Hakim, V. Musiime, A.J. Szubert, J. Mallewa, A. Siika, C. Agutu, S. Walker, S.L. Pett, M. Bwakura-Dangarembizi, A. Lugemwa, S. Kaunda, M. Karoney, G. Musoro, S. Kabahenda, K. Nathoo, K. Maitland, A. Griffiths, M.J. Thomason, C. Kityo, P. Mugyenyi, A.J. Prendergast, A.S. Walker, and D.M. Gibb, for the REALITY Trial Team*

- 1805 VIH+ > 5 ans, initiant ARV ,médiane CD4 : 37/mm^3
- Randomisation
  - Prophylaxie standard : CTX fort
  - Prophylaxie renforcée : CTX + INH/Vit B6 (12 sem.), fluconazole 100 mg (12 sem.), azithromycine 500 mg (5 j), albendazole 400 mg (1 fois)



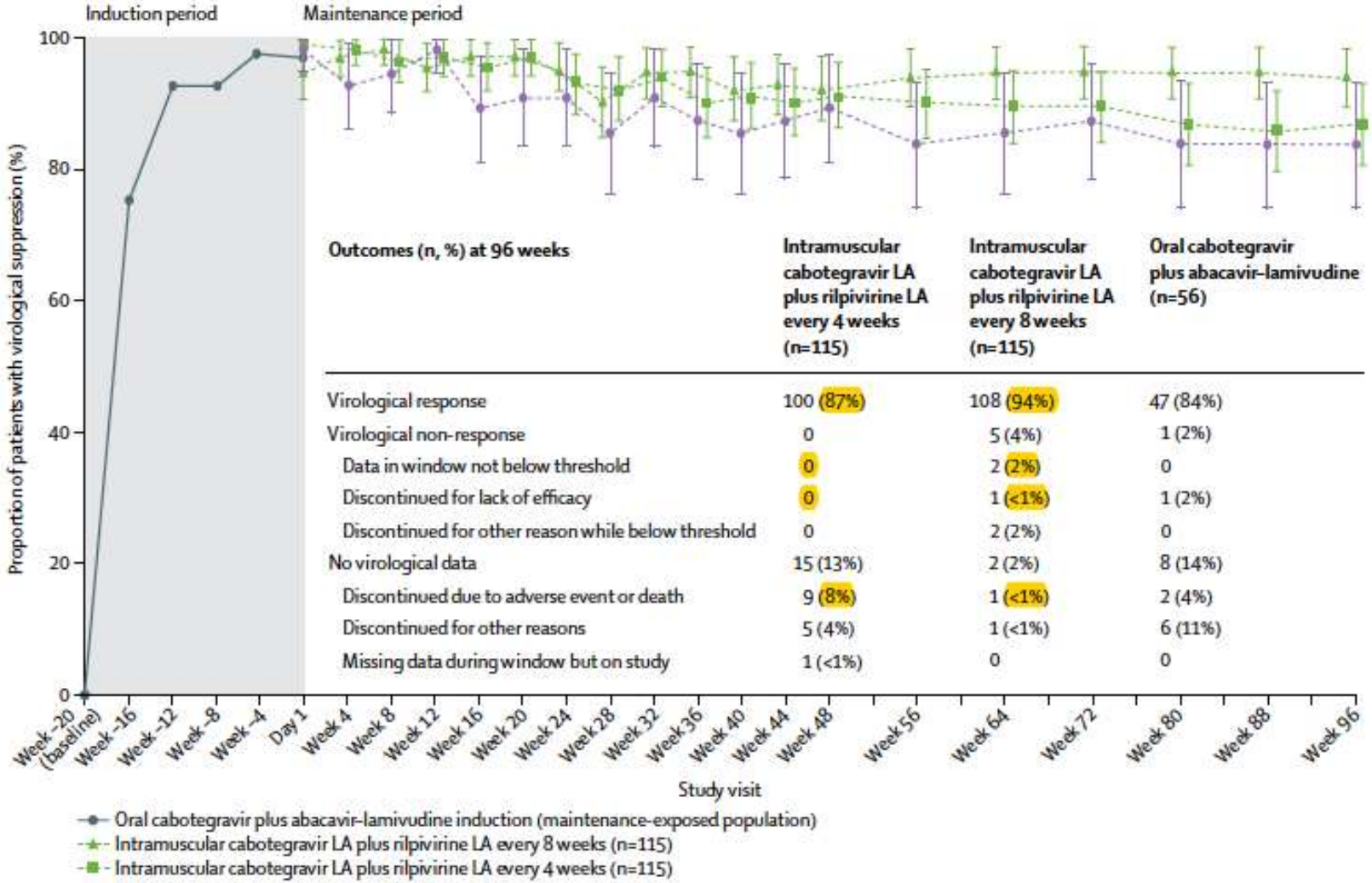
Wk 24: Hazard ratio, 0.73 (95% CI, 0.55–0.98); P=0.03
Wk 48: Hazard ratio, 0.76 (95% CI, 0.58–0.99); P=0.04



NEJM 2017;337:233-45

Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial

David A Margolis, Juan Gonzalez-Garcia, Hans-Jürgen Stellbrink, Joseph J Eron, Yazdan Yazdanpanah, Daniel Podzamczer, Thomas Lutz, Jonathan B Angel, Gary J Richmond, Bonaventura Clotet, Felix Gutierrez, Louis Sloan*, Marty St Clair, Miranda Murray, Susan L Ford, Joseph Mrus, Parul Patel, Herta Crauwels, Sandy K Griffith, Kenneth C Sutton, David Dorey, Kimberly Y Smith, Peter E Williams, William R Spreen



Outcomes (n, %) at 96 weeks	Intramuscular cabotegravir LA plus rilpivirine LA every 4 weeks (n=115)	Intramuscular cabotegravir LA plus rilpivirine LA every 8 weeks (n=115)	Oral cabotegravir plus abacavir–lamivudine (n=56)
Virological response	100 (87%)	108 (94%)	47 (84%)
Virological non-response	0	5 (4%)	1 (2%)
Data in window not below threshold	0	2 (2%)	0
Discontinued for lack of efficacy	0	1 (<1%)	1 (2%)
Discontinued for other reason while below threshold	0	2 (2%)	0
No virological data	15 (13%)	2 (2%)	8 (14%)
Discontinued due to adverse event or death	9 (8%)	1 (<1%)	2 (4%)
Discontinued for other reasons	5 (4%)	1 (<1%)	6 (11%)
Missing data during window but on study	1 (<1%)	0	0

Lancet 2017; 390: 1499–510

Merci pour votre attention

"What fits your busy schedule better, exercising one hour a day or being dead 24 hours a day?"