Thérapies antirétrovirales : quelles innovations ?

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30 years of drug development (FDA approval, originator)

1983

1987
- AZT

1990 - 2002
- Didanosine
- Zalcitabine
- Stavudine
- Lamivudine
- Saquinavir HG
- Saquinavir SGC
- Indinavir
- Nevirapine
- Ritonavir
- Combivir
- Delavirdine
- Nelfinavir
- Abacavir
- Efavirenz
- Amprenavir
- Didanosine EC
- Lopinavir/r
- Trizivir (FDC)
- Tenofovir DF

2003 -2008
- Atazanavir
- Emtricitabine
- Enfuvirtide
- Fos-APV
- Truvada (FDC)
- Tipranavir
- Atripla (FDC)
- Darunavir
- Maraviroc
- Raltegravir
- Etravirine

2011- 2016
- Rilpivirine/TDF/FTC
- Nevirapine XR
- Rilpivirine
- Elvitegravir/C/F/TDF
- Dolutegravir
- Cobicistat
- Dolutegravir/ABC/3TC
- Elvitegravir/C/F/TAF
- Darunavir/COBI
- Atazanavir/COBI
- FTC/TAF (10, 25 mg)
- Rilpivirine/TAF/FTC
- *Dolutegravir*

2017-
- Raltegravir HD
- *FTC/TDF*
- (D/C/F/TAF)*
- (Bictegravir/TAF/FTC)*
- (Dolutegravir/RIL)*
- *(Dolutegravir/3TC/TDF)**

Entry inhibitors | Integrase inhibitors (InSTI) | Protease inhibitors (PI)

Fusion inhibitors | RT (non) nucleosidic inhibitors (N-NRTI)

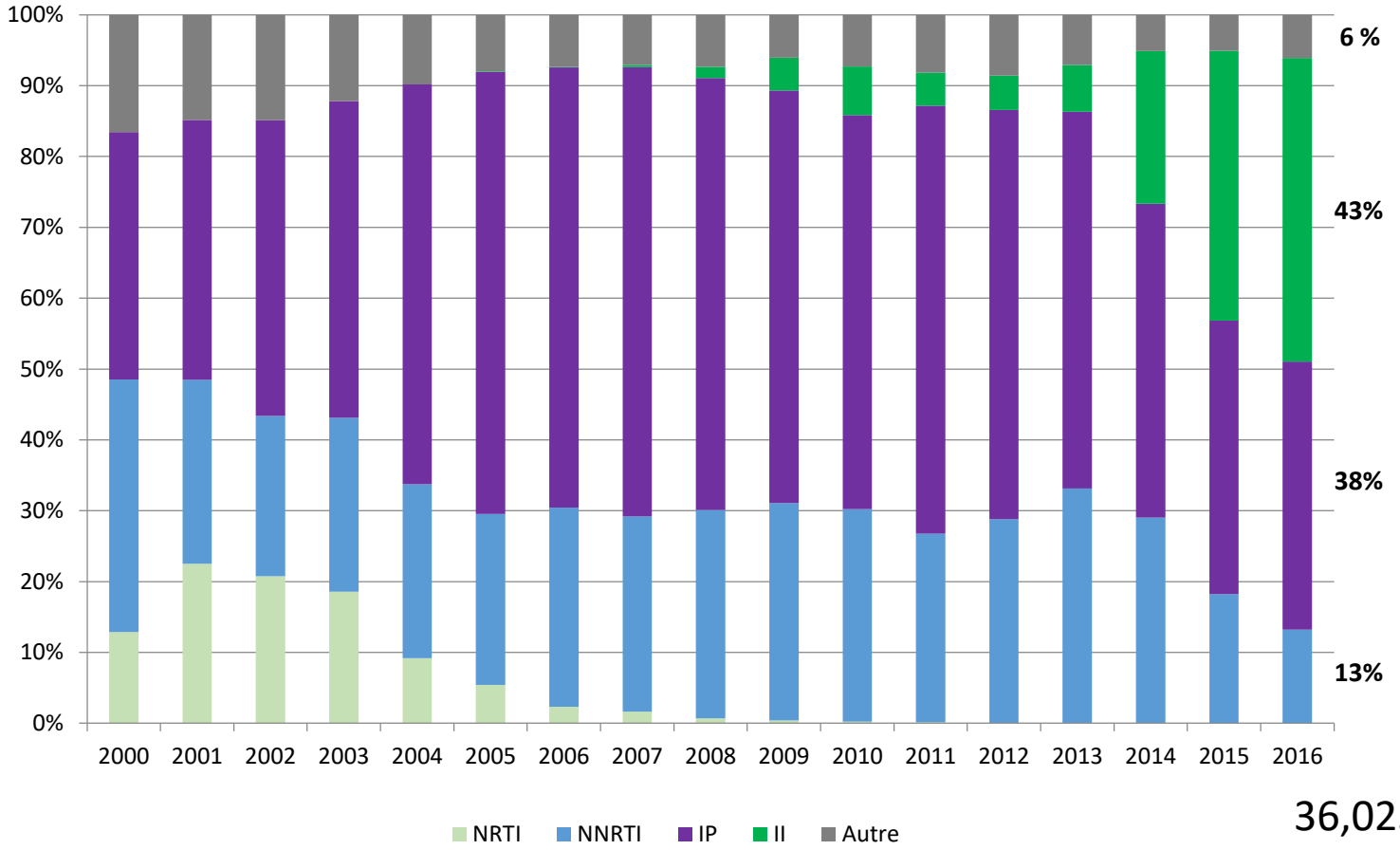
- *(submitted)
- *Generic versions*

Le développement des formes combinées associant plusieurs antirétroviraux : en une prise par jour

ATRIPLA	EVI(COM)PLERA	STRIBILD	TRIUMEQ	GENVOYA	DDEFSEY
					
TDF/FTC/EFV	TDF/FTC/RPV	TDF/FTC/EVG/cob	DTG/ABC/3TC	EVG/cob/FTC/TAF	TAF/FTC/RPV
	Take with food		Not with HBV co-infection	Take with food	Take with food
	VL < 100'000	Attn: drug-drug interactions	Must be HLA B*5701 neg.	Attn: drug-drug interactions	VL < 100'000
2006	2012	2014	2014	2015	2017

Stringent Regulatory Approval of two generic suppliers for DTG/3(F)TC/TDF expected: **Q1 2018**

Emérgence des combinaisons à base d'INSTI



36,023 patients initiating ART between 2000 and 2016 in the Dataids Clinical Cohort

Comparing preferred and alternative first line ART options in adults/adolescents with HIV in 2016

IAS, DHHS, EACS, WHO and French ART guidelines

GUIDELINES	NRTI BACKBONE				NNRTI			InSTI			PI		
	TAF/XTC	TDF/XTC	ABC/3TC	AZT/3TC	EFV	NVP	RIL	DTG	EVG/c	RAL	ATV/r	DRV/r	LPV/r
IAS (2016)													
DHHS (2016)													
EACS (2016)													
WHO (2016)													
FRENCH (2017)													

preferred alternative not recommended/special situations

Adapted from M Vitoria, French recommendations 2017 (Rapport Morlat), EACS October 2016, WHO guidelines 2016, DHHS (update July 2016), Günthard H et al, JAMA 2016

2016 WHO recommendations for first-line ART

TDF
+
3TC (or FTC)
+
$EFV_{600\ mg}$

1. **Une prise par jour, monitoring**
2. **Harmonisation thérapeutique** (*femme enceinte*, children, patients co-infectés *VIH-TB*, patients co-infectés VIH-VHB)

Alternative → **TDF + XTC + DTG**
TDF + XTC* + $EFV_{400\ mg}$

* XTC= 3TC ou FTC

ARV	2017		2018		2019		2020	
	Q3-Q4	Q1-Q2	Q3-Q4	Q1-Q2	Q3-Q4	Q1-Q2	Q3-Q4	
DTG	RADIO DAWNING ADVANZ-4		DOLPHIN 1 NAMSAL	DOLPHIN 2 D2EFT	INSPIRING	VESTED ODYSSEY ADVANCE	PANNA ING200336	
EFV400	SSAT 062 SSAT 063		NAMSAL					

Pregnant women* Children TB Adults

IMPAACT 1093

*

Marco Vitoria courtesy, adapted from Vitoria et al, Curr Opin HIV/AIDS, 12: 369-76 2017

**IAS 2017, Lamorde M et al, abstract # TUPDB0203 LB, Zash R et al, #MOAX0202 LB (Botswana), Vannappagari et al, MOPEB0283 (APR)*

Des stratégies pour : conserver l'efficacité, améilorer la tolérance, diminuer l'exposition, diminuer les intéractions, et diminuer les coûts

4

Kiat Ruxrungtham, WESY03 session, 11.30am *Christine Katlama, WESY03 session, 11.00am* *Anna [illegible]ova, WESY03 session, 11.20am*

BREATHER study, Butler K et al, Lancet 2016
ANRS 162-4D study, de Truchis et al AIDS 2016, THPEB063, IAS 2017 # MOPEB0321

Nouvelles combinaisons pour initiation des traitements

	Phase	Comparator	N=	% Women	Duration (week)	Main results
BICtegravir/TAF/FTC[1] (Gallant et al)	3	ABC/3TC/DTG	692	10	48	**Non inferior** (92.4 vs 93% <50 c/mL)
BICtegravir/TAF/FTC[2] (Sax et al)	3	TAF/FTC+DTG	645	12	48	**Non inferior** (89.4 vs 92.9% <50 c/mL)
DORavirine/FTC/TDF[3] (Squires et al)	3	EFV/FTC/TDF	734	15	48	**Non Inferior** (84.3 vs 80.8% <50 c/mL)
RALtegravir 1200mg QD[4] (P Cahn et al)	3	RAL 400 BID	802	15.4	96	**Non Inferior** (81.5 vs 80% <40 c/mL)

[1]Abstract # MOAB0105 LB [2]Abstract # TUPDB0201 LB [3]Abstract # TUAB0104 LB [4]Abstract # TULBPEB20

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

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

r (vs. raltegravir)

gravir/abacavir/3TC = VHB;

HLA B5701)

- Sans booster
  - (vs. Elvitegravir/cobicistat : *CYP3A4* inhibitor) = Intéraction médicamenteuse
- Barrière génétique elevée (vs. raltegravir; Elvitegravir/cobicistat)

CROI 2017
Abstract 45LB

DORAVIRINE IS NON-INFERIOR TO DARUNAVIR+RITONAVIR IN PHASE 3 TREATMENT-NAÏVE TRIAL AT WEEK 48

Jean-Michel Molina[1], Kathleen Squires[2], Paul Sax[3], Pedro Cahn[4], Johan Lombaard[5], Edwin DeJesus[6], Xia Xu[7], Bach-Yen Nguyen[7], George Hanna[7], and Carey Hwang[7] for the DRIVE-FORWARD Study Team

[1] University of Paris 7 and Hôpital Saint-Louis, Paris, France; [2] Thomas Jefferson University, Philadelphia, PA; [3] Brigham & Women's Hospital, Harvard Medical School, Boston, MA; [4] Fundación Huesped, Buenos Aires, Argentina; [5] Josha Research, Bloemfontein, South Africa; [6] Orlando Immunology Center, Orlando, FL; [7] Merck & Co., Inc., Kenilworth NJ, USA

DRIVE FORWARD

- Nouvelle génération de NNRTI
- Profil de résistance : activité *in vitro* contre les mutations de résistance les + prévalents (EFV/NVP)
- Profil intéressant pour ce qui est les Intéractions médicamenteuses
- Une fois par jour (combinaison fixe avec TDF/3TC)

Réduction des doses

Drug with potential for optimization	Clinical trial name (phase, sponsor)	Completed or planned completion	Main results
Efavirenz 600 vs 400 QD	ENCORE-1, phase 3 (Kirby Institute, Australia)	Lancet (2015) Puls R et al	**Non-inferiority (primary endpoint, week 48)**
Zidovudine 600 vs 400 BID	MINIZID, phase 2 (Geneva Univ Hosp, Switzerland)	HIV Med (2015) Rougemont M et al	**Less grade 3 and 4 AE in patients with baseline anemia**
Darunavir/r 800 vs 400 mg QD	ANRS-165 DARULIGHT, phase 2 (ANRS, France)	IAS 2017 pilot trial, abstract # **MOPEB0313** (Molina JM et al)	**Virological efficacy is maintained**
Darunavir/r 400 mg QD vs LPV/r 800/200 NCT02671383	WRHI052 phase 3 (Wits RHI, South Africa)	Enrollment completed (Venter F, personal communication)	**?** Results expected Q3 2018

Nouvelles stratégies de maintenance

(The prospect of life-time ART over perhaps 50 years or more makes simplified maintenance therapy particularly appealing)

- Monotherapie d'IP

- Bithérapie avec 3TC
  - PI/r + 3TC
  - **DTG + 3TC**

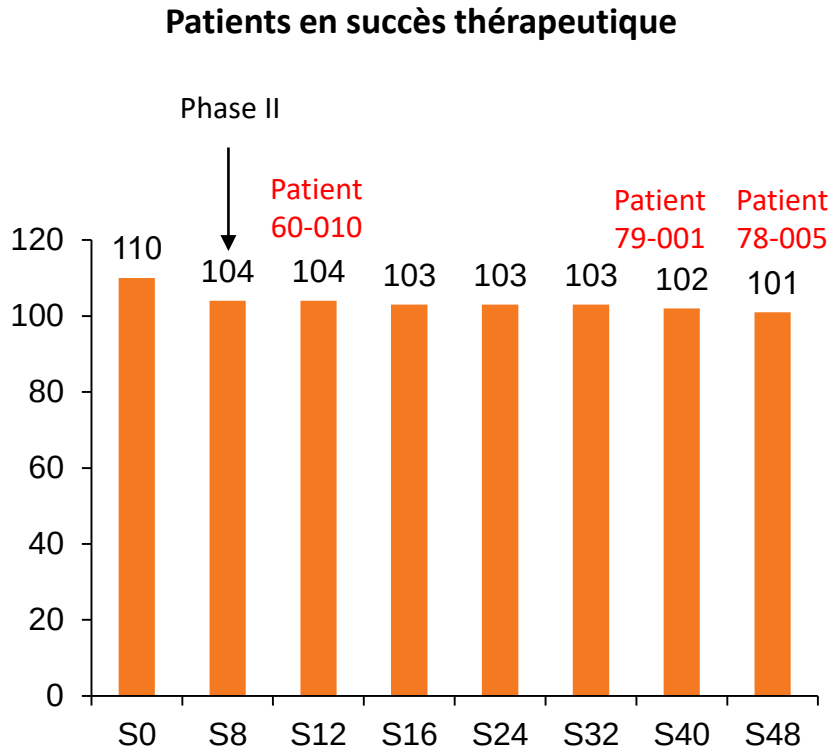
- Bithérapie avec NNRTI
  - **DTG + RPV**
  - **RAL + ETR**
  - DRV/r + ETR
  - DRV/r + RAL

Étude LAMIDOL-ANRS 167 : DTG + 3TC

Pourcentage de patients en succès thérapeutique après 48 semaines

- 97 % (101/104) sont en succès thérapeutique
- Bonne tolérance de la bithérapie
- À S48, 3 échecs

- 1 échec virologique à S12 (4 semaines de bithérapie)
- 1 perdu de vue à S40
- 1 modification de traitement à S48 par l'investigateur de l'étude



CROI 2017 - D'après Joly V et al., abstr. 458 actualisé

« A pilot study of dolutegravir (DTG) + lamivudine (3TC) for **initial** treatment of HIV-1-infected participants with HIV-1 RNA <500,000 copies/ml »

3 échecs : **1 résistance (R263R/K**; M184V)

Taiwo et al.

IAS2017

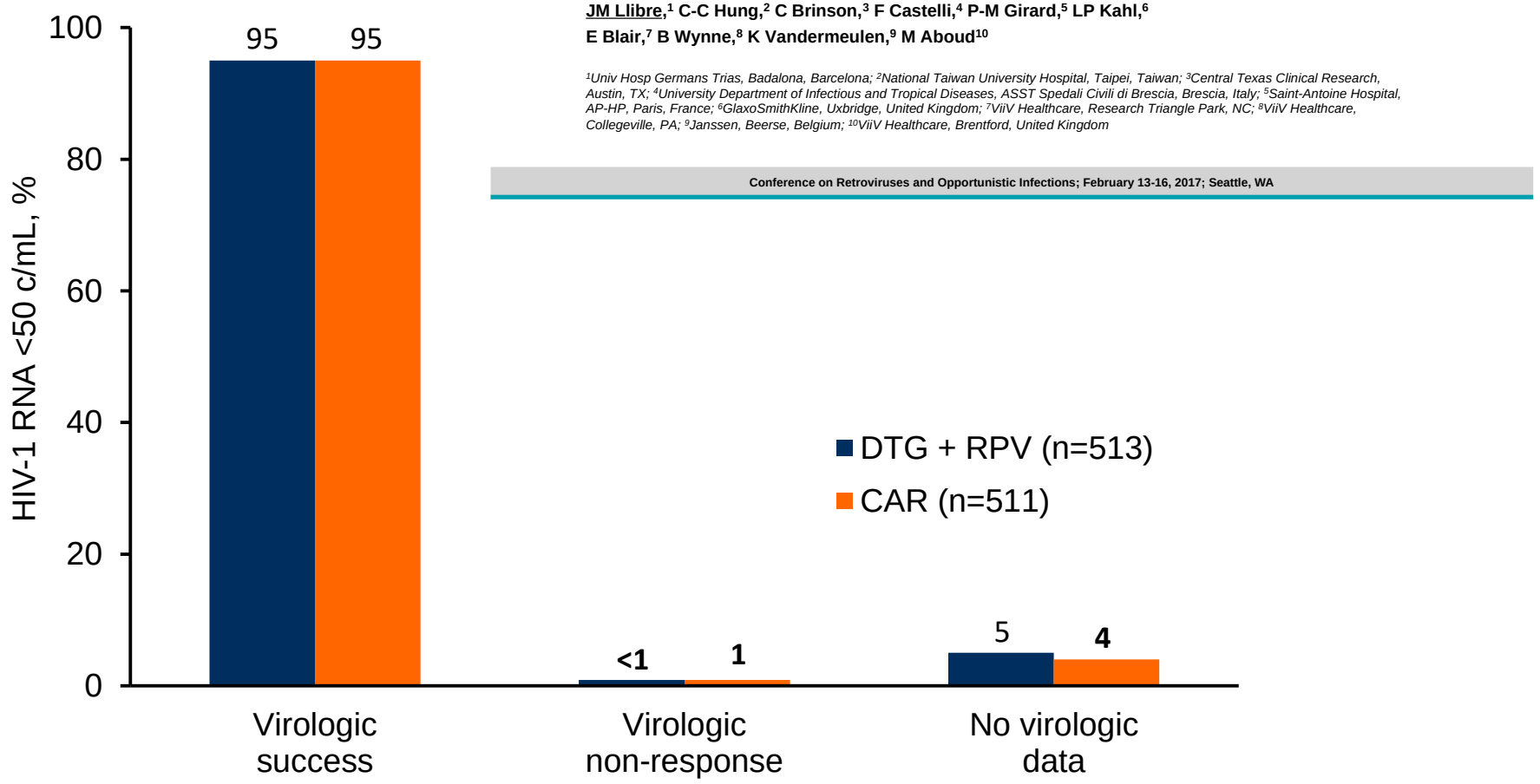
DTG + RPV

SWORD 1 & 2: Switch to DTG + RPV Maintains Virologic Suppression Through 48 Weeks, a Phase III Study

JM Llibre,[1] C-C Hung,[2] C Brinson,[3] F Castelli,[4] P-M Girard,[5] LP Kahl,[6] E Blair,[7] B Wynne,[8] K Vandermeulen,[9] M Aboud[10]

[1]Univ Hosp Germans Trias, Badalona, Barcelona; [2]National Taiwan University Hospital, Taipei, Taiwan; [3]Central Texas Clinical Research, Austin, TX; [4]University Department of Infectious and Tropical Diseases, ASST Spedali Civili di Brescia, Brescia, Italy; [5]Saint-Antoine Hospital, AP-HP, Paris, France; [6]GlaxoSmithKline, Uxbridge, United Kingdom; [7]ViiV Healthcare, Research Triangle Park, NC; [8]ViiV Healthcare, Collegeville, PA; [9]Janssen, Beerse, Belgium; [10]ViiV Healthcare, Brentford, United Kingdom

Conference on Retroviruses and Opportunistic Infections; February 13-16, 2017; Seattle, WA



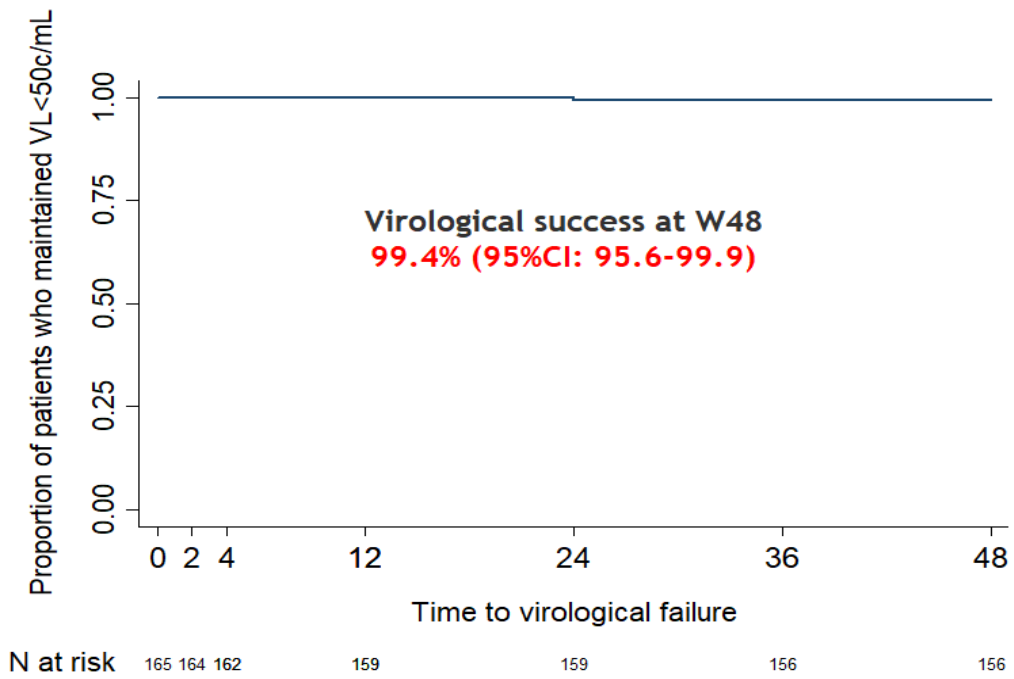
ETRAL : switch from PI regimen to RAL/ETR

- 160 patients

CD4 current/nadir 700 /209

ART

2 NRTIs + PI/r	65%
NNRTI + PI/r	7%
Mono PI/r	21%



One Protocol defined virological failure
W24 11 607/18472
ETR R RAL S

Katlama C et Al IAS Paris 2017 absT MOPEB0314

Diminution de nombre de jour de Traitment

ESSAI ANRS 162 – 4D

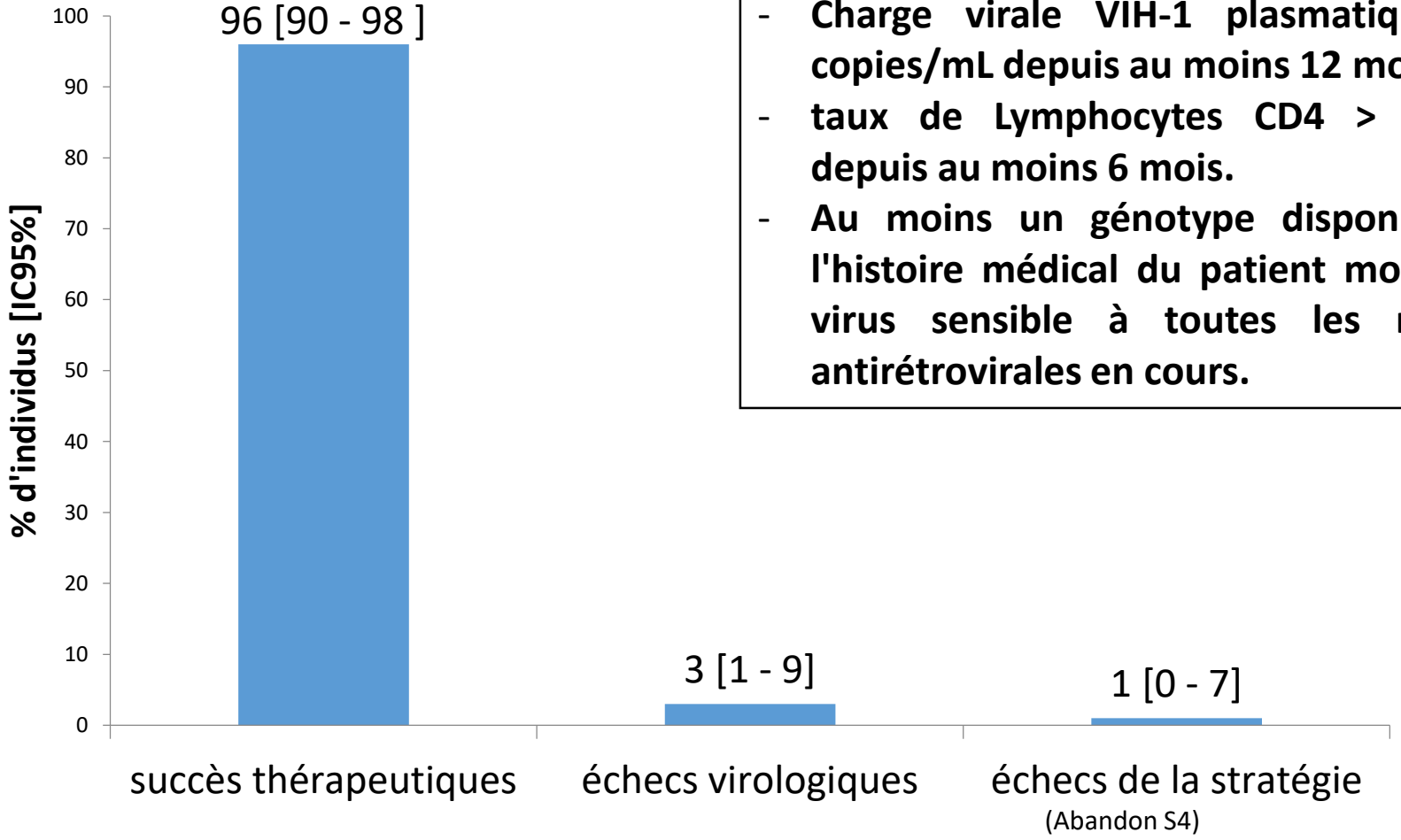
Objectif principal

Évaluer à 48 semaines, la capacité à maintenir le succès thérapeutique, d'une stratégie de prise d'un traitement antirétroviral 4 jours consécutifs sur 7 jours, chez des patients infectés par le VIH-1 ayant une charge virale indétectable depuis au moins 12 mois, en traitement de suite d'un même traitement pris depuis au moins 4 mois.

Protocole ANRS162 - 4D; De Truchis et al.
09.03.2016

Taux de succès à S48 (n=100)

(Estimation de Kaplan-Meier)



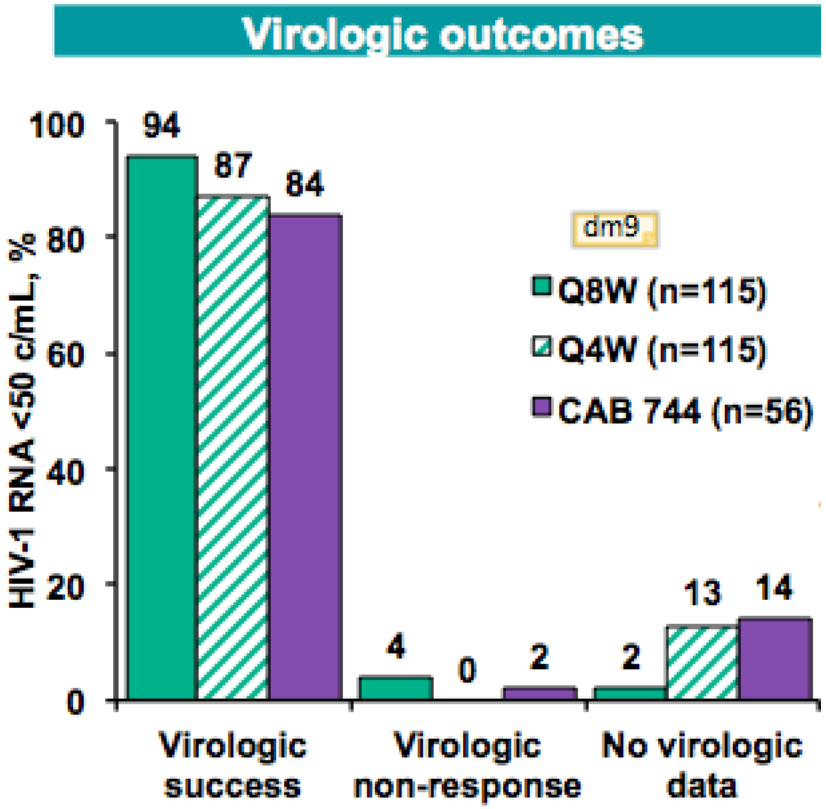
- **Charge virale VIH-1 plasmatique ≤ 50 copies/mL depuis au moins 12 mois**
- **taux de Lymphocytes CD4 > 250/mm³ depuis au moins 6 mois.**
- **Au moins un génotype disponible dans l'histoire médical du patient montrant un virus sensible à toutes les molécules antirétrovirales en cours.**

Antirétroviraux à longue durée d'action

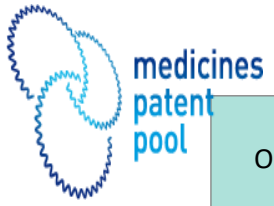
Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial

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 Gutierre. Parul Patel, Herta Crauwels, Sandy K Griffith, Kenneth C Sutton, David

Lancet 2017



HIV pipeline in clinical evaluation (viral suppression)



Phase I	Phase II	Phase III
Doravirine Oral nanoformulations NNRTI *Merck*	**ABX464** Rev inhibitor[6] *Abivax*	**Albuvirtide[1] (FB006M)** Entry inhibitor *Frontier Biotech* Filed with CFDA
MK-8591 (EFdA)	**GSK2838232** Requires a booster Maturation inhibitor *ViiV*	**Ibalizumab[2] (TMB-355)** Entry inhibitor; mAb (not an ARV) *TaiMed Biologics, Theratechnologies*
MK-8507 Unknown MOA *Merck*	**Elsulfavirine (VM1500)** NNRTI *Roche → Viriom*	**Dapivirine (TMC120; DPV)** NNRTI *Janssen → IPM*
MK-2048 INI *NIH; Merck*	**Rilpivirine-LAI (TMC278; RPV)** NNRTI PrEP with oral induction *PATH, NIH; Janssen*	
PC-1005 (MIV-150/zinc acetate) NNRTI *Population Council*	**PRO-140 (PA14)[4]** Not for X4-tropic HIV Entry inhibitor; mAb (not an ARV) *CytoDyn*	+ **VRC-01** bNAb *Rockefeller Univ.* ?
	Sifuvirtide[5] (FS-0101) Entry inhibitor *FusoGen*	
	Cenicriviroc[3] (TBR-652; CVC) Not for X4-tropic HIV Entry inhibitor *Takeda → Tobira*	

Fostemsavir

Phase III
Doravirine (MK-1439; DOR) NNRTI *Merck*
Bictegravir (GS-9883) INI *Gilead, Filed with FDA*
Cabotegravir-LAI (GSK-744; CAB) INI PrEP with oral induction *NIH; ViiV*
Cabotegravir-LAI + Rilpivirine-LAI Maintenance strategy with oral induction *ViiV + Janssen*

List not exhaustive. Shock-n-kill strategies, gene/cell therapies and non-oral immunotherapies are not included.

Medicines Patent Pool. Last updated on: 5/30/2017

IAS2017

Oral

Other parenteral

Long-acting injection (LAI)[8]

Topical microbicide

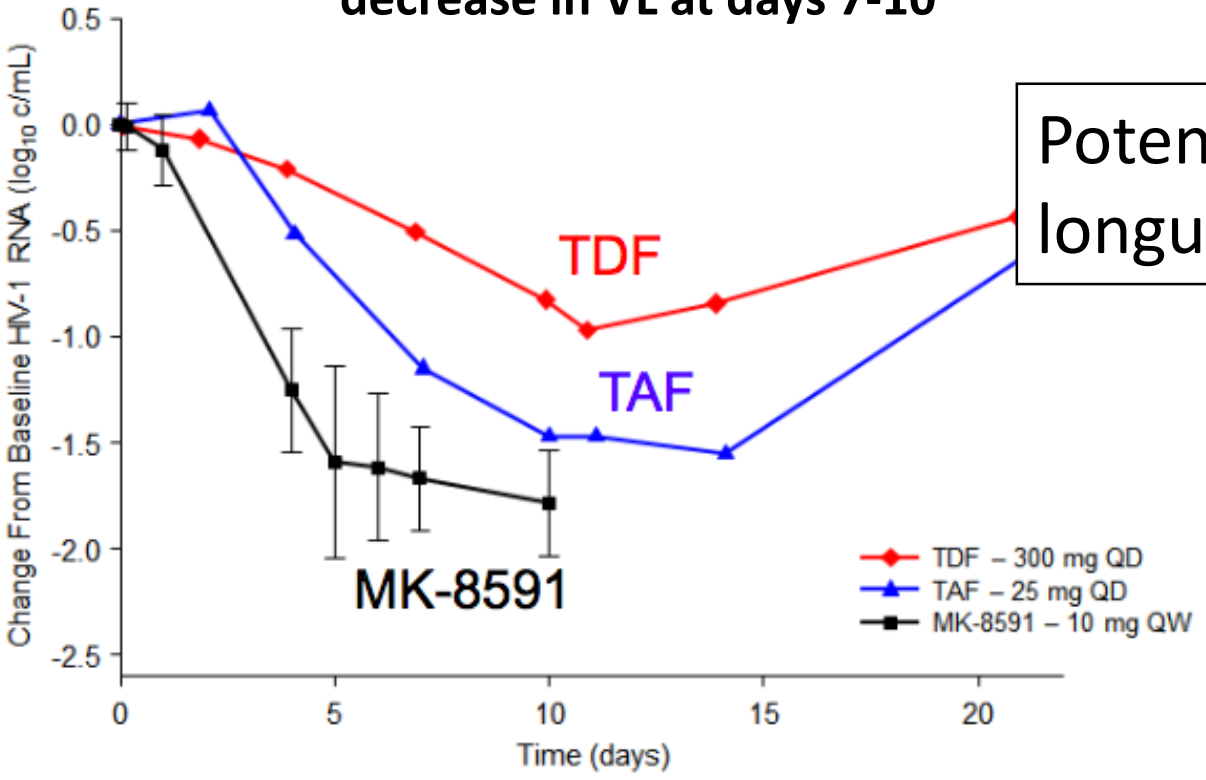
Potential first-in-class

Planning stage ? **Cabotegravir-LAI + Rilpivirine-LAI** *ViiV + Janssen* + **VRC-01-LS** bNAb *Rockefeller Univ.*

Paredes R et al, abstract # TULBPEB22

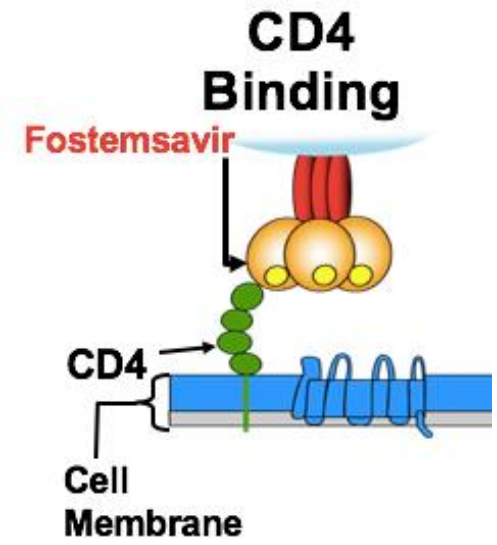
A new nucleoside NRTTI* MK-8591 (EFdA)(Phase 1)

MK-8591 (phase 1b):
A single once-weekly 10 mg oral dose results in 1.6 log decrease in VL at days 7-10

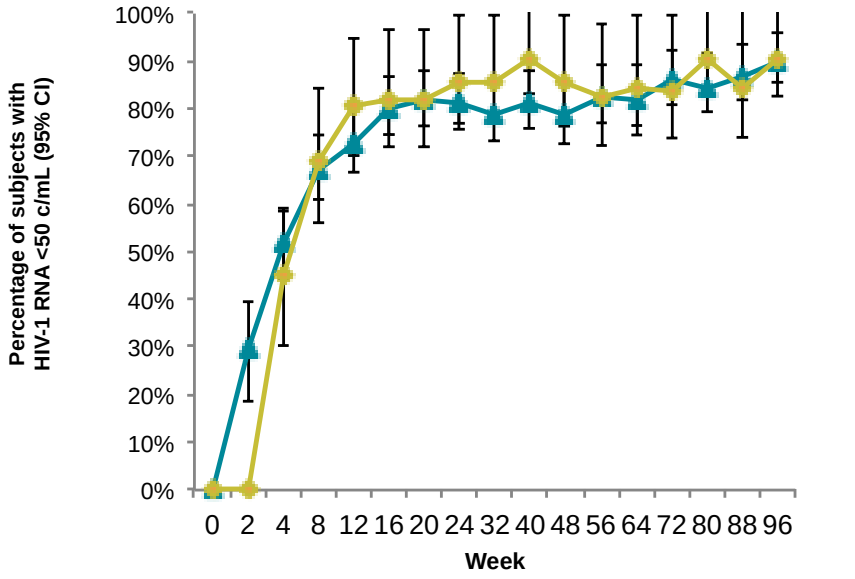


Potentiel : ARV à longue durée d'action

PHASE 3 - Fostemsavir (GSK3684934) - attachment inhibitor



Efficacy At Week 96: Observed Analysis

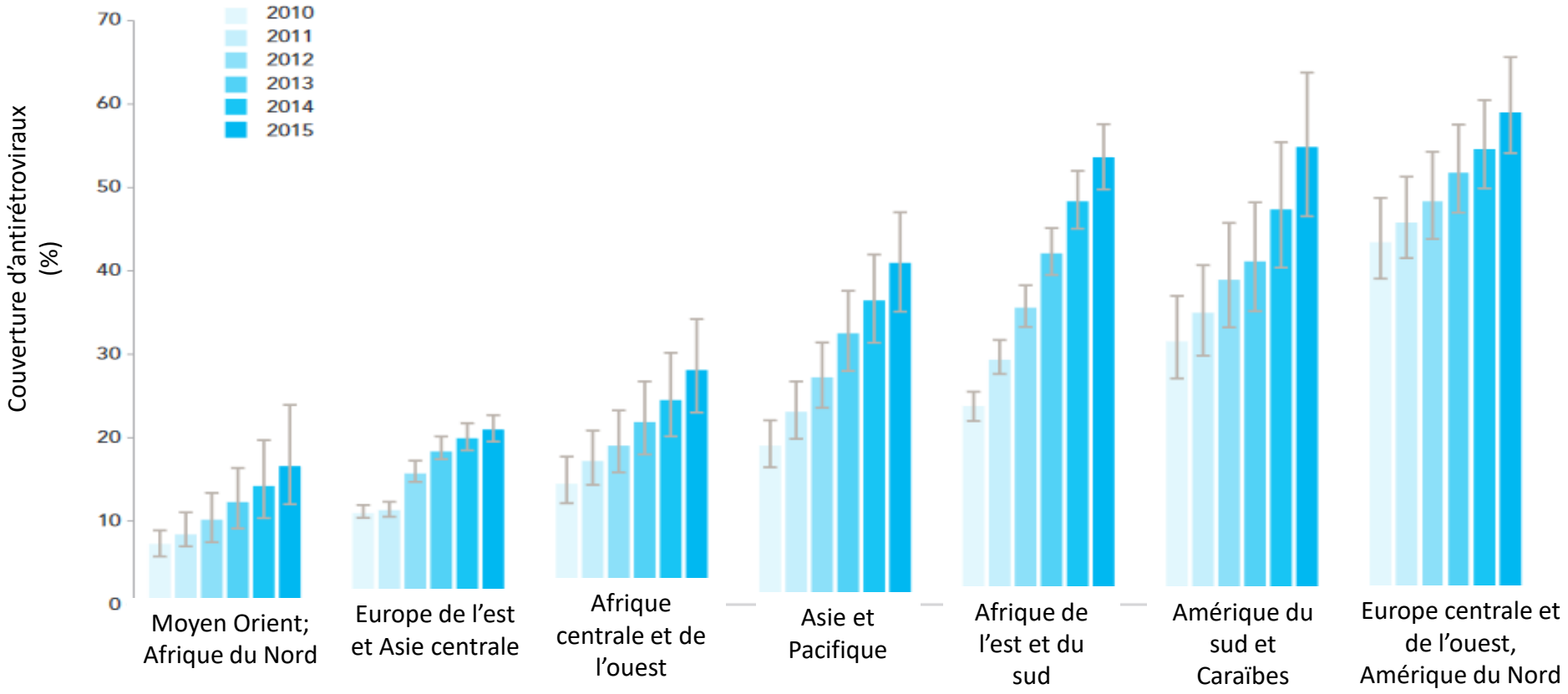


Proportion of subjects with <50 c/mL at week 96		
	GSK3684934 1200 mg QD	90%
	ATV/r 300 mg/ 100 mg QD	90%

Fostemsavir (GSK3684934, previously BMS-663068), the prodrug of temsavir (GSK2616713, previously BMS-626529). Langley DR et al. Proteins 2015; 83:331–350. Llamoso C et al. HIV Glasgow 2016; Glasgow, UK. Oral #335A/B. Thomson M et al, Antivir Ther 2016 Dec 6, phase 2b 48 week results

Un accès aux antirétroviraux encore insuffisant

- 53 % des PVVIH ont accès aux ARV
- Grandes disparités dans le monde



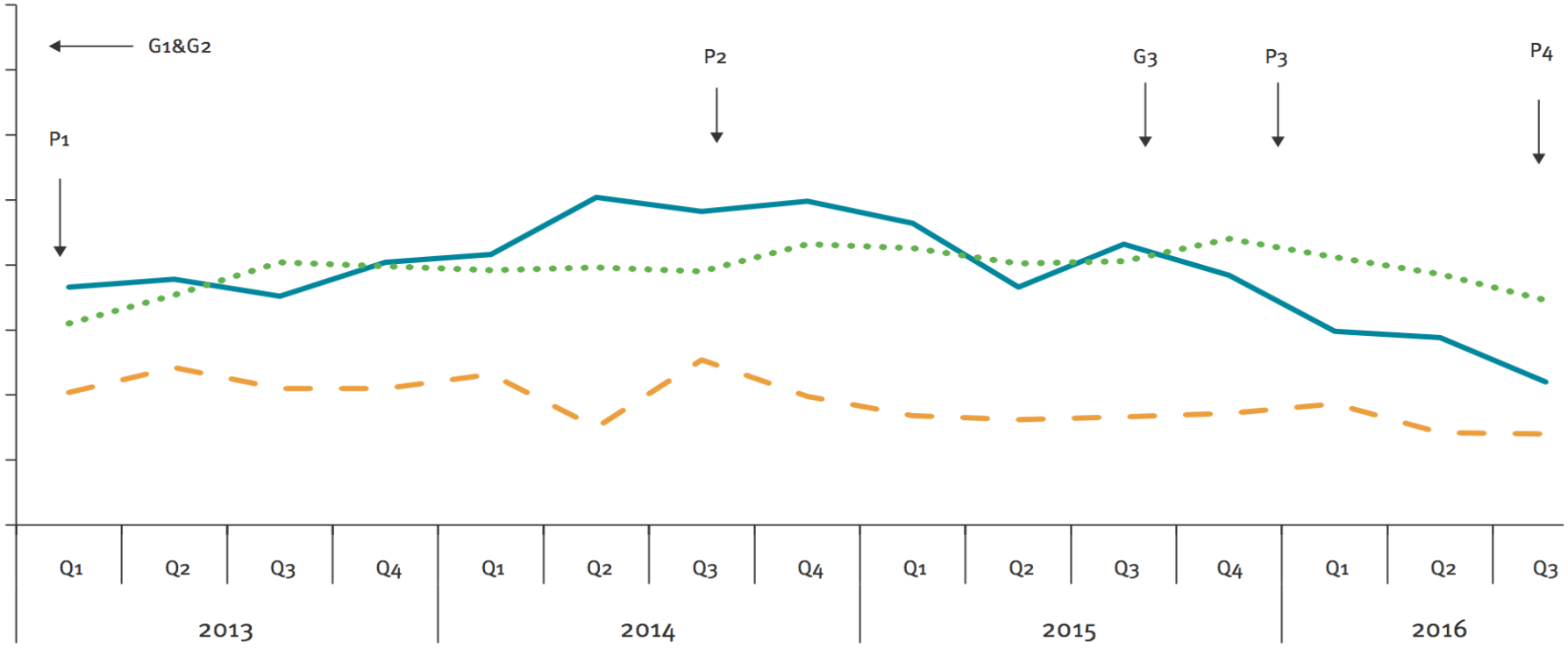
Fiche d'information 2016, statistiques mondiales, ONUSIDA

New HIV diagnoses among men who have sex w… …ics by ye… …
(n = …

Dépistage

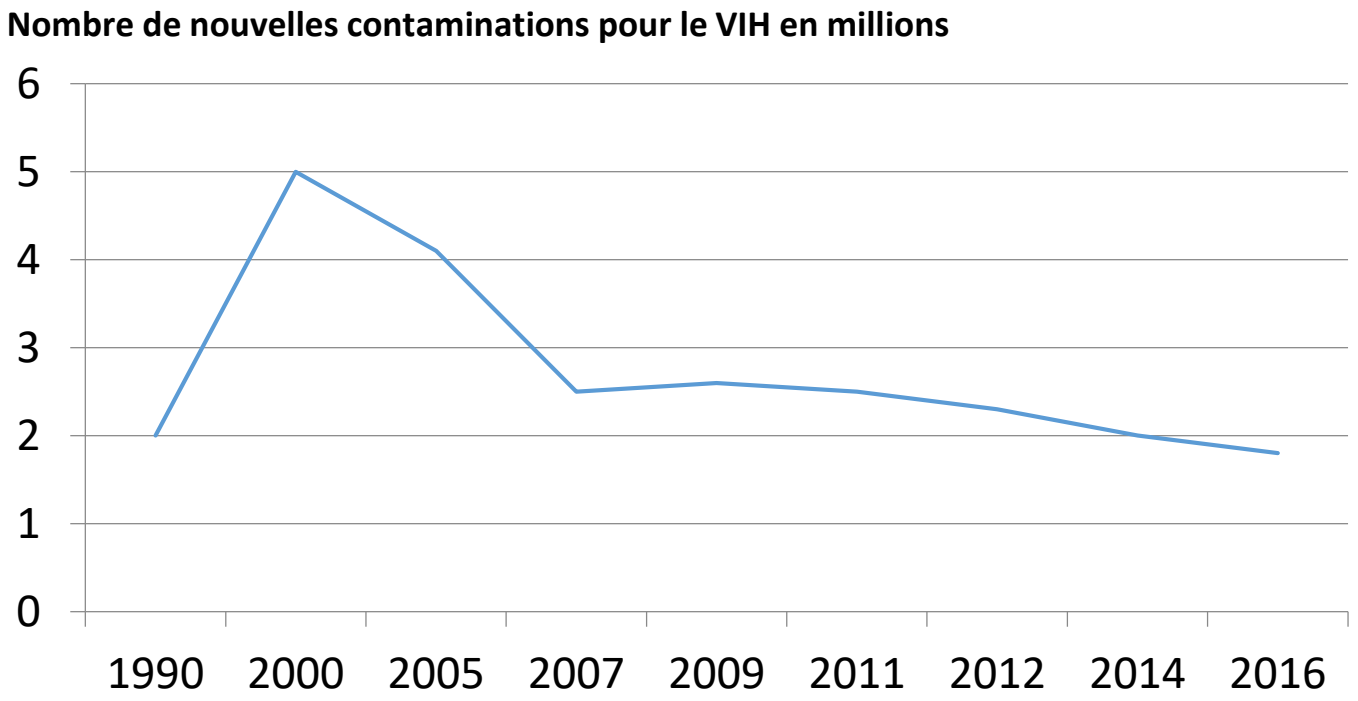
Lien avec le système de soins

Traitement immédiat



Brown et al Eurosurveillance 2017

Une incidence en diminution dans le monde



Sauf dans 2 régions du monde :

- Moyen Orient; Afrique du Nord (+ 26% en 15 ans)
- Europe Centrale (+ 30% en 15 ans)

Rapport ONUSIDA 2015

Remerciements

- Alexandra Calmy
- Pascal Pugliese
- Christine Katlama
- Roland Landmann
- Marion Parisey
- Constance Delaugerre