Stratégies thérapeutiques des patients infectés par le VIH: données récentes

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Plan

- Traitement ARV en 2016: Quand? Comment? Quoi?
  - Traitement ARV de 1ère ligne
  - Traitement ARV de maintenance chez les patients en succès
  - Traitement de l'infection HCV
- Épidémiologie mondiale et objectifs de traitement
- La PreP à la mode
- Le concept TasP (Treatment as Prevention): Où en est-on?

Essai START: traitement ARV précoce

The NEW ENGLAND JOURNAL of MEDICINE

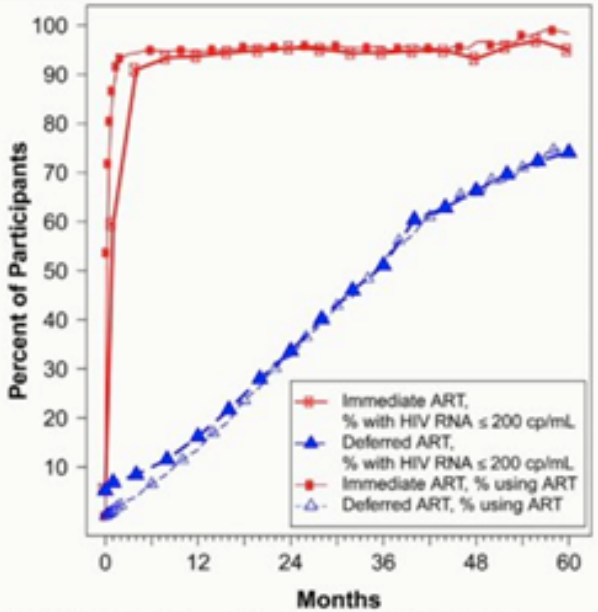
ESTABLISHED IN 1812 AUGUST 27, 2015 VOL. 373 NO. 9

Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection

The INSIGHT START Study Group*

START

Percent on ART and with HIV-RNA ≤ 200 c/mL



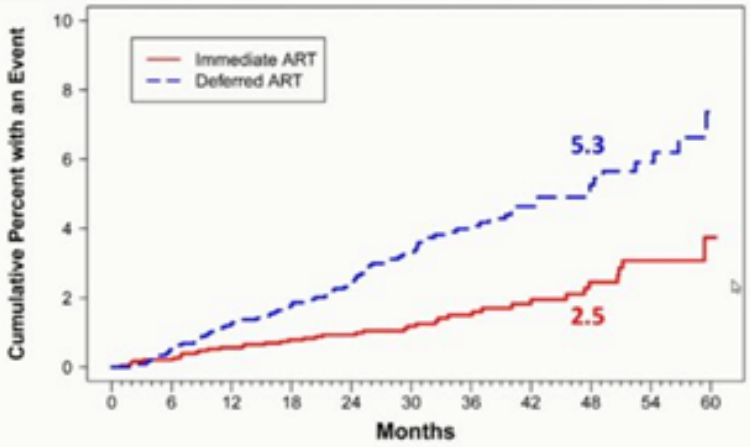
	% of Follow-up on ART
Immediate	94
Deferred	28

Deferred Arm:
Median time to ART
3 years (IQR 1.6-4.8)
(projected 4 years)

INSIGHT START Study Group. N Engl J Med 2015; 373:795-807

START

Primary Endpoint – Serious AIDS or Non-AIDS Events



	Immediate ART	Deferred ART
No. with Event (%)	42 (1.8%)	96 (4.1%)
Rate/100PY	0.60	1.38
HR (Imm/Def)	0.43 (95% CI: 0.30 to 0.62, p <0.001)	

INSIGHT START Study Group. N Engl J Med 2015; 373:795-807

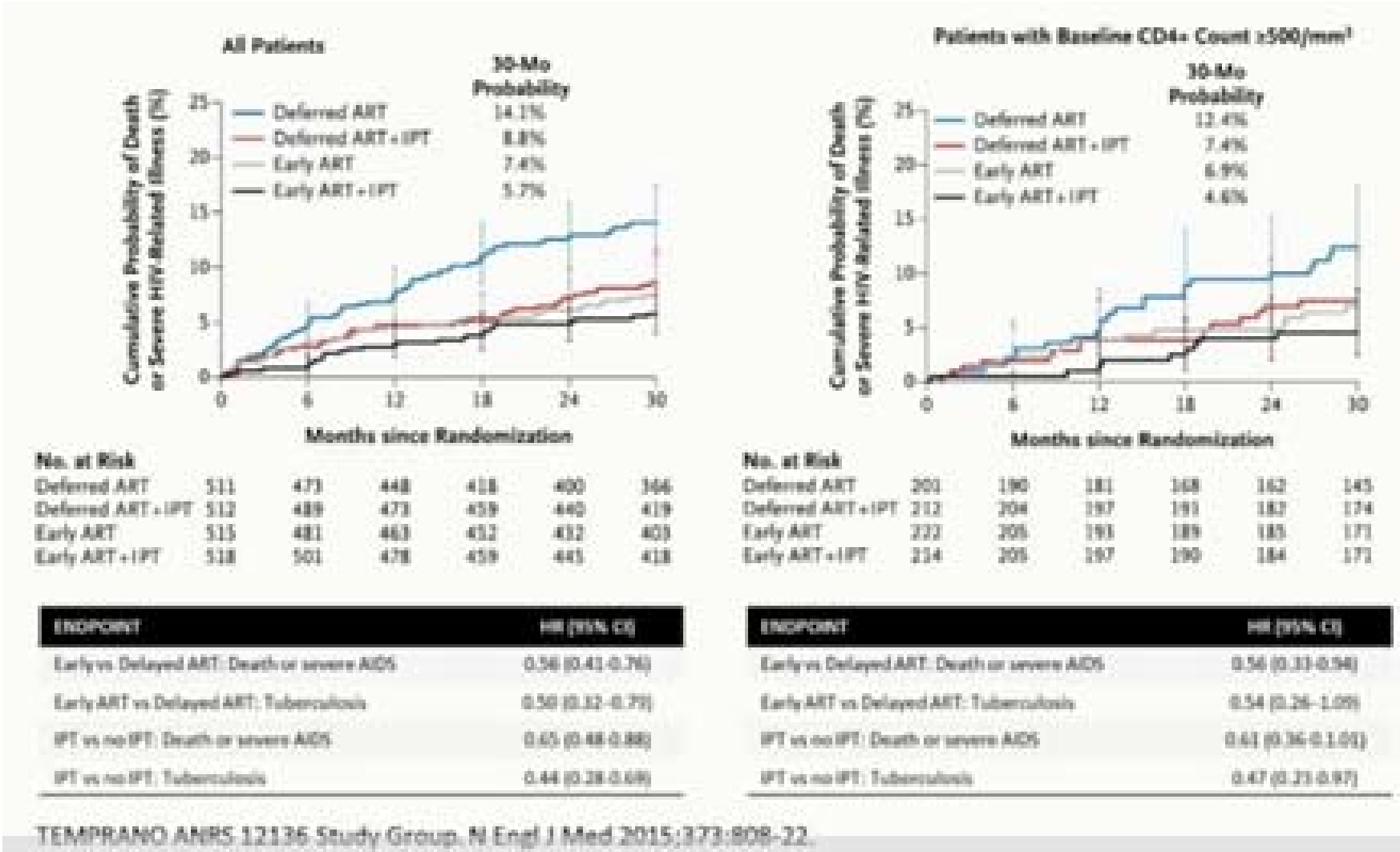
Essai Temprano:
Tt précoce ARV+/-INH

ORIGINAL ARTICLE

A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa

The TEMPRANO ANRS 12136 Study Group*

N ENGL J MED 373;9 NEJM.ORG AUGUST 27, 2015



ENDPOINT	HR (95% CI)
Early vs. Delayed ART: Death or severe AIDS	0.56 (0.41-0.76)
Early ART vs. Delayed ART: Tuberculosis	0.50 (0.32-0.79)
IPT vs no IPT: Death or severe AIDS	0.65 (0.48-0.88)
IPT vs no IPT: Tuberculosis	0.44 (0.28-0.69)

ENDPOINT	HR (95% CI)
Early vs Delayed ART: Death or severe AIDS	0.56 (0.33-0.94)
Early ART vs Delayed ART: Tuberculosis	0.54 (0.26-1.09)
IPT vs no IPT: Death or severe AIDS	0.61 (0.36-1.01)
IPT vs no IPT: Tuberculosis	0.47 (0.23-0.97)

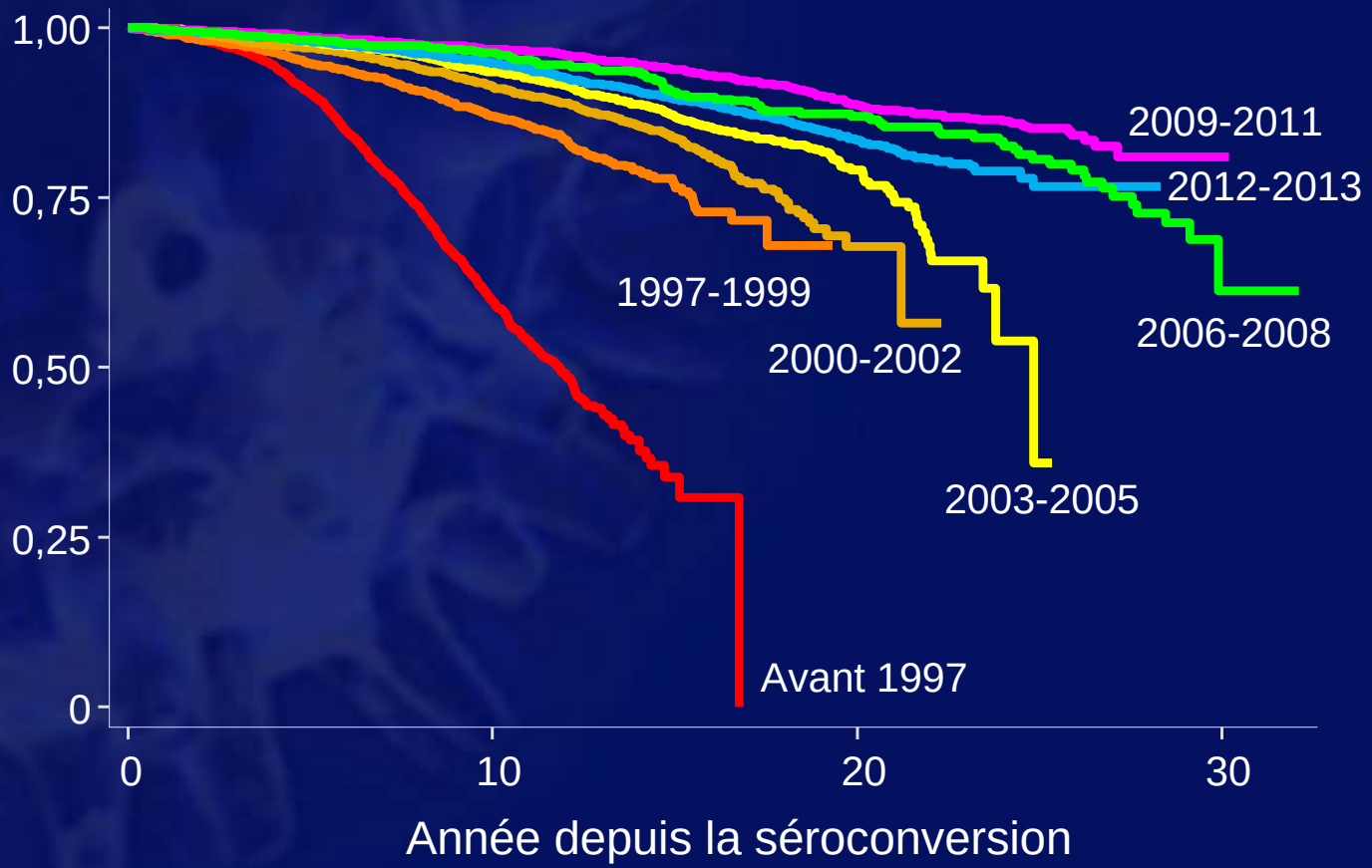
TEMPRANO ANRS 12136 Study Group. N Engl J Med 2015;373:808-22.

le meilleur ...de la CROI 2015

Survie après séroconversion VIH : évolution de 1997 à 2013

- Cohorte CASCADE, 30 855 patients avec date de séroconversion correctement estimée (suivi : 234 249 années-personne)
- Modèle de Cox (Kaplan-Meier) estimant le délai entre séroconversion et décès, ajusté sur sexe, mode d'acquisition du VIH, âge à la séroconversion et primo-infection

Survie estimée selon la date de séroconversion



Probabilité de survie 10 ans après la séroconversion (IC 95 %)

< 1997	0,60 (0,58 - 0,62)
1997-1999	0,87 (0,85 - 0,88)
2000-2002	0,91 (0,90 - 0,92)
2003-2005	0,94 (0,93 - 0,95)
2006-2008	0,95 (0,94 - 0,96)
2009-2011	0,97 (0,96 - 0,97)
2012-2013	0,96 (0,95 - 0,97)

Olson A, CROI 2015, Abs. 1051

Efficacité et tolérance comparatives des traitement ARV de 1ère ligne: « a systematic review and network meta-analysis »

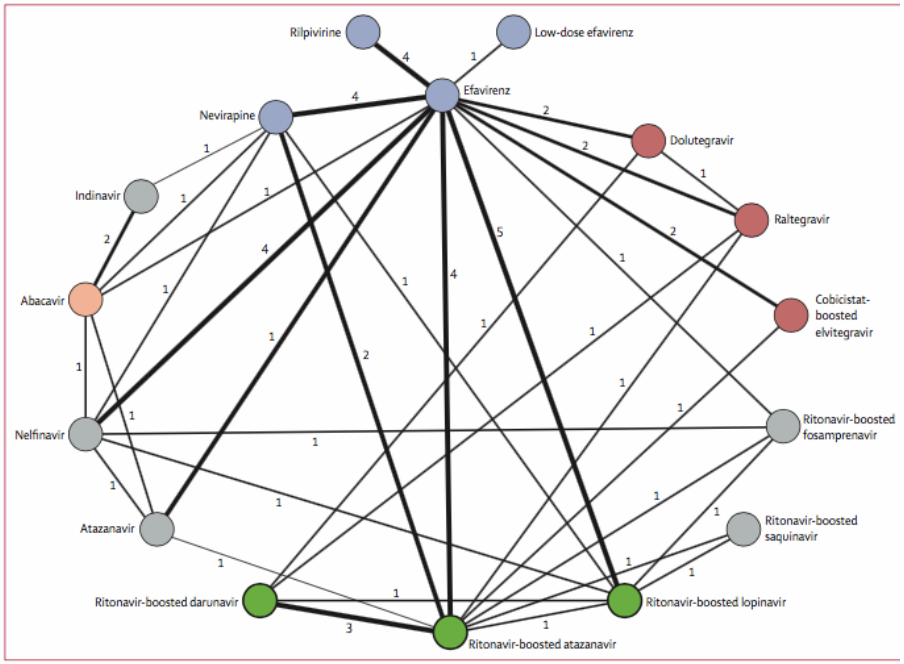


Figure 2: **Network of eligible comparisons between treatments**
Overall, the network included 34 032 patients randomly assigned to 161 treatment groups across 71 trials. Circles (nodes) in the diagrams represent individual treatments, lines between circles represent availability of head-to-head evidence between two treatments, and the numbers on the lines are the number of randomised clinical trials informing each head-to-head comparison. The colours represent antiretroviral classes, with grey representing protease inhibitors that are no longer commonly used in practice, which are included in the network as connectors.

EFV	**1·90 (1·40–2·59)**	**1·45 (1·07–1·95)**	1·10 (0·77–1·59)	0·69 (0·48–1·03)	0·93 (0·74–1·18)	0·99 (0·71–1·40)	**0·49 (0·30–0·82)**	1·19 (0·73–1·95)	1·34 (0·92–1·94)
1·87 (1·34–2·64)	DTG	0·76 (0·56–1·03)	**0·58 (0·37–0·92)**	**0·36 (0·24–0·56)**	**0·49 (0·35–0·69)**	**0·52 (0·37–0·74)**	**0·26 (0·14–0·47)**	0·63 (0·35–1·11)	0·71 (0·44–1·14)
1·40 (1·02–2·59)	0·75 (0·53–1·05)	RAL	0·76 (0·49–1·18)	**0·48 (0·32–0·73)**	**0·64 (0·47–0·88)**	**0·68 (0·48–0·97)**	**0·34 (0·19–0·61)**	0·82 (0·46–1·44)	0·93 (0·57–1·49)
1·28 (0·87–1·89)	0·68 (0·41–1·14)	0·91 (0·56–1·50)	EVG/c	0·63 (0·39–1·03)	0·84 (0·59–1·22)	0·90 (0·57–1·44)	**0·45 (0·24–0·83)**	1·09 (0·58–1·98)	1·22 (0·72–2·03)
0·76 (0·59–0·98)	**0·40 (0·27–0·60)**	**0·54 (0·37–0·78)**	**0·59 (0·38–0·92)**	LPV/r	1·34 (0·96–1·85)	1·43 (1·00–2·00)	0·72 (0·39–1·27)	1·73 (0·91–3·11)	**1·94 (1·12–3·21)**
0·90 (0·74–1·10)	**0·48 (0·33–0·69)**	**0·64 (0·46–0·89)**	0·70 (0·48–1·04)	1·18 (0·92–1·54)	ATV/r	1·07 (0·78–1·48)	**0·54 (0·31–0·92)**	1·28 (0·73–2·20)	1·45 (0·92–2·22)
0·91 (0·66–1·28)	**0·49 (0·33–0·72)**	**0·65 (0·45–0·94)**	0·71 (0·44–1·16)	1·21 (0·87–1·69)	1·02 (0·74–1·40)	DRV/r	**0·50 (0·27–0·90)**	1·20 (0·65–2·17)	1·36 (0·80–2·21)
0·87 (0·70–1·07)	**0·46 (0·32–0·68)**	**0·62 (0·43–0·89)**	0·68 (0·44–1·04)	1·15 (0·85–1·54)	0·97 (0·76–1·23)	0·95 (0·65–1·37)	NVP	**2·42 (1·18–4·88)**	**2·72 (1·46–5·11)**
1·16 (0·67–2·02)	0·62 (0·33–1·17)	0·82 (0·44–1·55)	0·90 (0·46–1·77)	1·52 (0·83–2·59)	1·29 (0·72–2·31)	1·26 (0·67–2·39)	1·33 (0·74–2·40)	low EFV	1·13 (0·61–2·13)
1·18 (0·90–1·55)	**0·63 (0·41–0·98)**	0·85 (0·55–1·28)	0·92 (0·57–1·48)	**1·57 (1·07–2·25)**	1·32 (0·93–1·83)	1·29 (0·83–1·98)	1·36 (0·96–1·92)	1·02 (0·56–1·87)	RPV

Treatment | 48 week network results, OR (95% CI) | 96 week network results, OR (95% CI)

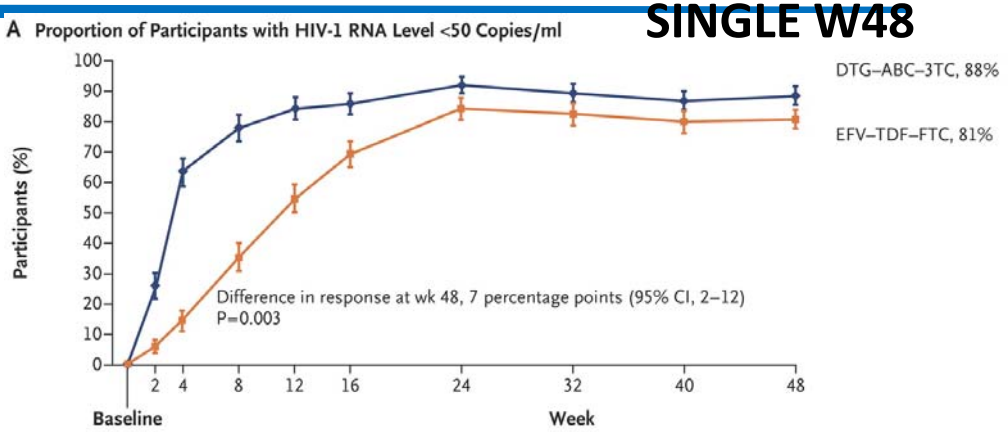
Figure 3: **Random-effects network meta-analyses of the relative efficacy of antiretrovirals for viral suppression**
Data are OR (95% CI) of the row treatment relative to the column treatment (eg, the effect of dolutegravir relative to efavirenz is 1·87 with respect to viral suppression at 48 weeks). Bold values indicate comparisons that are statistically significant. ORs above 1 indicate higher efficacy in viral suppression. OR=odds ratio. EFV=efavirenz.

Steve Kanters ***Lancet HIV* 2016; 3: e510–20**

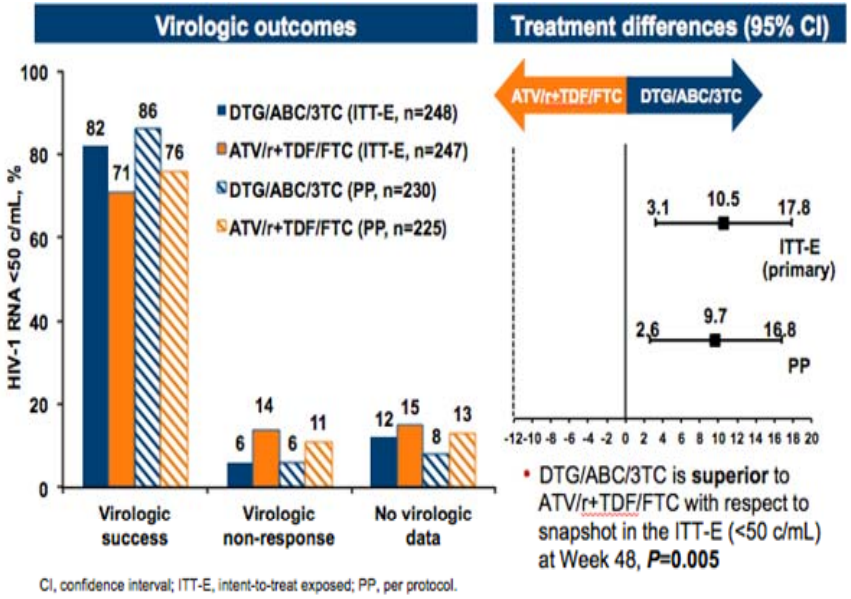
Études randomisées: INSTIs vs INNRT/ PI

- DTG > EFV (**SINGLE**)
- RAL >ATV/r et DRV/r (**ACTG A5257**)[1]
- Dolutegravir >DRV/r (**FLAMINGO**)[2]
- EVG/cobi >ATV/r (femmes) (**WAVES**)[3]
- DTG/ABC/3TC > ATV/r + TDF/FTC femmes (**ARIA**)[4]

SINGLE W48



ARIA: Wk 48 VL <50



CI, confidence interval; ITT-E, intent-to-treat exposed; PP, per protocol.

[1] Lennox J et al, Ann Int Med, 2014; [2]Clotet B et al, Lancet, 2014; [3]Squires K, et al. Lancet HIV, 2016; [4]C. Orell et al. International AIDS Conference, July 2016, Durban, South Africa. TUAC1021

Vers le TAF…

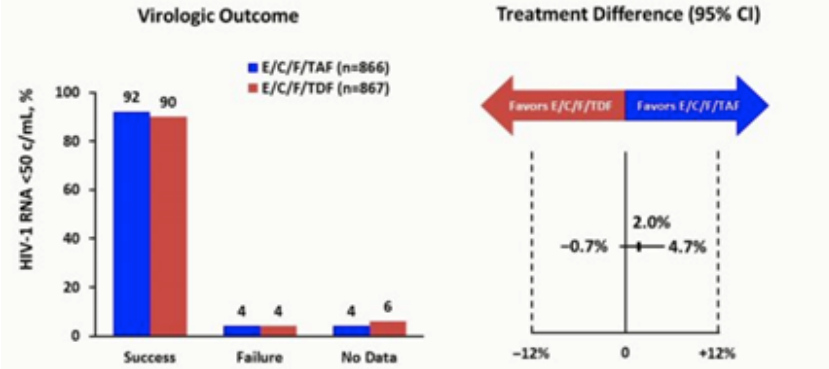
Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials

Paul E Sax, David Wohl, Michael T Yin, Frank Post, Edwin DeJesus, Michael Saag, Anton Pozniak, Melanie Thompson, Daniel Podzamczer, Jean Michel Molina, Shinichi Oka, Ellen Koenig, Benoit Trottier, Jaime Andrade-Villanueva, Gordon Crofoot, Joseph M Custodio, Andrew Plummer, Lijie Zhong, Huyen Cao, Hal Martin, Christian Callebaut, Andrew K Cheng, Marshall W Fordyce, Scott McCallister, for the GS-US-292-0104/0111 Study Team*

Lancet 2015; 385: 2606–15

TAF vs TDF

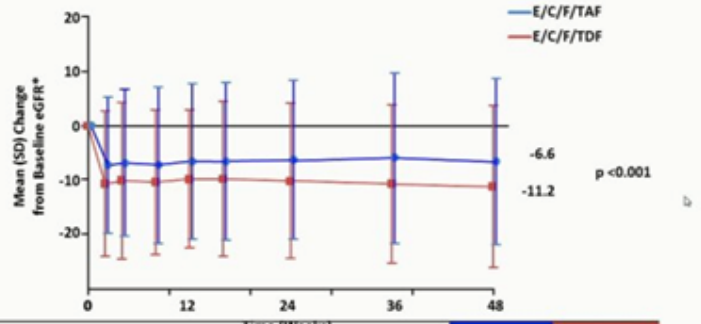
Virologic Results



Similar response rates, irrespective of age, sex, race, HIV-1 RNA, and CD4 cell count

TAF vs TDF

Renal Safety

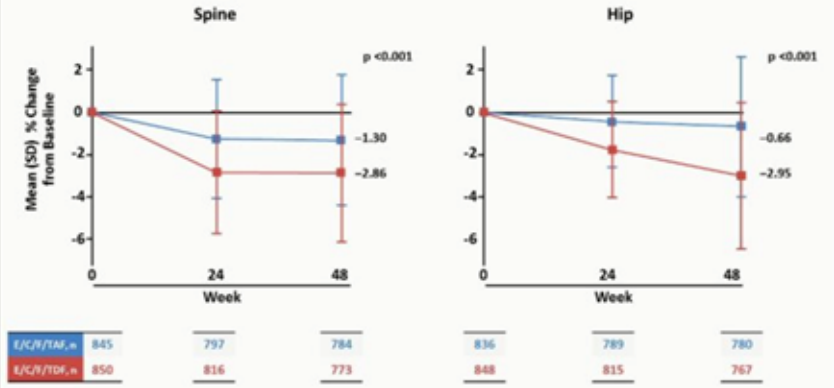


	n (%)	E/C/F/TAF n=866	E/C/F/TDF n=867
Events	Renal adverse events leading to discontinuation	0	4 (0.5)
	Tubulopathy/Fanconi syndrome	0	0

Sax PE, et al. Lancet 2015; 385:2606-15

TAF vs TDF

Spine and Hip BMD



Sax PE, et al. Lancet 2015; 385:2606-15

Clinical Review & Education

Special Communication

Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults 2016 Recommendations of the International Antiviral Society–USA Panel

Huldrych F. Günthard, MD; Michael S. Saag, MD; Constance A. Benson, MD; Carlos del Rio, MD; Joseph J. Eron, MD; Joel E. Gallant, MD, MPH; Jennifer F. Hoy, MBBS, FRACP; Michael J. Mugavero, MD, MHSc; Paul E. [illegible] MD; Melanie A. Thompson, MD; Rajesh T. Gandhi, MD; Raphael J. Landovitz, MD; Davey M. Smith, MD; Donna M. Jacobsen, BS; Paul A. Volberding, MD

Table 3. Recommended Initial Antiretroviral Therapy Regimens[a]

Regimen	Rating
Dolutegravir/abacavir/lamivudine	AIa
Dolutegravir plus tenofovir alafenamide/emtricitabine[b]	AIa
Elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine[b]	AIa
Raltegravir plus tenofovir alafenamide/emtricitabine[b]	AIII

Table 5. Advantages and Disadvantages of Initial Antiretroviral Therapy Options for Patients in Whom InSTIs Are Not an Option[a]

	Darunavir (Boosted With Cobicistat or Ritonavir) Plus TAF/Emtricitabine, TDF/Emtricitabine, or Abacavir/Lamivudine[b]	Efavirenz/TDF/Emtricitabine	Rilpivirine/TAF (or TDF)/Emtricitabine
Advantages	Low risk of resistance with virologic failure, even with intermittent adherence	High efficacy in patients with baseline HIV RNA >100 000 copies/mL Extensive experience in patients with concomitant tuberculosis Widely available globally	Lowest risk of rash among NNRTI-based therapies Low risk of metabolic adverse effects Smallest tablet among single-pill regimens
Disadvantages	Requires pharmacokinetic boosting; many drug interactions Ritonavir-boosted darunavir inferior to raltegravir and dolutegravir in separate comparative clinical trials[37,39] Results of comparative, fully powered studies of cobicistat-boosted darunavir as initial therapy are not yet available	Relatively high rate of rash No single-tablet form available with TAF High rates of neuropsychiatric adverse effects Increased risk of suicidality in 1 study[55]; avoid in patients with history of depression	Not recommended for patients with HIV RNA >100 000 copies/mL or CD4 cell count <200/μL owing to increased risk of virologic failure Must be taken with a meal to optimize absorption Should not be administered with proton pump inhibitors; stagger dosing if given with an H_2 blocker

Options recommandées pour l'initiation d'un premier traitement ARV

2 INTI	INNTI	Nb cp/ Nb prises par jour	Commentaires
TénofovirDF/Emtricitabine 245/200 mg x 1	Rilpivirine 25 mg x 1	1/1	Uniquement si CV < 5 log copies/ml. Précaution si CD4< 200/mm^3 Précaution si clairance de la créatinine < 80 ml/min. Surveillance rénale. Prise au cours d'un repas. Association à un IPP contre-indiquée
2 INTI	**INI**		**Commentaires**
TénofovirDF/Emtricitabine 245/200 mg x 1	Dolutégravir 50 mg x 1	2/1	Précaution si clairance de la créatinine < 80 ml/min. Surveillance rénale. Peu d'interactions médicamenteuses avec le dolutégravir
Abacavir/Lamivudine 600/300 mg x1	Dolutégravir 50 mg x 1	1/1	Uniquement si HLA-B*5701 négatif Peu d'interactions médicamenteuses avec le dolutégravir
TénofovirDF/Emtricitabine 245/200 mg x 1	Elvitégravir/C 150/150 mg x 1	1/1	Association contre-indiquée si clairance de la créatinine < 70 ml/min. Précaution si clairance de la créatinine < 90 ml/min. Surveillance rénale. Interactions médicamenteuses avec cobicistat
TénofovirDF/Emtricitabine 245/200 mg x 1	Raltégravir 400 mg x 2	3/2	Précaution si clairance de la créatinine < 80 ml/min. Surveillance rénale. Pas d'interaction médicamenteuse avec le raltégravir
2 INTI	**IP/r**		**Commentaires**
TénofovirDF/Emtricitabine 245/200 mg x1	Darunavir/r 800/100 mg x 1	3/1	Intérêt particulier dans les indications suivantes : - immunodépression avancée - charge virale plasmatique élevée - nécessité d'entreprendre un traitement sans délai - femme enceinte Précaution si clairance de la créatinine < 80 ml/min. Surveillance rénale. Interactions médicamenteuses avec le ritonavir

Antiretroviral Therapy: The Future



HIV-1 discovered

1983

ZDV monotherapy

1987

ZDV/3TC

1995

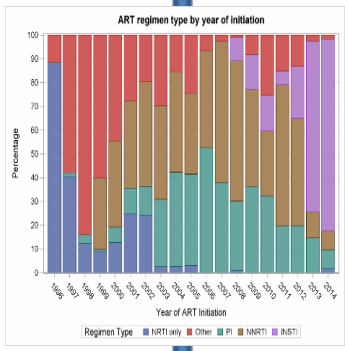
Triple Drug Therapy

1996


Single Tablet Regimens

2006

The Integrase Era



2012-13

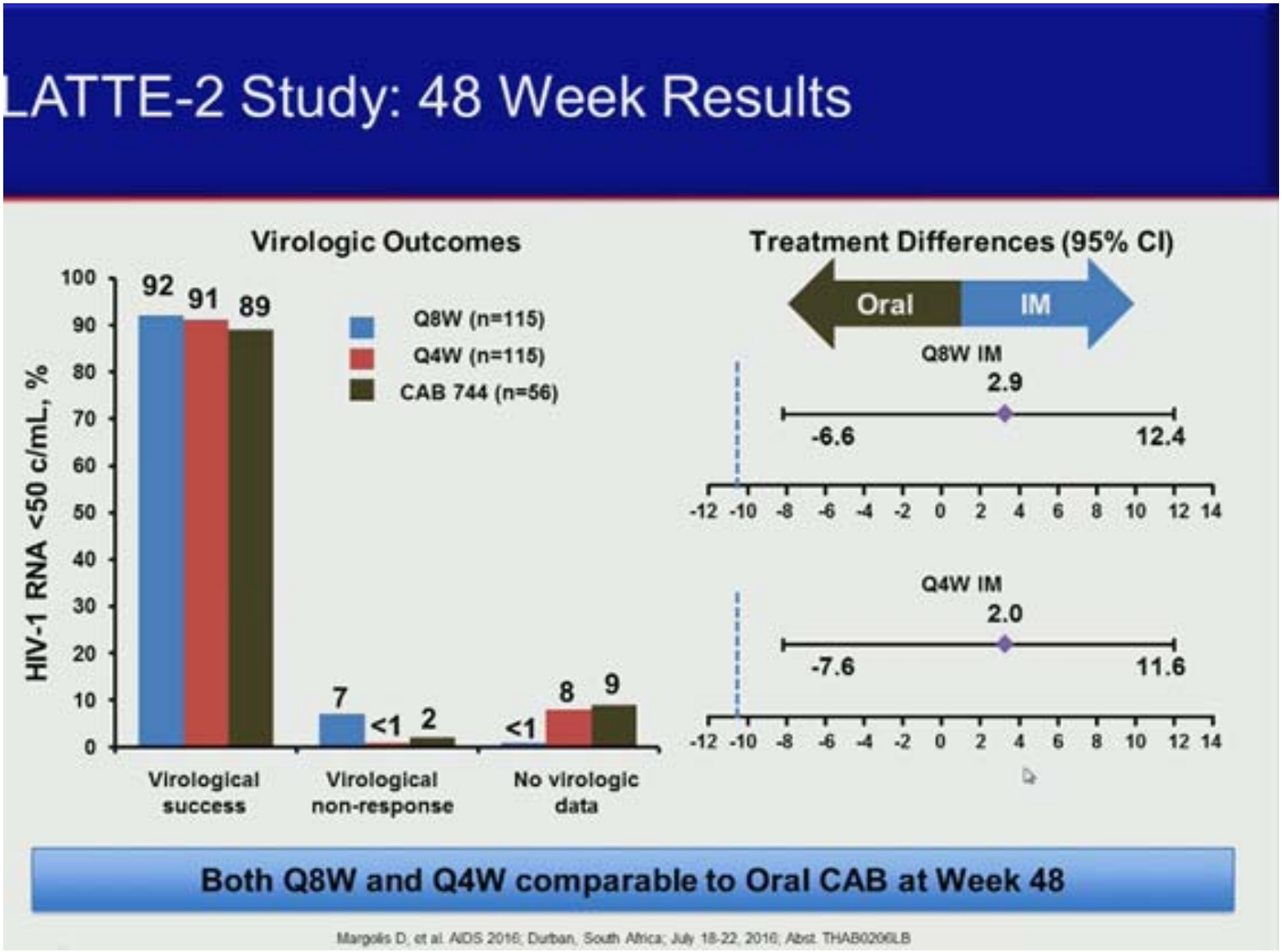
Long Acting Injectable?

2017

?????

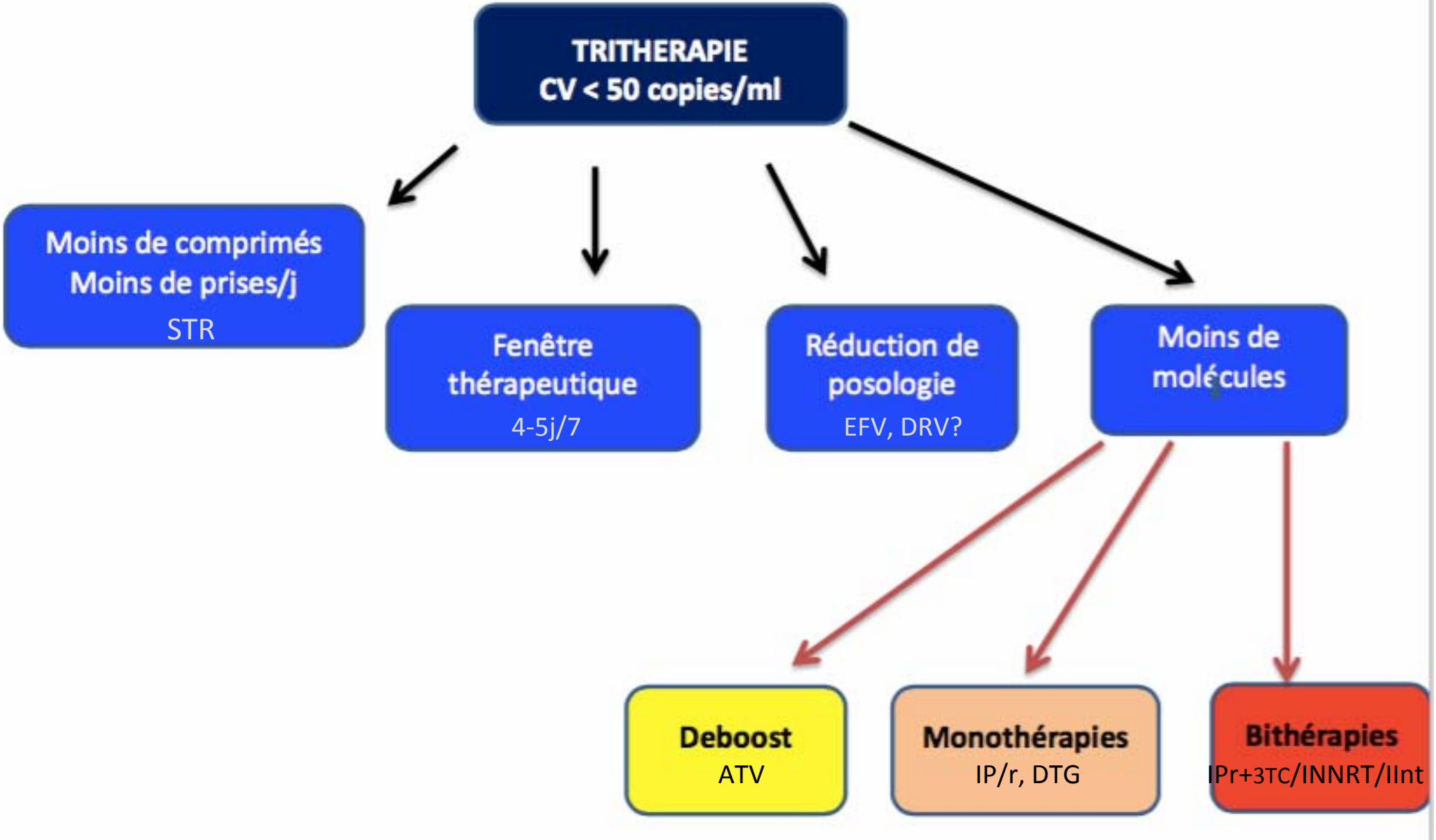
2020

Essai LATTE:
ARV à longue durée d'action



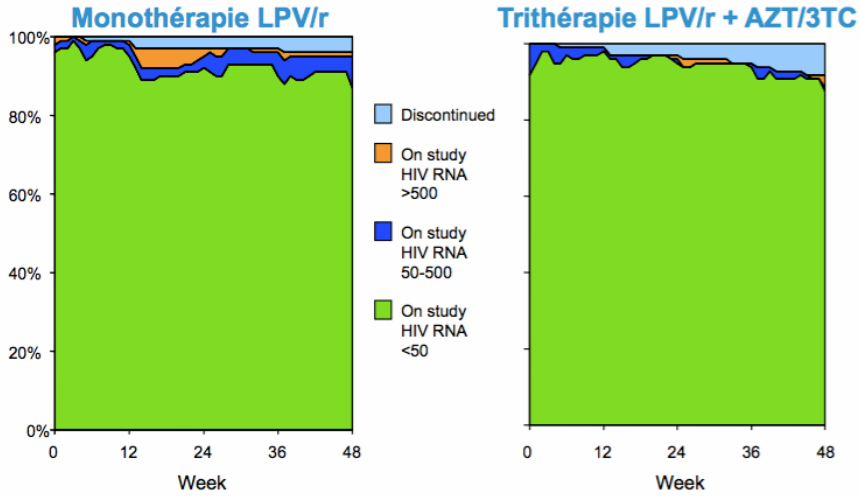
ARV en succès: simplification/allègement

Options de maintenance



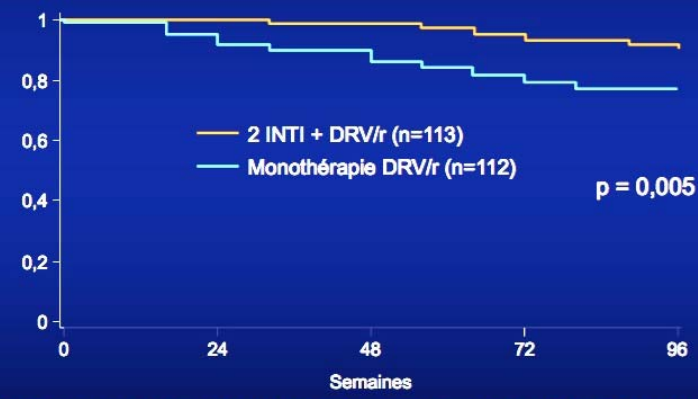
Maintenance en monothérapie d'antiprotéases

Essai OK 04: Monothérapie LPV/r vs Trithérapie en maintenance



Pulido F. *et al. AIDS* 2008.

Essai MONOI : rebonds virologiques (2 CV consécutives > 50 c/ml)



Dans le bras monothérapie: au moins 1 rebond chez 24 patients (21,4%) vs 9 (8%) dans bras trithérapie

Marcelin AG, CROI 2011, Abs. 533 et Lambert-Niclot S et al. JID 2011

Essai PIVOT : résultats à long terme d'un essai de switch vers monothérapie d'IP/r

le meilleur ...de la CROI 2014

Critère de jugement principal : perte d'options thérapeutiques à 3 ans, définie par l'apparition d'une nouvelle résistance de niveau intermédiaire ou haute à au moins 1 ARV auquel le virus était sensible à l'inclusion

Résultats entre l'inclusion et la fin de l'essai (médiane suivi 44 mois)

	Trithérapie (n = 291)	Monothérapie IP/r* (n = 296)	Différence Tri – Mono IP/r (IC 95 %)	p
Rebond CV > 50 c/ml, confirmé, n (%)	8 (3,2 %)	95 (35,0 %)	31,8 % (24,6 à 39,0 %)	< 0,001
Perte d'options thérapeutiques à M36, n (%)	2 (0,7 %)	6 (2,1 %)	1,4 (-0,4 à 3,4 %)	0,15
Perte d'options thérapeutiques fin d'essai, n (%)	4 (1,8 %)	6 (2,1 %)	0,2 % (-2,5 à 2,6 %)	0,85
Evolution CD4/mm³, moyenne (ET)	+91 (9)	+108 (9)	+17 (-10 à +43)	0,21
Evénements indésirables grade 3/4 %	55 %	46 %	-8,4 % (-16,4 à 0,3 %)	0,043
Evolution fonction neuro-cognitives (NPZ-5), moyenne (ET)	+0,51 (0,04)	+0,50 (0,04)	-0,01 (-0,11 à + 0,09)	0,86
Cout des ARV (£), moyenne	30 230	21 260	-8 970	-

* DRV/r : 80 % ; LPV/r : 14 %, autres : 7%

Aucune résistance acquise au DRV, 1 résistance acquise à ATV

Paton N, CROI 2014, Abs. 550LB; Lancet HIV Oct 2015

Méta-analyse Bithérapies VS Trithérapies

Lancet HIV 2016
Published Online
May 31, 2016

Amit C Achhra, Gwamaka Mwasakifwa, Janaki Amin, Mark A Boyd

	Dual therapy (n/N)	Triple therapy (n/N)	Relative risk (95% CI)
First-line trials			
NEAT001[11]	47/398	38/400	1·24 (0·83–1·86)
RADAR[20]	15/40	7/43	2·30 (1·05–5·06)
GARDEL[19]	25/214	33/202	0·72 (0·44–1·16)
SPARTAN[21]	8/45	6/25	0·74 (0·29–1·89)
PROGRESS[23]	17/101	16/105	1·10 (0·59–2·06)
CCTG 589[24]	8/26	4/25	1·92 (0·66–5·59)
Kalead[34]	34/72	37/80	1·02 (0·73–1·43)
ACTG5142[13]	72/250	77/250	0·94 (0·71–1·22)
Subtotal (I^2=25·4%, p=0·226)	**226/1146**	**218/1130**	**1·05 (0·86–1·28)**
Switch trials			
PROBE[25]	1/30	3/30	0·33 (0·04–3·03)
OLE[26]	10/118	11/121	0·93 (0·41–2·11)
SALTZ[27]	30/140	33/141	0·92 (0·59–1·42)
ATLAS-M[29]	14/133	27/133	0·52 (0·28–0·94)
HARNESS[30]	22/72	5/37	2·26 (0·93–5·49)
SPARE[31]	4/28	1/30	4·29 (0·51–36·06)
KITE[32]	2/39	2/20	0·51 (0·08–3·38)
COOL[33]	13/71	2/72	6·59 (1·54–28·16)
Subtotal (I^2=61·0%, p=0·012)	**96/631**	**84/584**	**1·13 (0·64–1·99)**
Overall (I^2=45·1%, p=0·026)	**322/1777**	**302/1714**	**1·06 (0·85–1·32)**

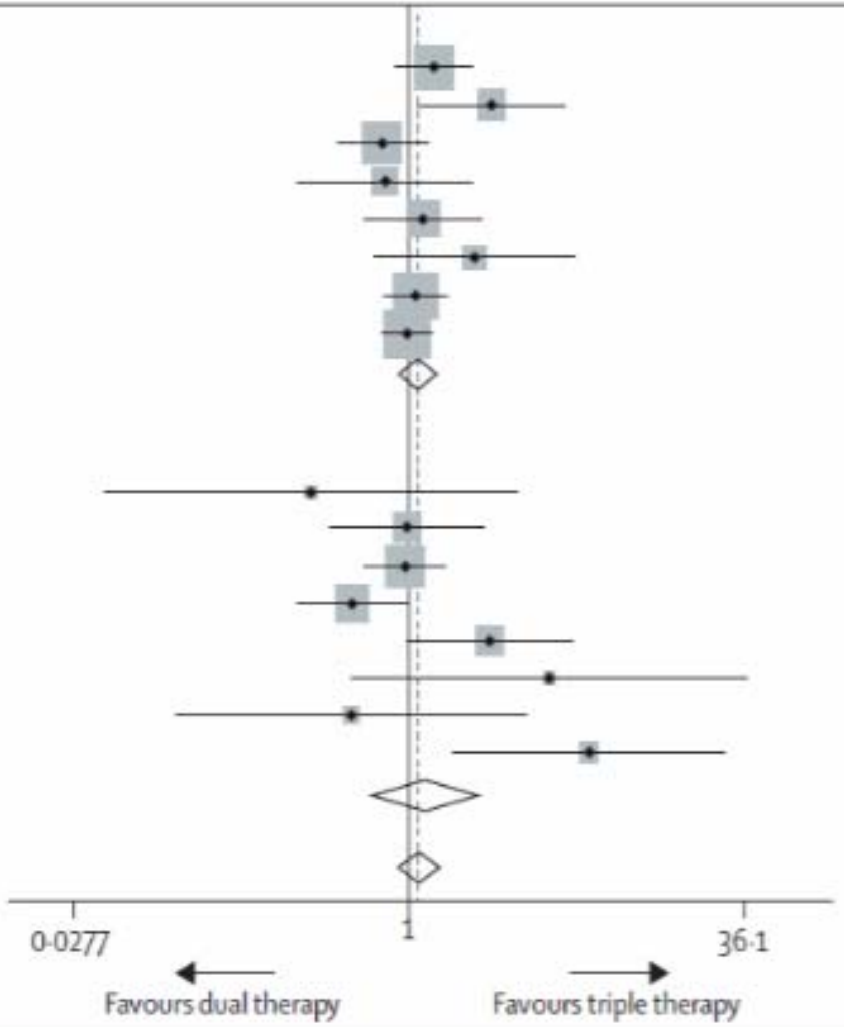
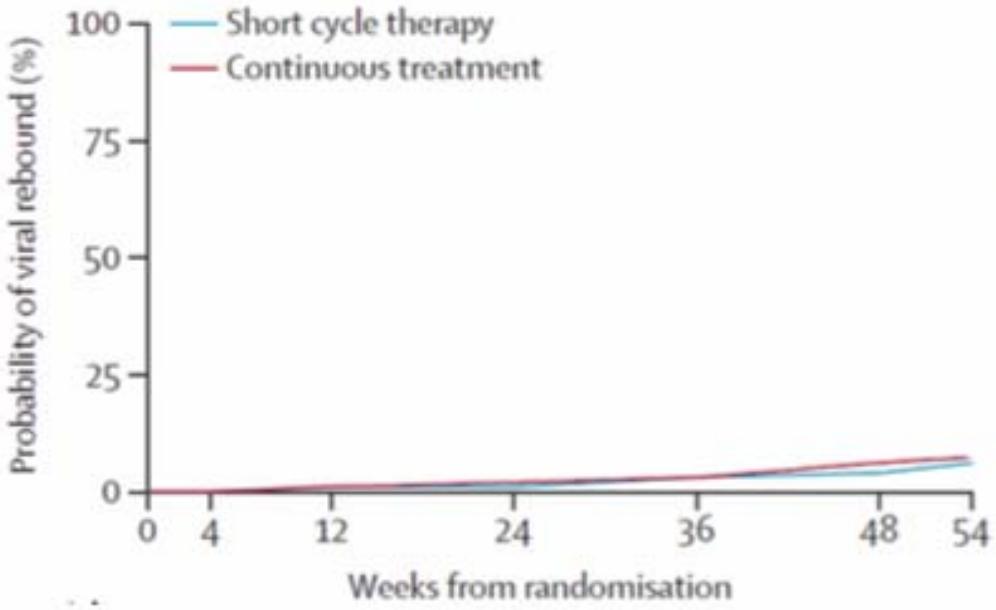


Figure 3: Meta-analysis of the primary virological outcome by trial type (first-line and switch studies), excluding maraviroc trials

Weekends-off efavirenz-based antiretroviral therapy in HIV-infected children, adolescents, and young adults (BREATHER): a randomised, open-label, non-inferiority, phase 2/3 trial

Lancet HIV 2016; 3: e421–30

*The BREATHER (PENTA 16) Trial Group**



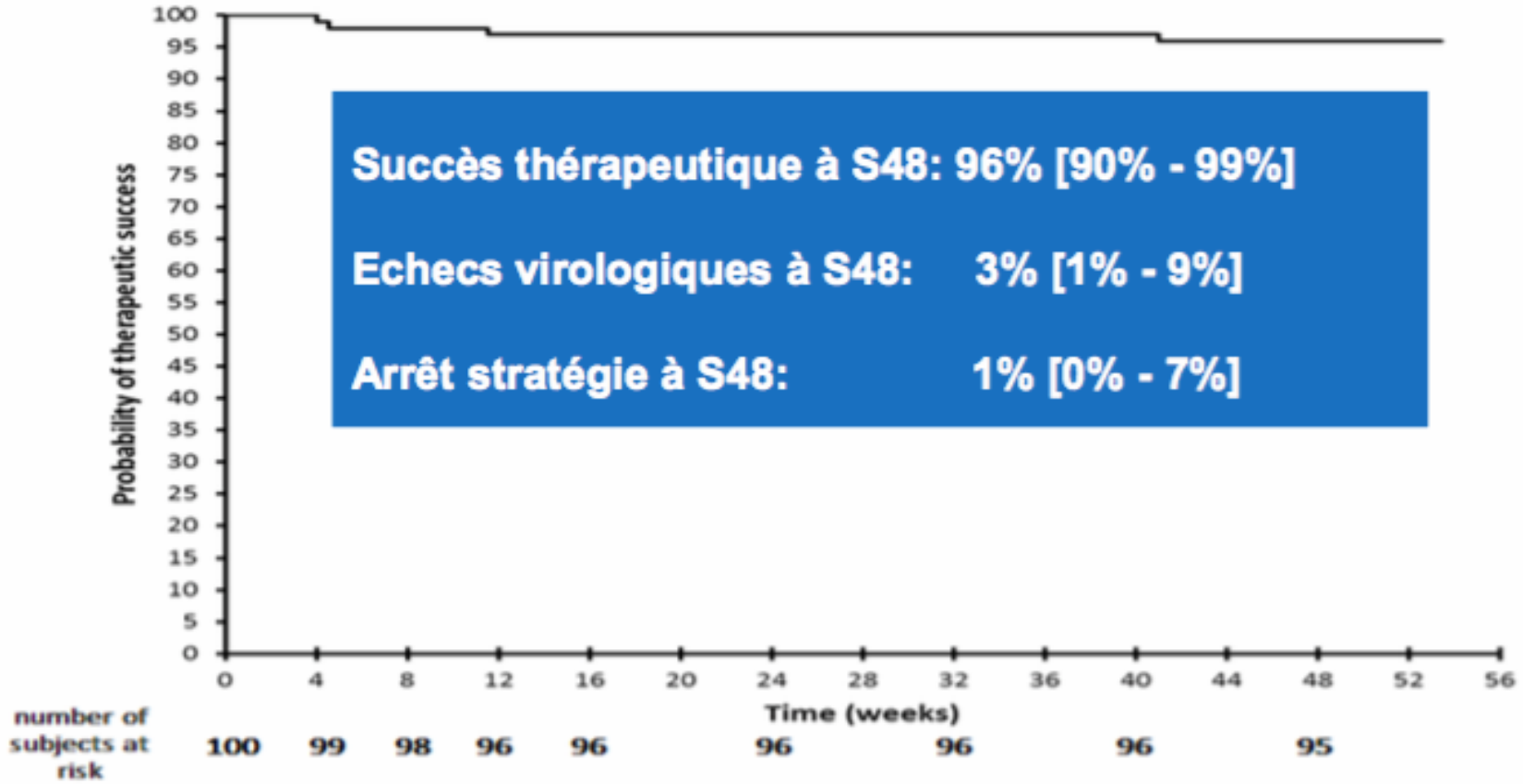
	Short cycle therapy (n=99)	Continuous therapy (n=100)
Primary endpoint		
Participants with confirmed viral load ≥50 copies/mL	6 (6%)	7 (7%)

Six (6%) patients assigned to the short cycle therapy versus seven (7%) assigned to continuous therapy had confirmed viral load 50 copies per mL or higher (difference –1·2%, 90% CI –7·3 to 4·9, non-inferiority shown). 13 grade 3 or 4 events occurred in the short cycle therapy group and 14 in the continuous therapy group (p=0·89). Two ART-related adverse events (one gynaecomastia and one spontaneous abortion) occurred in the short cycle therapy group compared with 14 (p=0·02) in the continuous therapy group (five lipodystrophy, two gynaecomastia, one suicidal ideation, one dizziness, one headache and syncope, one spontaneous abortion, one neutropenia, and two raised transaminases).

Essai ANRS 162-4D : allégement 4 jours/7

Essai monobras évaluant la capacité d'une trithérapie (avec 2 INTI TDF/FTC: 89%, ABC/3TC:11% **+ IP/r** 29% (DRV/r: 15, ATV/r 13, LPV/r: 1) **ou INNTI** 71% (EFV: 40, ETV: 5, RPV: 26)**) réduite à 4 jours consécutifs sur 7, de maintenir un succès thérapeutique (CV <50 et maintien stratégie 4j/7)**

Probabilité de succès thérapeutique (courbe de Kaplan-Meier)



- **3 échecs virologiques** (à S4, S8, S40 avec CV à 785,124 et 969 c/ml) avec re-suppression avec reprise 7 jours sur 7
- **1 arrêt de la stratégie** à S4 dû à anxiété et asthénie

Pierre de Truchis , IAC Durban, Abs. THEB063

Plan

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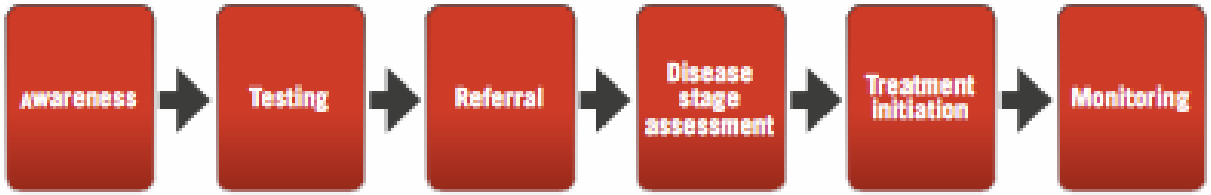
- Le concept TasP (Treatment as Prevention): Où en est-on?

OMS/WHO

« Over 1 million treated with highly effective hepatitis C medicines »

- 27 OCTOBER 2016 | GENEVA - Over one million people in low- and middle-income countries have been treated with a revolutionary new cure for hepatitis C since its introduction two years ago.
- The new medicines have a cure rate of over 95%, fewer side effects than previously available therapies, and can completely cure the disease within three months. But at an initial estimated price of some US$85 000 they were unaffordable even in high-income countries.
- Thanks to a series of access strategies supported by the World Health Organization (WHO) and other partners, a range of low- and middle-income countries, including Argentina, Brazil, Egypt, Georgia, Indonesia, **Morocco**, Nigeria, Pakistan, Philippines, Romania, Rwanda, Thailand and Ukraine – are beginning to succeed in getting drugs to people who need them. Strategies include competition from generic medicines through licensing agreements, local production and price negotiations.

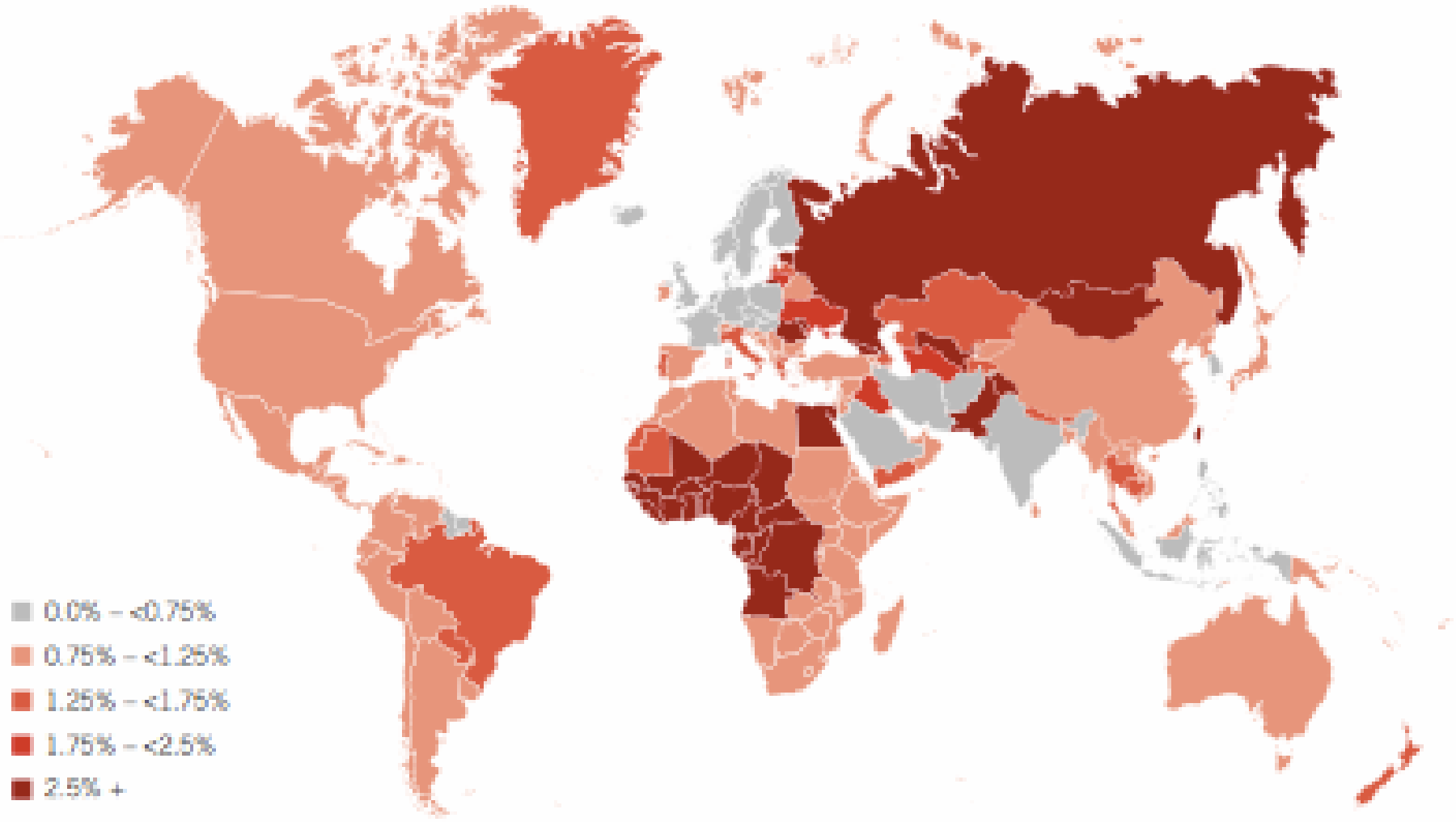
FIG. 2.1. The HCV treatment cascade



World Health Organization

Infection HCV: 80 Millions de patients à traiter

FIG. 1.1. Global prevalence of viraemic HCV (reported and extrapolated)



Source: Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology of the hepatitis C virus infection. J Hepatol. 2014; 61 (1 Suppl): S45–57 (2).

TABLE 2.1. Summary of recommended preferred treatment regimens with treatment durations*

Persons without cirrhosis

Genotype	Daclatasvir/sofosbuvir	Ledipasvir/sofosbuvir	Sofosbuvir/ribavirin
Genotype 1	12 weeks	12 weeks[a]	
Genotype 2			12 weeks
Genotype 3	12 weeks		24 weeks
Genotype 4	12 weeks	12 weeks	
Genotype 5		12 weeks	
Genotype 6		12 weeks	

Persons with cirrhosis

Genotype	Daclatasvir/sofosbuvir	Daclatasvir/sofosbuvir/ribavirin	Ledipasvir/sofosbuvir	Ledipasvir/sofosbuvir/ribavirin	Sofosbuvir/ribavirin
Genotype 1	24 weeks	12 weeks	24 weeks	12 weeks[b]	
Genotype 2					16 weeks
Genotype 3		24 weeks			
Genotype 4	24 weeks	12 weeks	24 weeks	12 weeks[b]	
Genotype 5			24 weeks	12 weeks[b]	
Genotype 6			24 weeks	12 weeks[b]	

* Treatment durations are adapted from the 2015 guidelines of the American Association for the Study of Liver Diseases (AASLD) (50) and European Association for the Study of the Liver (EASL) (51).

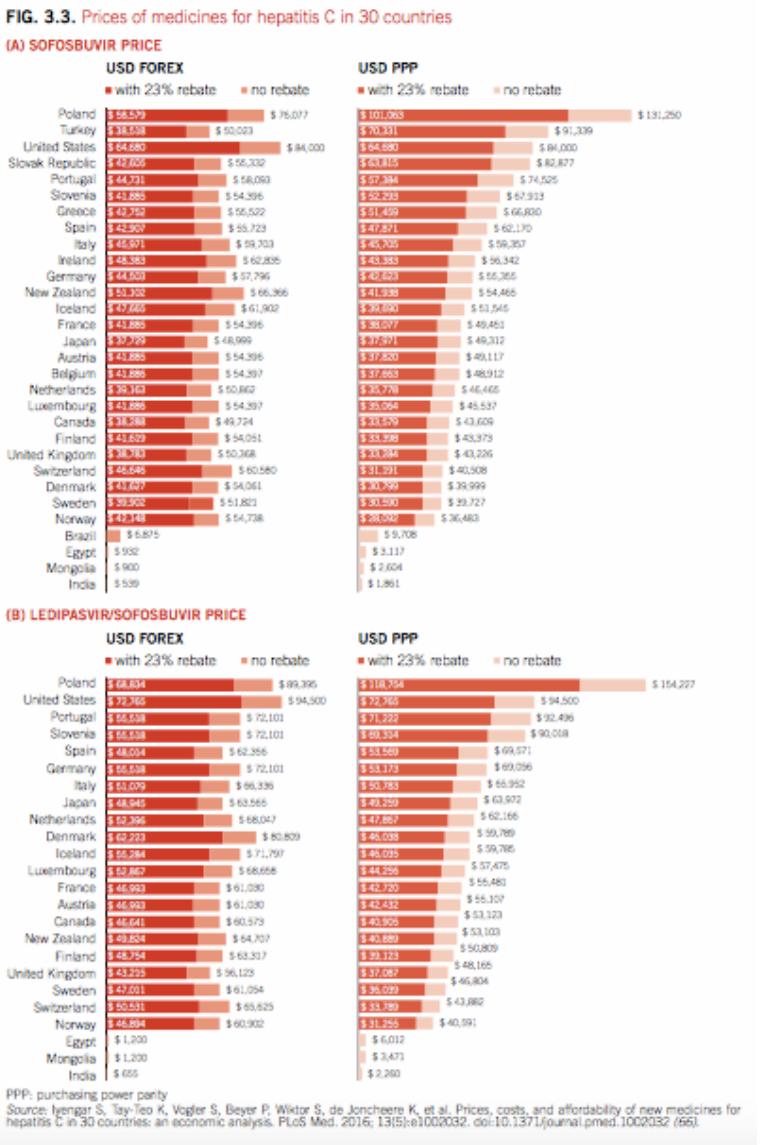
[a] Treatment may be shortened to 8 weeks in treatment-naive persons without cirrhosis if their baseline HCV RNA level is below 6 million (6.8 log) IU/mL. The duration of treatment should be shortened with caution.

[b] If platelet count <75 x 10^3/µL, then 24 weeks' treatment with ribavirin should be given.

HCV: le problème du coût

80 millions de patients à traiter!

FIG. 3.3. Prices of medicines for hepatitis C in 30 countries



PPP: purchasing power parity

Source: Iyengar S, Tay-Teo K, Vogler S, Beyer P, Wiktor S, de Joncheere K, et al. Prices, costs, and affordability of new medicines for hepatitis C in 30 countries: an economic analysis. PLoS Med. 2016; 13(5):e1002032. doi:10.1371/journal.pmed.1002032 (66).

FIG. 3.1. The price of a 28-day supply of sofosbuvir in different countries

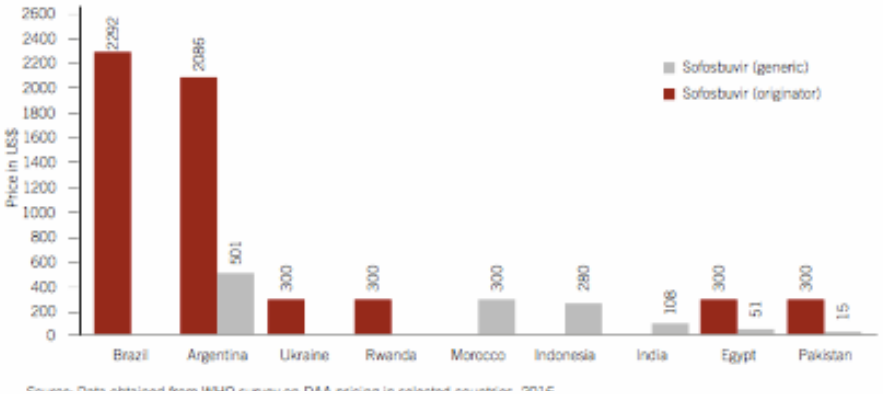
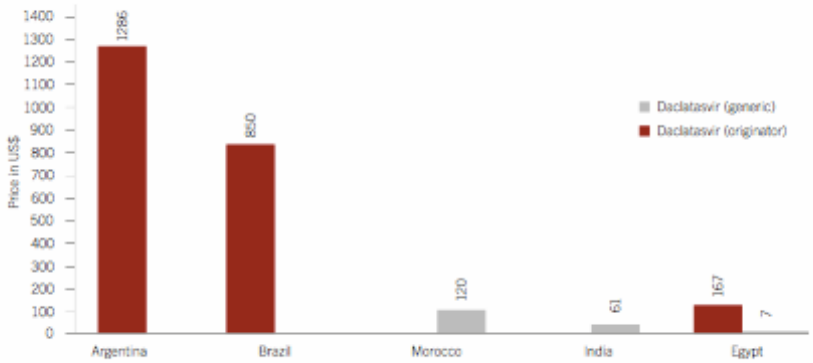


FIG. 3.2. The price of a 28-day supply of daclatasvir in different countries



Source: Data obtained from WHO survey on DAA pricing in selected countries, 2016

Morocco established its national HCV programme in 2012; it provides HCV diagnostics, genotyping and liver disease staging, and has treated over 1700 people with pegylated interferon and ribavirin. The country is currently developing a national strategy and updating its treatment guidelines. The primary patents for sofosbuvir, ledipasvir and daclatasvir were not filed in Morocco, allowing for local production and importation of generic products. While Morocco was not included in the initial license agreement on sofosbuvir, ledipasvir and velpatasvir, it was added when the geographical scope was expanded. Morocco is also included in the voluntary licensing agreement for daclatasvir and can thus procure the API for these DAAs from licensed suppliers as well. The Minister of Health of Morocco has announced the goal of "Morocco without hepatitis C in 2030" (33). Morocco also benefits from a strong civil society movement, including the International Treatment Preparedness Coalition-Middle East North Africa (ITPC-MENA) and The Association against AIDS (ALCS), the "Collectif pour le droit à la santé Maroc" that lobby for increased access.

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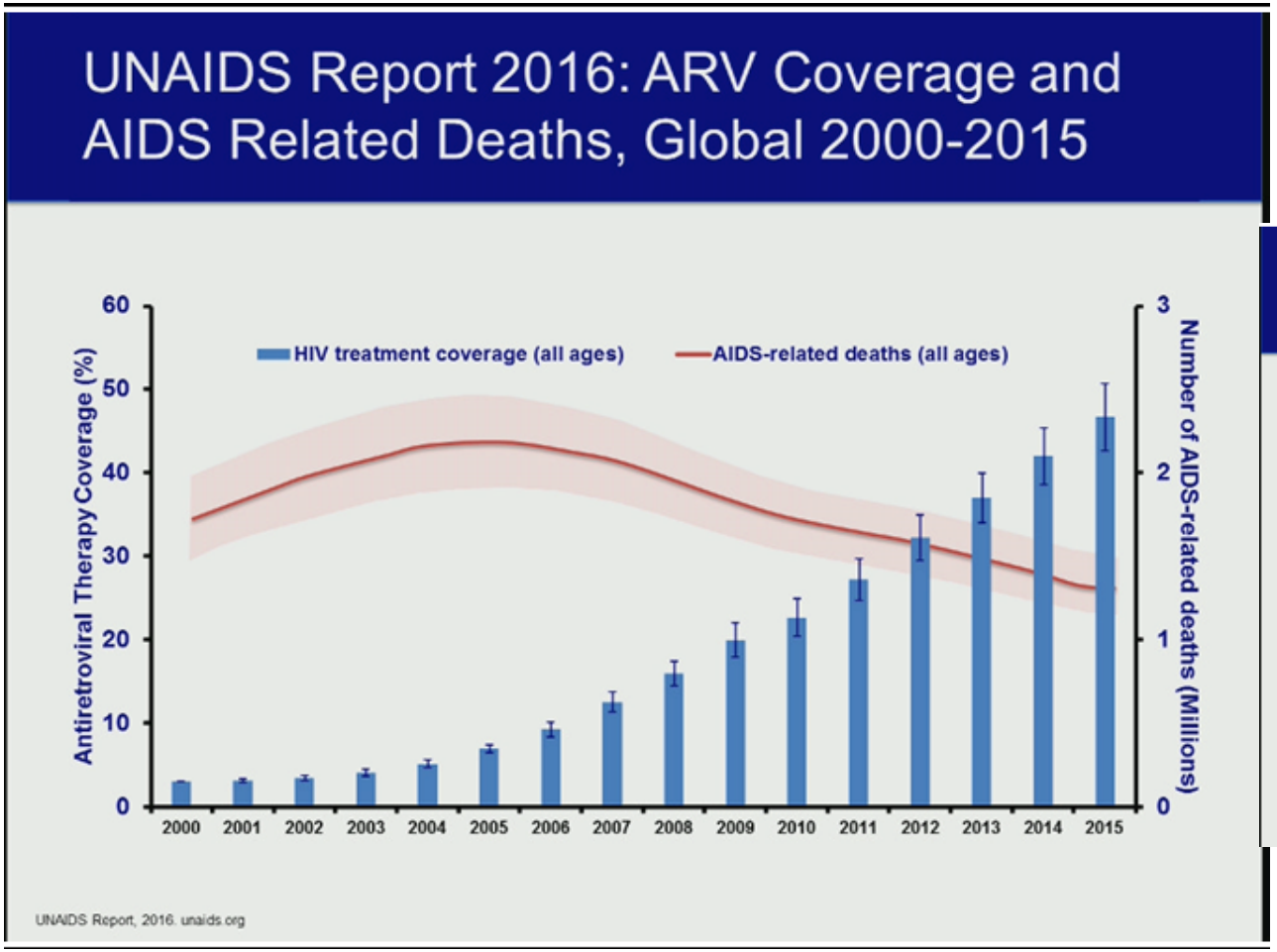
Objectifs OMS/ONUSIDA: mettre fin au SIDA d'ici 2030

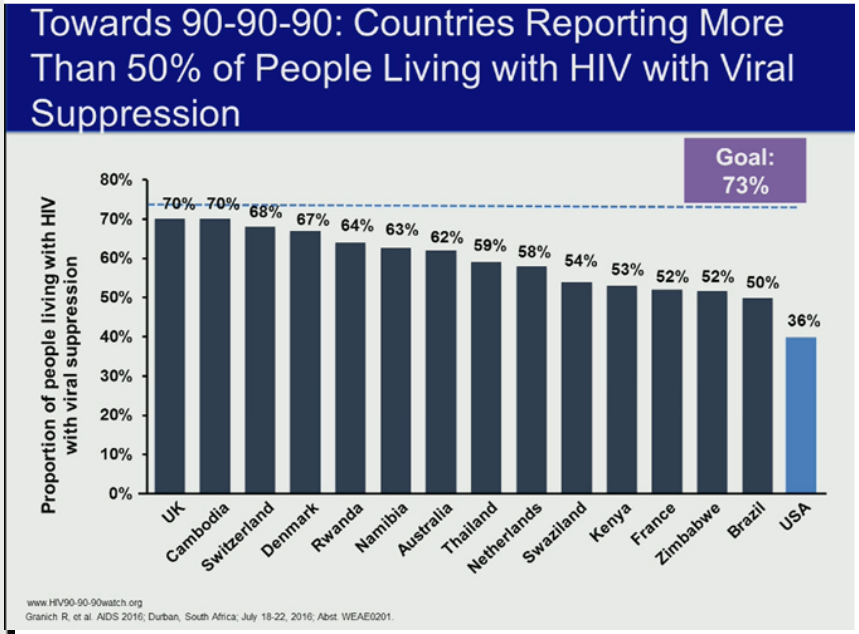
d'ici 2020 :

d'ici 2030 :

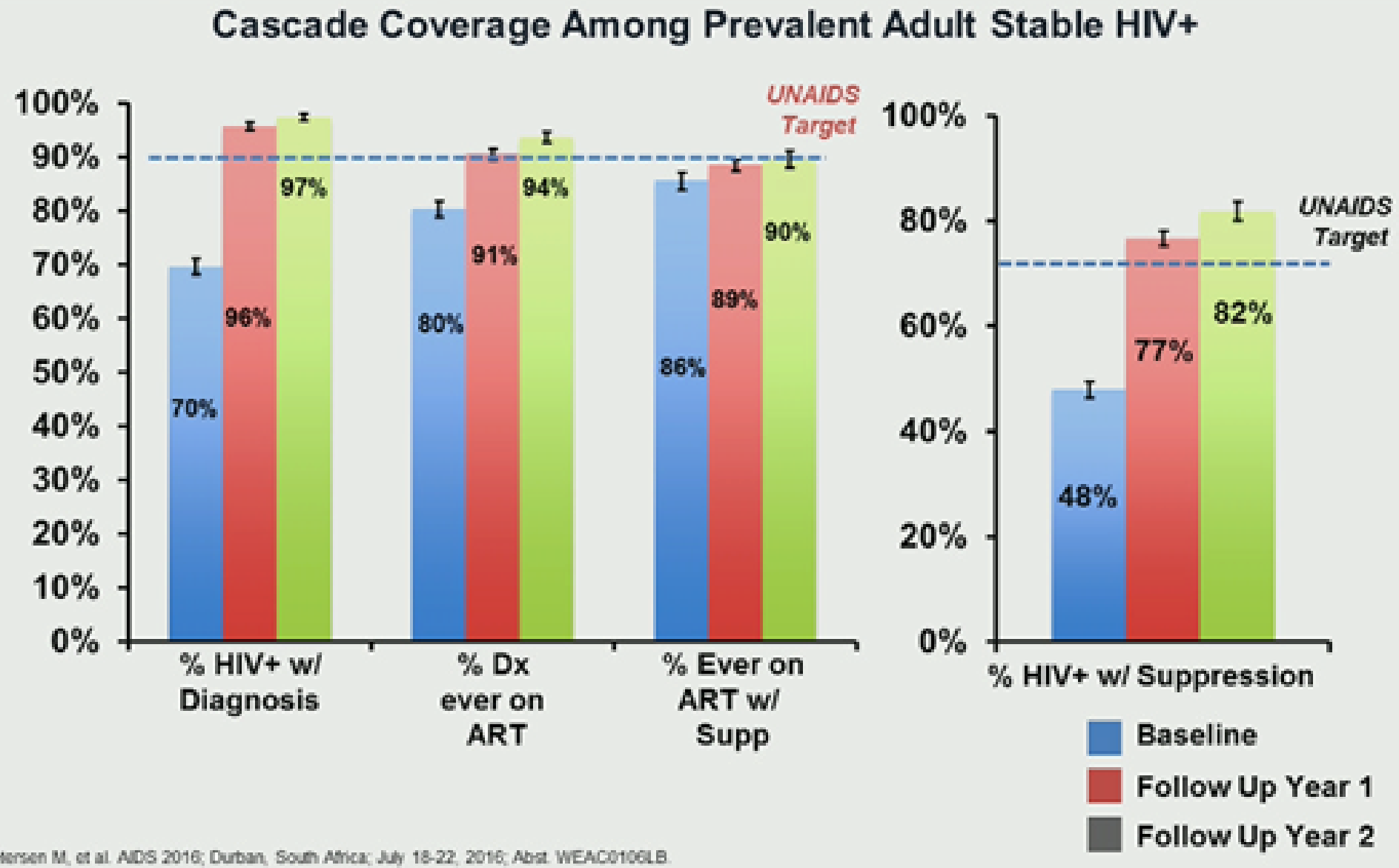
- 90% (puis 95%) des personnes séropositives connaissent leur statut sérologique ;
- 90% (puis 95%) des personnes connaissant leur séropositivité, reçoivent des traitements antirétroviraux ;
- 90% (puis 95%) des personnes sous traitements antirétroviraux ont une charge virale indétectable.

Amélioration de la couverture ARV dans le monde



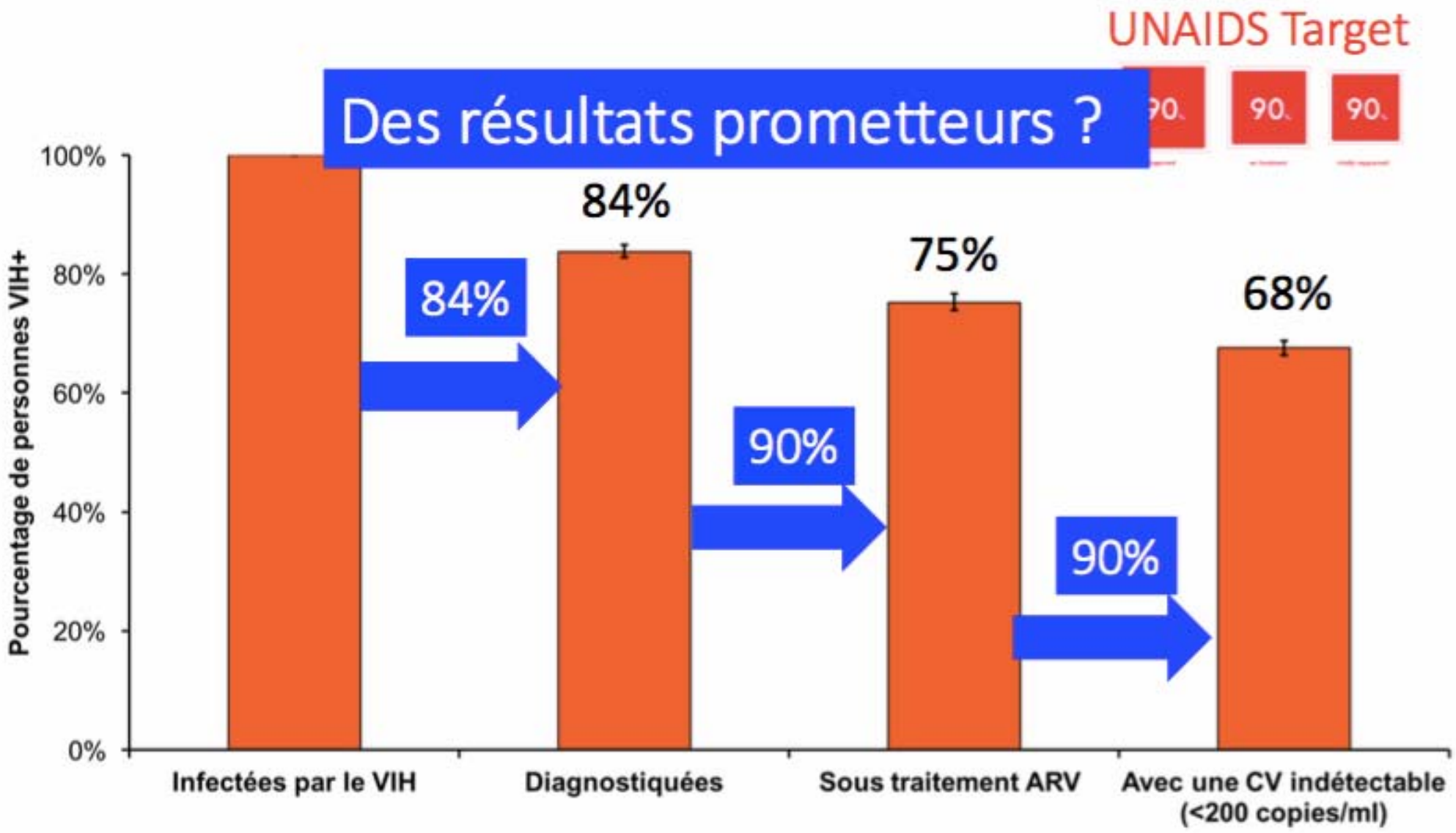


Exceeding UNAIDS 90-90-90 Target with Intensive Testing and Treatment Program in Kenya and Uganda



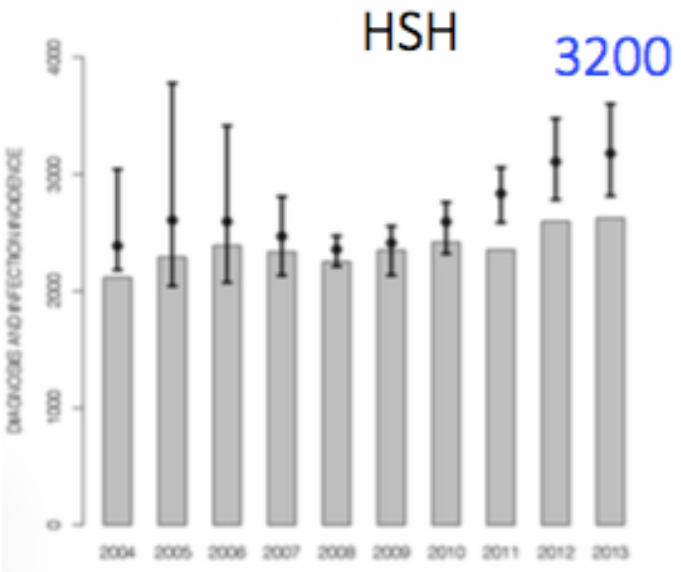
Petersen M, et al. AIDS 2016; Durban, South Africa; July 18-22, 2016; Abst. WEAC0106LB.

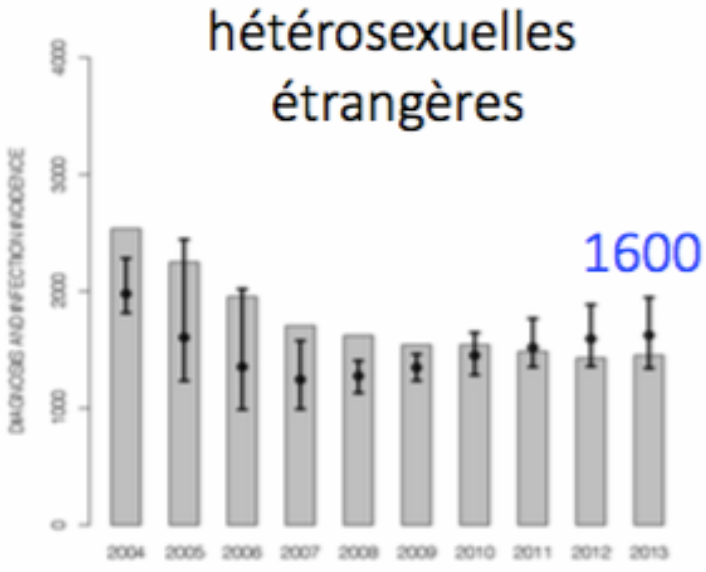
Cascade de la prise en charge en France en 2013*

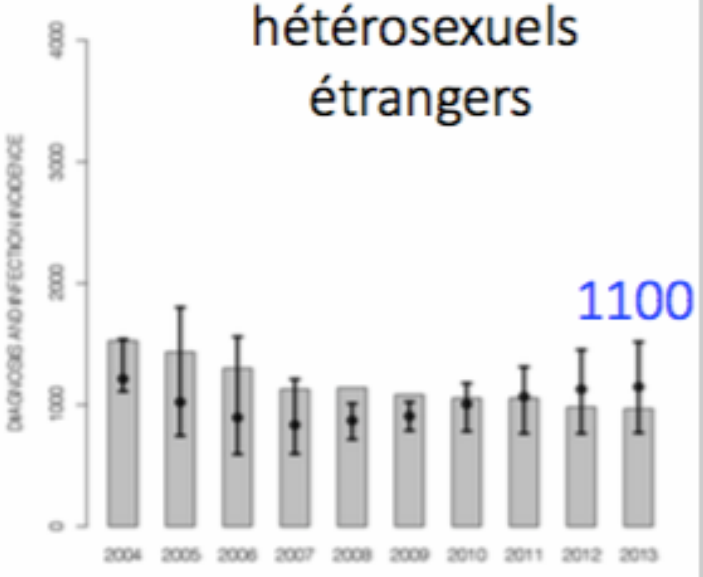


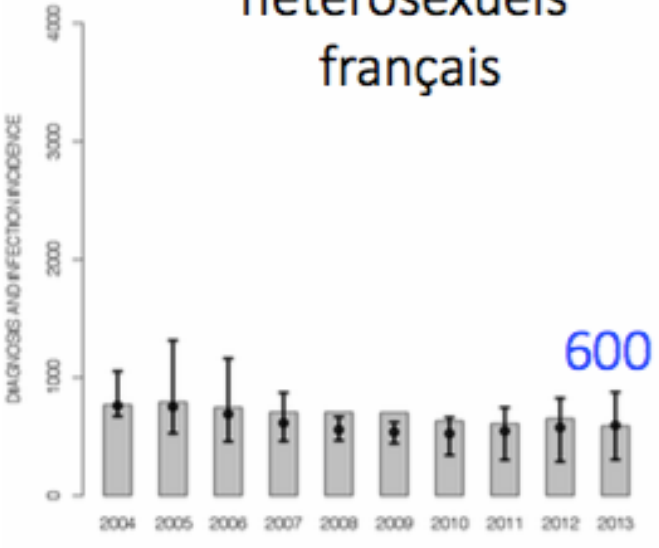
J Supervie, 2016

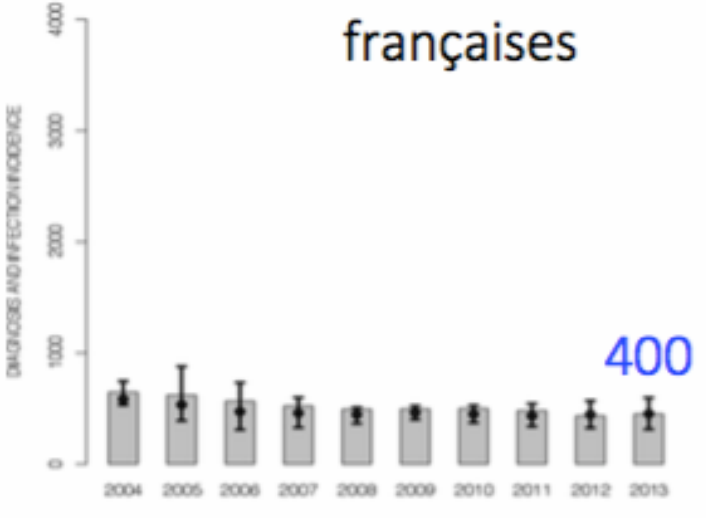
Nombre de nouvelles infections en France 2004-2013

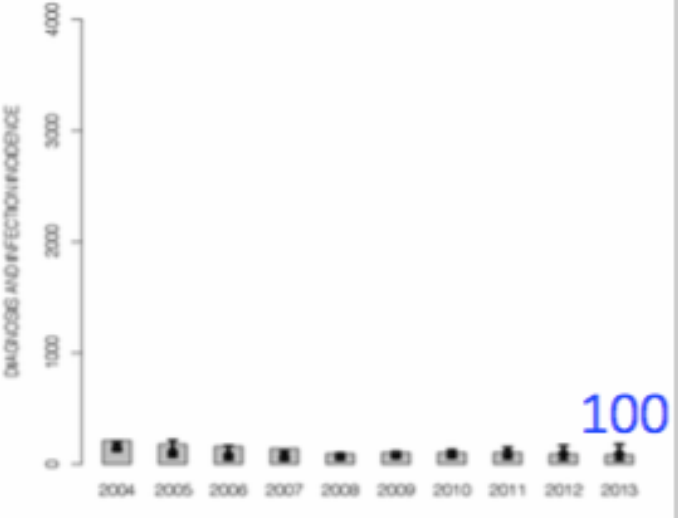












Marty L., Cazein F., Pillonel J., Costagiola D., Supervie V., PROJET ANRS INDIC et HERMETIC

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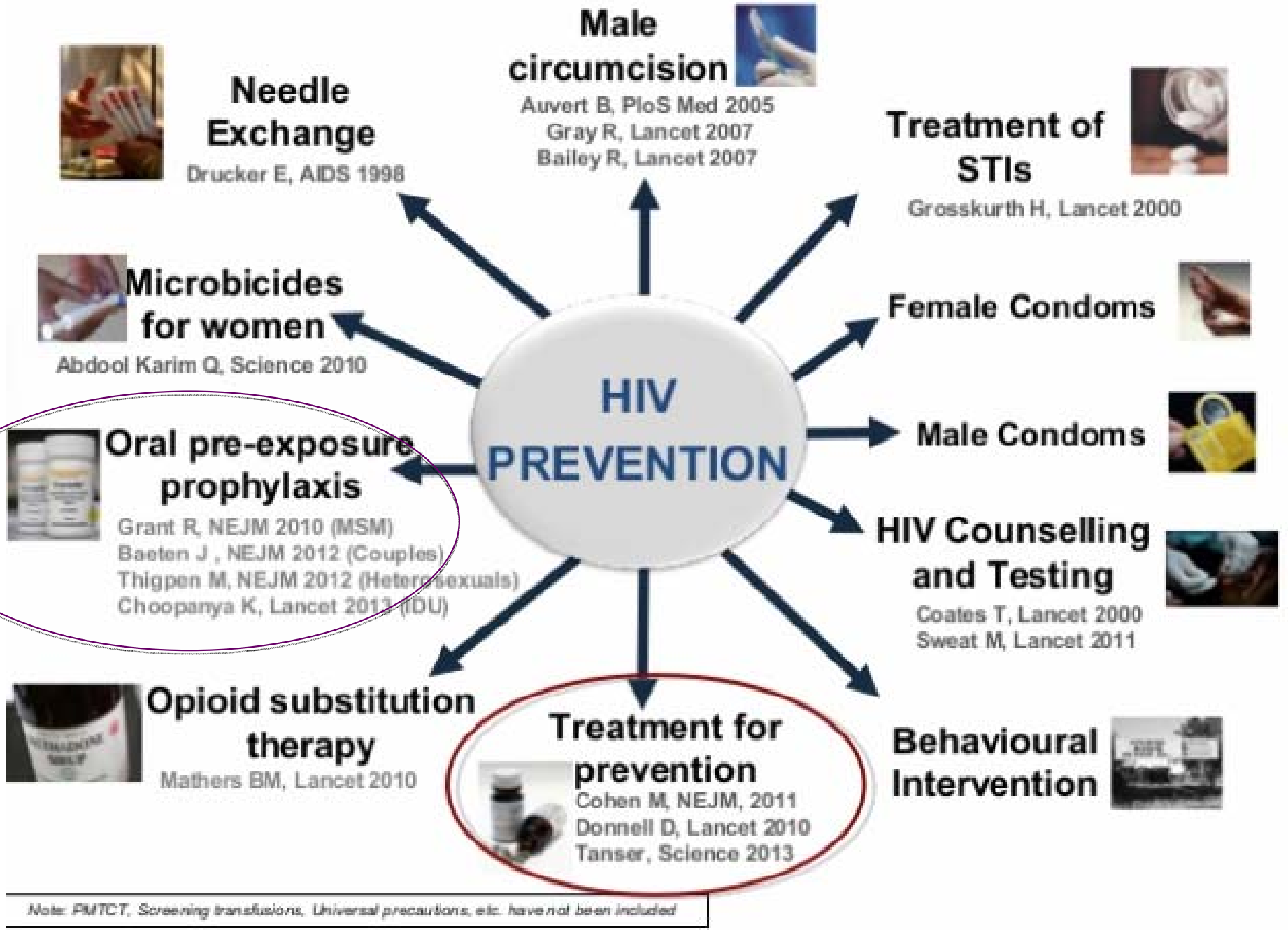
Treatment as Prevention

TasP

risque de 96%

Pre-exposure prophylaxis

PrEP

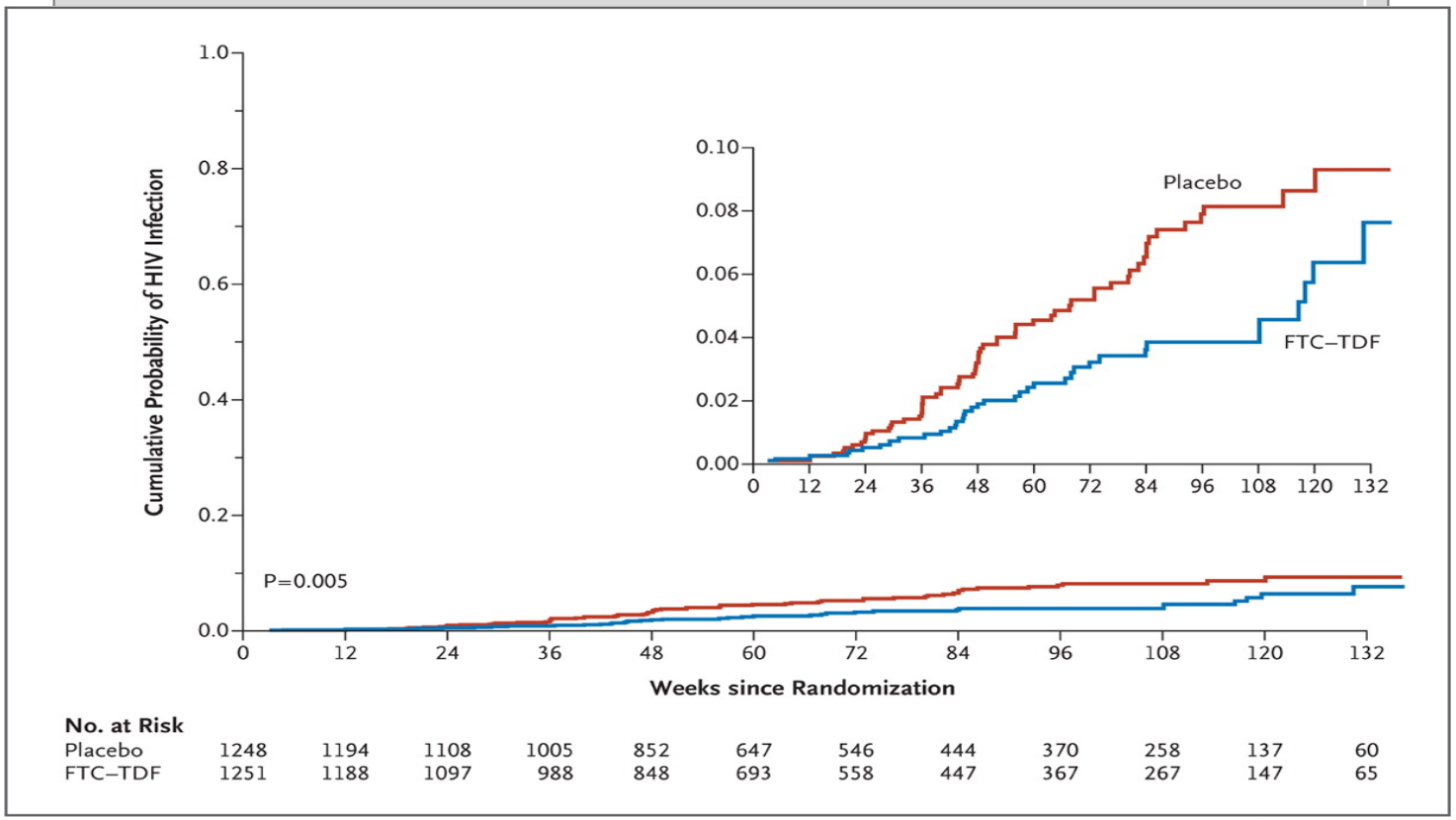

HIV PREVENTION
Needle Exchange
Drucker E, AIDS 1998
Male circumcision
Auvert B, PloS Med 2005
Gray R, Lancet 2007
Bailey R, Lancet 2007
Treatment of STIs
Grosskurth H, Lancet 2000
Microbicides for women
Abdool Karim Q, Science 2010
Female Condoms
Oral pre-exposure prophylaxis
Grant R, NEJM 2010 (MSM)
Baeten J , NEJM 2012 (Couples)
Thigpen M, NEJM 2012 (Heterosexuals)
Choopanya K, Lancet 2013 (IDU)
Male Condoms
HIV Counselling and Testing
Coates T, Lancet 2000
Sweat M, Lancet 2011
Opioid substitution therapy
Mathers BM, Lancet 2010
Treatment for prevention
Cohen M, NEJM, 2011
Donnell D, Lancet 2010
Tanser, Science 2013
Behavioural Intervention
Note: PMTCT, Screening transfusions, Universal precautions, etc. have not been included

PrEP: essai iPrEX

- HSH non infectés à haut risque de VIH

TDF/FTC 1 cp/jour (n=1251)

Placebo 1 cp/jour (n=1248)

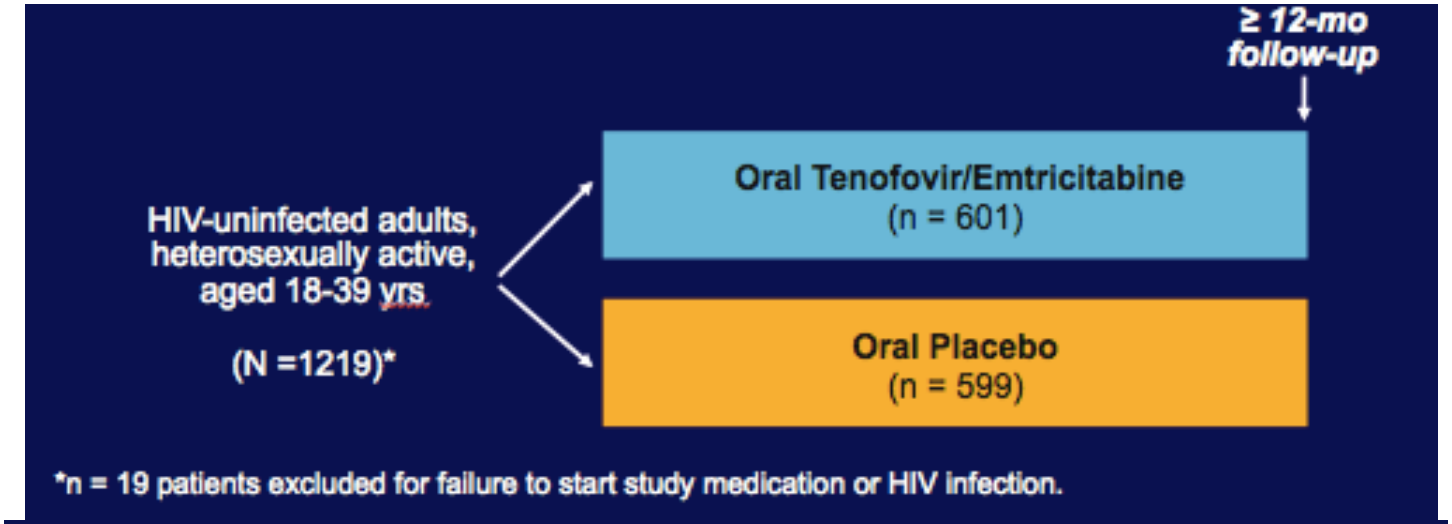


Incidence VIH: **-44%**

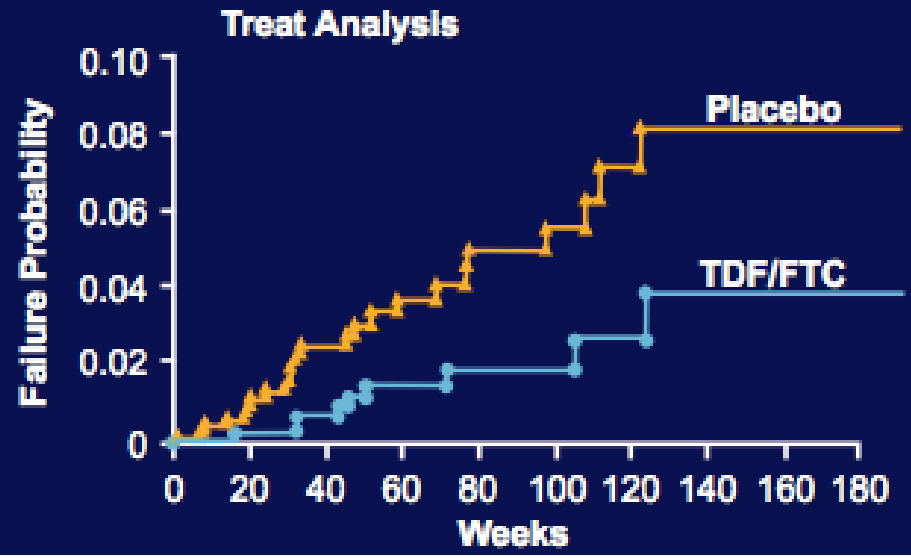
Grant RM et al N Engl J Med, Nov 23, 2010

PrEP: essai TDF2:

PrEP TDF/FTC chez les hétérosexuels HIV- au Botswana



- **effet protecteur de TDF/FTC: 62.2% (95% CI: 21.5-83.4; p= 0.03)**
- **Protection idem H→F et F→H**



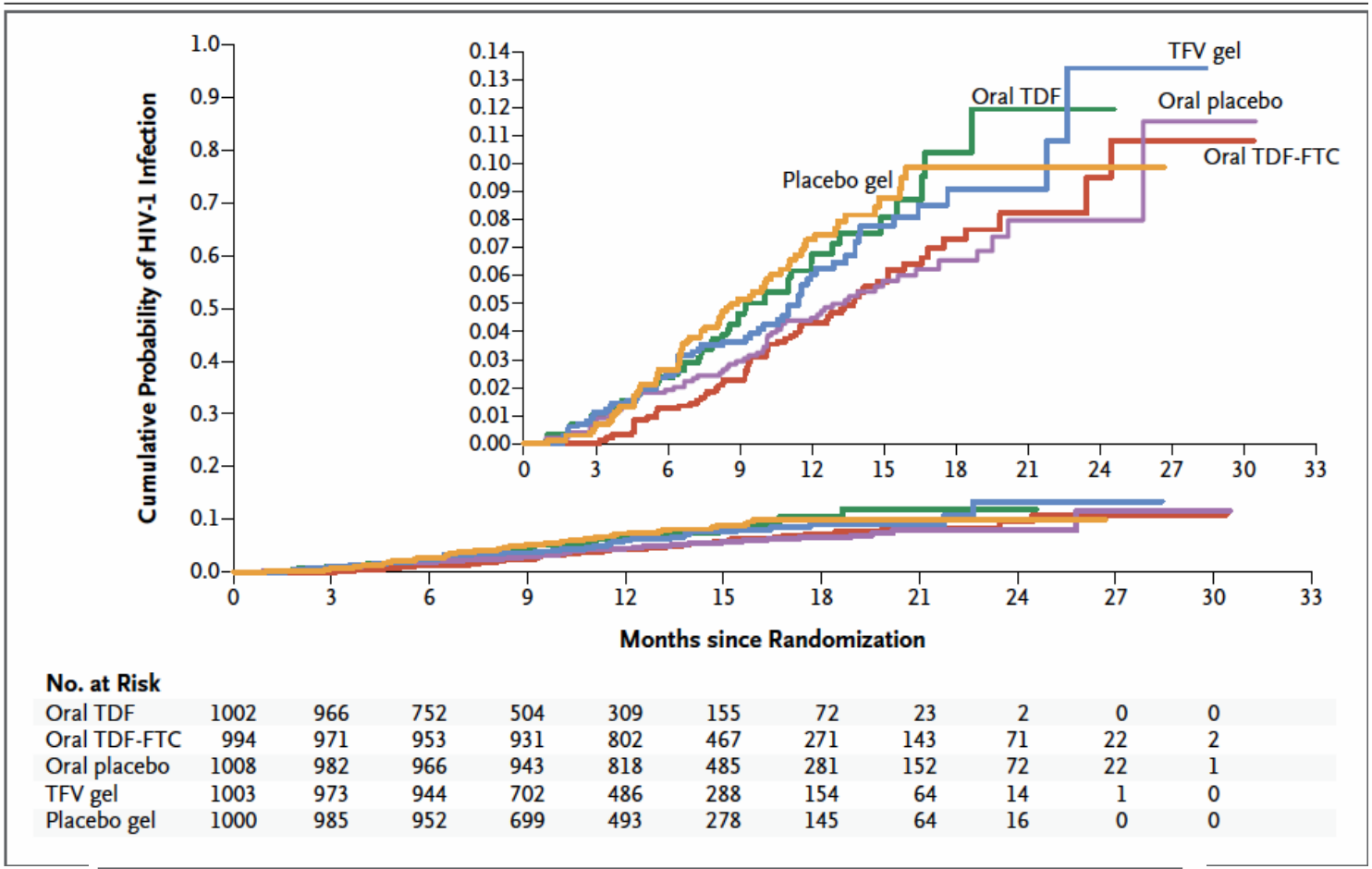
-62%

Thigpen MC, et al., N Engl J Med. 2012

Essai VOICE: faible efficacité PrEP chez les femmes en Afrique subsaharienne

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



No. at Risk

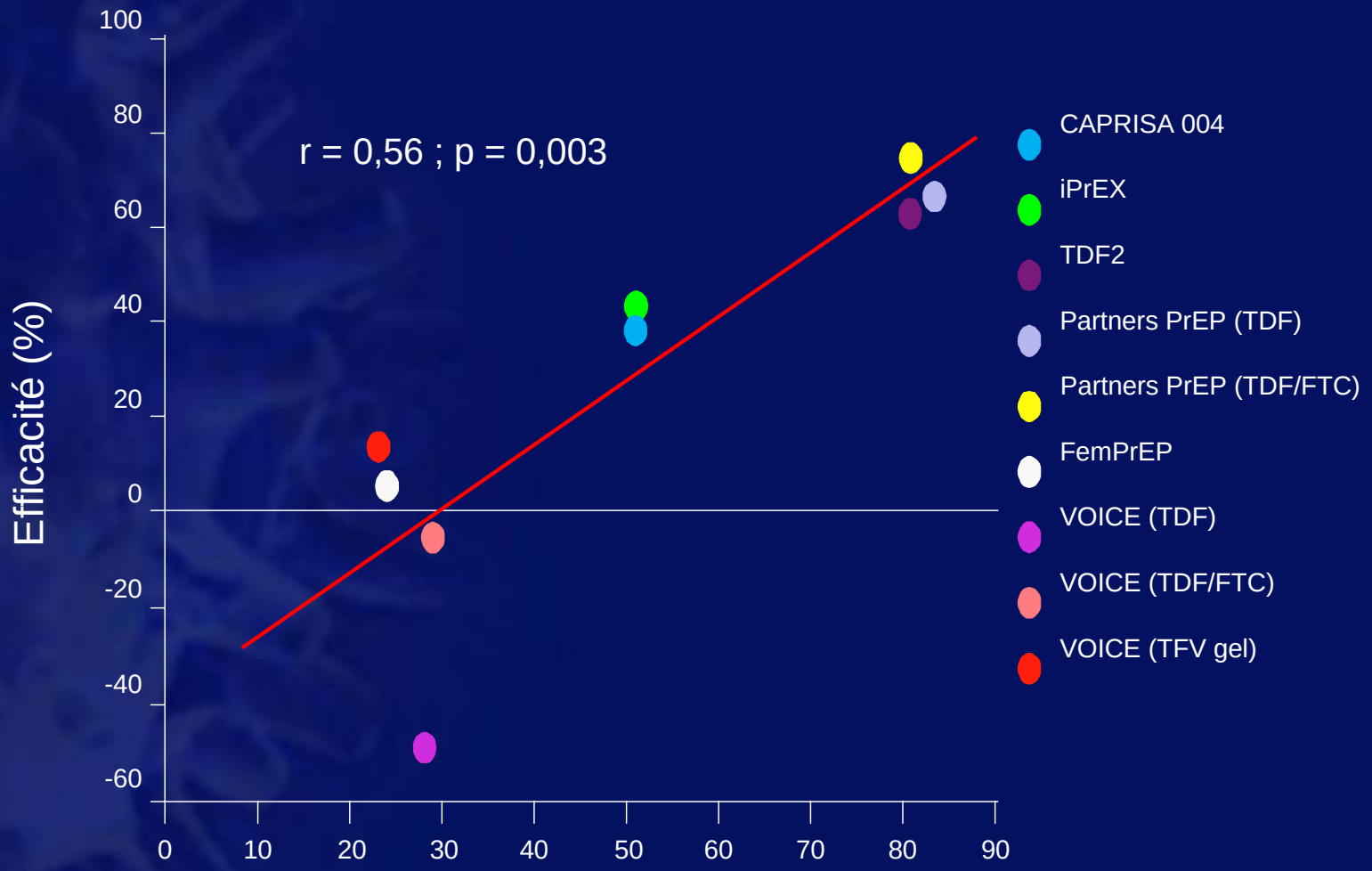
Oral TDF	1002	966	752	504	309	155	72	23	2	0	0
Oral TDF-FTC	994	971	953	931	802	467	271	143	71	22	2
Oral placebo	1008	982	966	943	818	485	281	152	72	22	1
TFV gel	1003	973	944	702	486	288	154	64	14	1	0
Placebo gel	1000	985	952	699	493	278	145	64	16	0	0

Table 3. **Primary Efficacy Results.**

Result	Oral TDF*		Oral TDF-FTC	Oral Placebo	TFV Gel	Placebo Gel
	Active Agent	Placebo				
Person-years	823	838	1284	1308	1024	1030
Number of HIV-1 infections	52	35	61	60	61	70
HIV-1 incidence — cases per 100 person-years (95% CI)	6.3 (4.7–8.3)	4.2 (2.9–5.8)	4.7 (3.6–6.1)	4.6 (3.5–5.9)	6.0 (4.6–7.6)	6.8 (5.3–8.6)
Hazard ratio (95% CI)	1.49 (0.97–2.29)	—	1.04 (0.73–1.49)	—	0.85 (0.61–1.21)	—
P value	0.07	—	0.81	—	0.37	—

PrEP

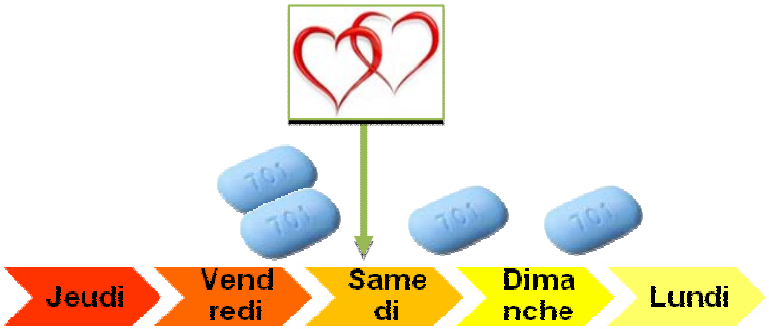
correlation forte entre efficacité et adhérence



Landovitz RJ, CROI 2015, Abs. 20

Essai Ipergay:

efficacité PrEP « à la demande »



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

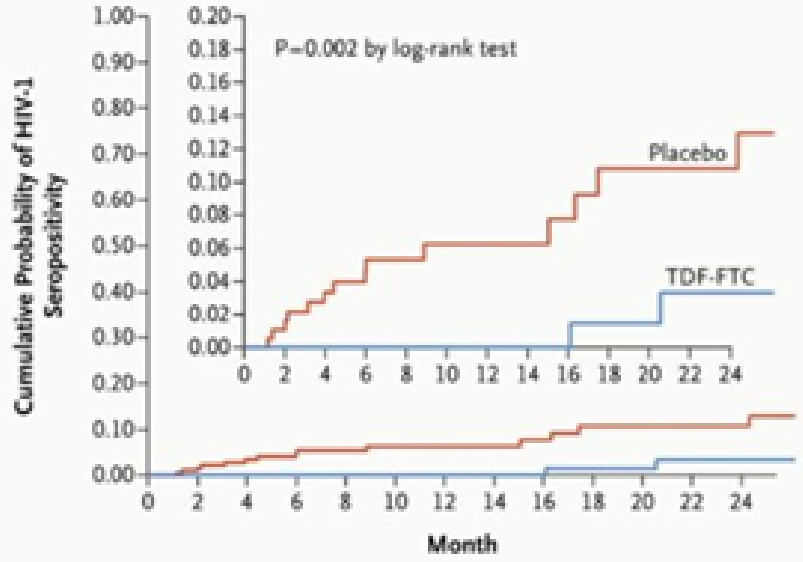
On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection

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

N ENGL J MED 373;23 NEJM.ORG DECEMBER 3, 2015

IPERGAY Study: On Demand PrEP

Probability of HIV Infection



No. at Risk					
Placebo	201	141	74	55	42
TDF-FTC	199	141	82	58	43

Molina J-M, et al. N Engl J Med 2015:373:2237-46.

Incidence VIH: -**86%**

PrEP : Nouvelles thérapeutiques / voies d'administration

- Nouvelles thérapeutiques

	Mécanisme	Voie	Posologie	Stade de l'étude
Maraviroc (MVC)	Antagoniste de CCR5	orale	1 fois par jour	Phase 2 En recrutement
Rilpivirine (RPV)-LA	NNRTI	Injectable, IM	1 fois par mois	Phase pilote 1 Phase 2 planifiée
Dapivirine	NNRTI	anneau	1 fois par mois	Phase 3 en recrutement
ibalizumab	Anticorps monoclonal, inhibiteur d'entrée	Injectable, SC	1 fois par semaine	Phase 1 pilote
744-LAP	Inhibiteur d'intégrase	Injectable, IM	1 fois par trimestre	Phase pilote 1 Phase 2 planifiée


Comprimé


Gel

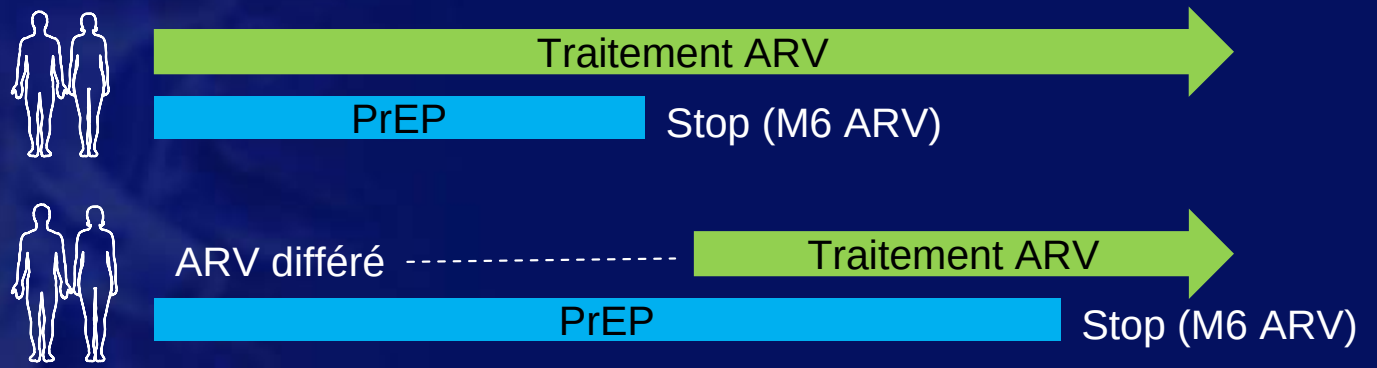

Film vaginal


Anneau vaginal


Injection

PrEP et traitement ARV sont complémentaires « PrEP as a bridge to ART »

- ARV et PrEP sont 2 outils de prévention complémentaires:
  - Le risque de transmission sexuelle persiste dans les 6 mois suivant initiation ARV [1]
  - La PrEP n'est pas toujours correctement suivie
- **Partners Demonstration Project** : étude ouverte Kenya et Ouganda Tt ARV + PrEP en prévention du VIH chez les couples hétérosexuels séro-discordants à haut risque ; conseils de prévention et promotion de l'observance
  - ARV chez le partenaire VIH+
  - PrEP chez le partenaire VIH- : TDF/FTC 1/j jusqu'à M6 de ARV du partenaire



	N infections	Incidence (IC 95 %)
Attendu	39,7	5,2 (3,7 – 6,9)
Observé	2*	0,2 (0,00 – 0,9)

Réduction relative de l'incidence de l'infection VIH = **96 %** (IC 95 % : 81-99) ; p < 0,0001

Baeten J, CROI 2015, Abs. 24 ; 1. Mujugira A, CROI 2015, Abs. 989

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- Épidémiologie mondiale et objectifs de traitement
- La PreP à la mode
- Le concept TasP (Treatment as Prevention): Où en est-on?

Etude HPTN 052

Efficacité du traitement ARV pour la prévention du risque de transmission chez les couples séro-discordants

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 11, 2011 VOL. 365 NO. 6

Prevention of HIV-1 Infection with Early Antiretroviral Therapy

Myron S. Cohen, M.D., Ying Q. Chen, Ph.D., Marybeth McCauley, M.P.H., Theresa Gamble, Ph.D., Mina C. Hosseinipour, M.D., Nagalingeswaran Kumarasamy, M.B., B.S., James G. Hakim, M.D., Johnstone Kumwenda, F.R.C.P., Beatriz Grinsztejn, M.D., Jose H.S. Pilotto, M.D., Sheela V. Godbole, M.D., Sanjay Mehendale, M.D., Suwat Chariyalertsak, M.D., Breno R. Santos, M.D., Kenneth H. Mayer, M.D., Irving F. Hoffman, P.A., Susan H. Eshleman, M.D., Estelle Piwowar-Manning, M.T., Lei Wang, Ph.D., Joseph Makhema, F.R.C.P., Lisa A. Mills, M.D., Guy de Bruyn, M.B., B.Ch., Ian Sanne, M.B., B.Ch., Joseph Eron, M.D., Joel Gallant, M.D., Diane Havlir, M.D., Susan Swindells, M.B., B.S., Heather Ribaudo, Ph.D., Vanessa Elharrar, M.D., David Burns, M.D., Taha E. Taha, M.B., B.S., Karin Nielsen-Saines, M.D., David Celentano, Sc.D., Max Essex, D.V.M., and Thomas R. Fleming, Ph.D., for the HPTN 052 Study Team*

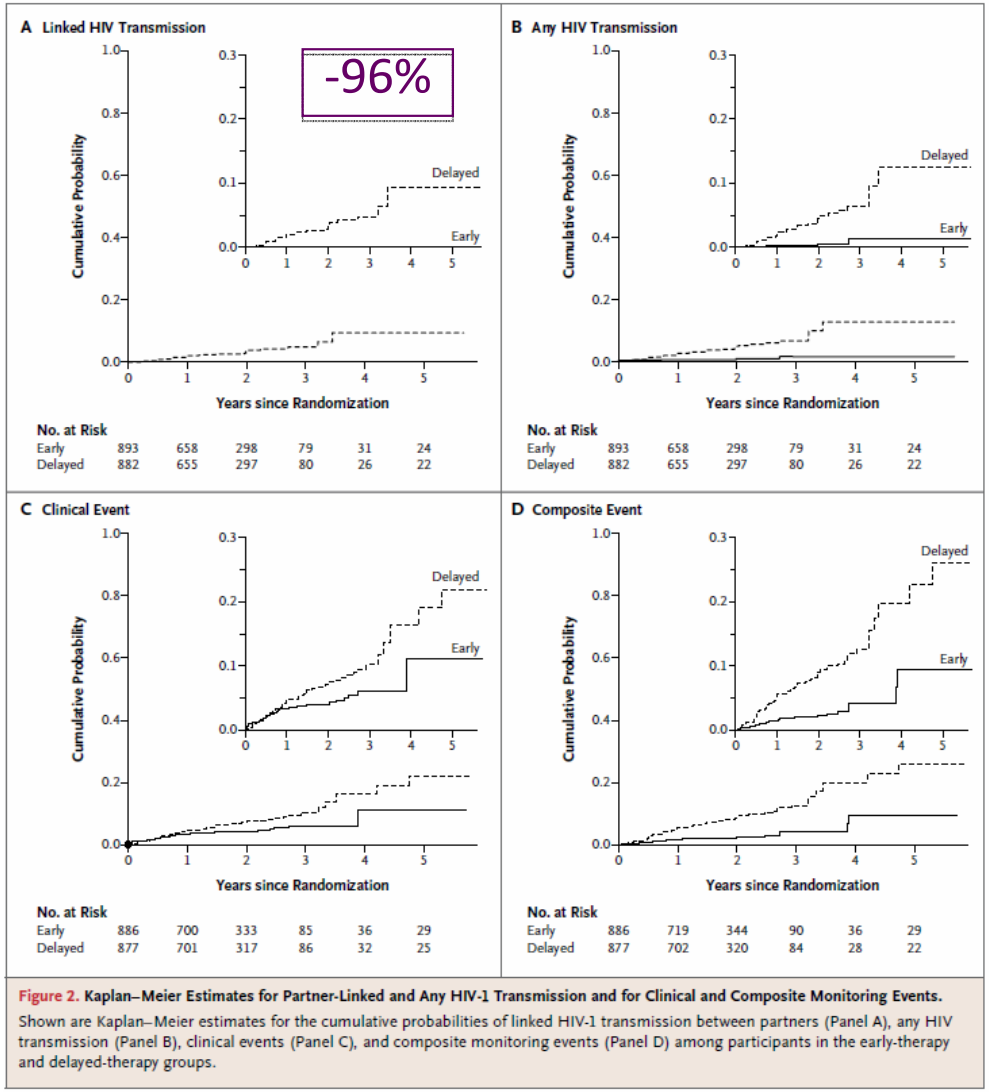


Figure 2. Kaplan–Meier Estimates for Partner-Linked and Any HIV-1 Transmission and for Clinical and Composite Monitoring Events.
Shown are Kaplan–Meier estimates for the cumulative probabilities of linked HIV-1 transmission between partners (Panel A), any HIV transmission (Panel B), clinical events (Panel C), and composite monitoring events (Panel D) among participants in the early-therapy and delayed-therapy groups.

Table 2. Incidence of Partner-Linked and Any HIV-1 Transmission and Clinical and Composite Events.

Variable	Early Therapy			Delayed Therapy			Hazard or Rate Ratio (95% CI)*
	Events	Person-yr	Rate (95% CI)	Events	Person-yr	Rate (95% CI)	
		no.	%		*no.*	%	
Linked transmission							
Total	1	1585.3	0.1 (0.0–0.4)	27	1567.3	1.7 (1.1–2.5)	0.04 (0.01–0.27)
1 yr	1	819.0	0.1 (0.0–0.7)	16	813.3	2.0 (1.1–3.2)	0.06 (0.00–0.40)
2–3 yr	0	686.5	0.0 (0.0–0.5)	9	682.8	1.3 (0.6–2.5)	0.00 (0.00–0.50)
>3 yr	0	79.9	0.0 (0.0–4.6)	2	71.2	2.8 (0.3–10.1)	0.00 (0.00–4.75)
Any transmission†							
Total	4	1585.3	0.3 (0.1–0.6)	35	1567.3	2.2 (1.6–3.1)	0.11 (0.04–0.32)
1 yr	2	819.0	0.2 (0.0–0.9)	18	813.3	2.2 (1.3–3.5)	0.11 (0.01–0.46)
2–3 yr	2	686.5	0.3 (0.0–1.1)	14	682.8	2.1 (1.1–3.4)	0.14 (0.02–0.62)
>3 yr	0	79.9	0.0 (0.0–4.6)	3	71.2	4.2 (0.9–12.3)	0.00 (0.00–2.16)
Clinical events‡							
Total	40	1661.9	2.4 (1.7–3.3)	65	1641.8	4.0 (3.1–5.0)	0.59 (0.40–0.88)
1 yr	29	831.0	3.5 (2.3–5.0)	39	832.6	4.7 (3.3–6.4)	0.75 (0.44–1.24)
2–3 yr	9	739.8	1.2 (0.6–2.3)	21	725.7	2.9 (1.8–4.4)	0.42 (0.17–0.96)
>3 yr	2	91.1	2.2 (0.3–7.9)	5	83.6	6.0 (1.9–14.0)	0.37 (0.04–2.24)
Composite events§							
Total	23	1700.1	1.4 (0.9–2.0)	79	1642.0	4.8 (3.8–6.0)	0.28 (0.18–0.45)
1 yr	13	843.7	1.5 (0.8–2.6)	47	833.9	5.6 (4.1–7.5)	0.27 (0.14–0.51)
2–3 yr	8	763.8	1.0 (0.5–2.1)	26	732.5	3.5 (2.3–5.2)	0.30 (0.12–0.67)
>3 yr	2	92.6	2.2 (0.3–7.8)	6	75.5	7.9 (2.9–17.3)	0.27 (0.03–1.52)

Cohen, NEJM, 2011

The NEW ENGLAND JOURNAL of MEDICINE

Suivi HPTN-052

ORIGINAL ARTICLE

Antiretroviral Therapy for the Prevention of HIV-1 Transmission

M.S. Cohen, Y.Q. Chen, M. McCauley, T. Gamble, M.C. Hosseinipour, N. Kumarasamy, J.G. Hakim, J. Kumwenda, B. Grinsztejn, J.H.S. Pilotto, S.V. Godbole, S. Chariyalertsak, B.R. Santos, K.H. Mayer, I.F. Hoffman, S.H. Eshleman, E. Piwowar-Manning, L. Cottle, X.C. Zhang, J. Makhema, L.A. Mills, R. Panchia, S. Faesen, J. Eron, J. Gallant, D. Havlir, S. Swindells, V. Elharrar, D. Burns, T.E. Taha, K. Nielsen-Saines, D.D. Celentano, M. Essex, S.E. Hudelson, A.D. Redd, and T.R. Fleming, for the HPTN 052 Study Team*

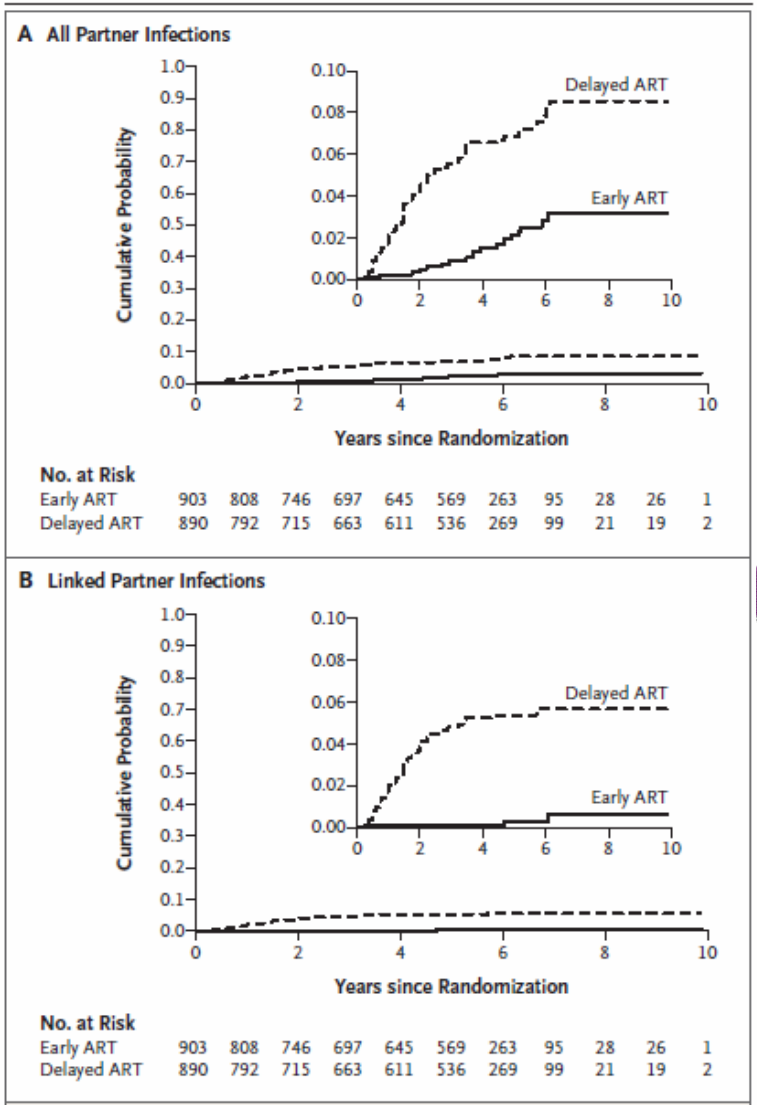


Figure 2. Kaplan–Meier Estimates of the Risk of HIV-1 Infection among Partners of Index Participants.

Shown are the cumulative probabilities of all partner infections (Panel A) and genetically linked partner infections (Panel B) during study follow-up. The insets show the same data on an expanded y axis.

Table 3. Hazard Ratios for the Association of All Partner Infections and Linked Partner Infections with Study Group, Clinical Factors, and Demographic Factors (Intention-to-Treat Analysis).*

Variable	All Partner Infections		Linked Partner Infections	
	Univariate Analysis	Multivariate Analysis	Univariate Analysis	Multivariate Analysis
	hazard ratio (95% CI)			
Early vs. delayed ART with follow-up through May 2015	0.32 (0.19–0.54)	0.34 (0.20–0.57)	0.07 (0.02–0.22)	0.08 (0.02–0.25)
Baseline CD4+ count per 100 increment	1.19 (1.02–1.38)	1.21 (1.04–1.41)	1.22 (1.02–1.47)	1.25 (1.05–1.48)
Baseline viral load per unit $\log_{10}$ increment	1.08 (0.82–1.42)	1.18 (0.89–1.56)	1.70 (1.15–2.51)	1.88 (1.24–2.87)
Male sex vs. female sex of index participant	0.85 (0.54–1.35)	0.86 (0.54–1.39)	0.94 (0.52–1.70)	0.86 (0.47–1.59)
Baseline condom use of 100% vs. <100% by either partner	0.34 (0.19–0.64)	0.33 (0.18–0.61)	0.35 (0.16–0.76)	0.34 (0.15–0.75)

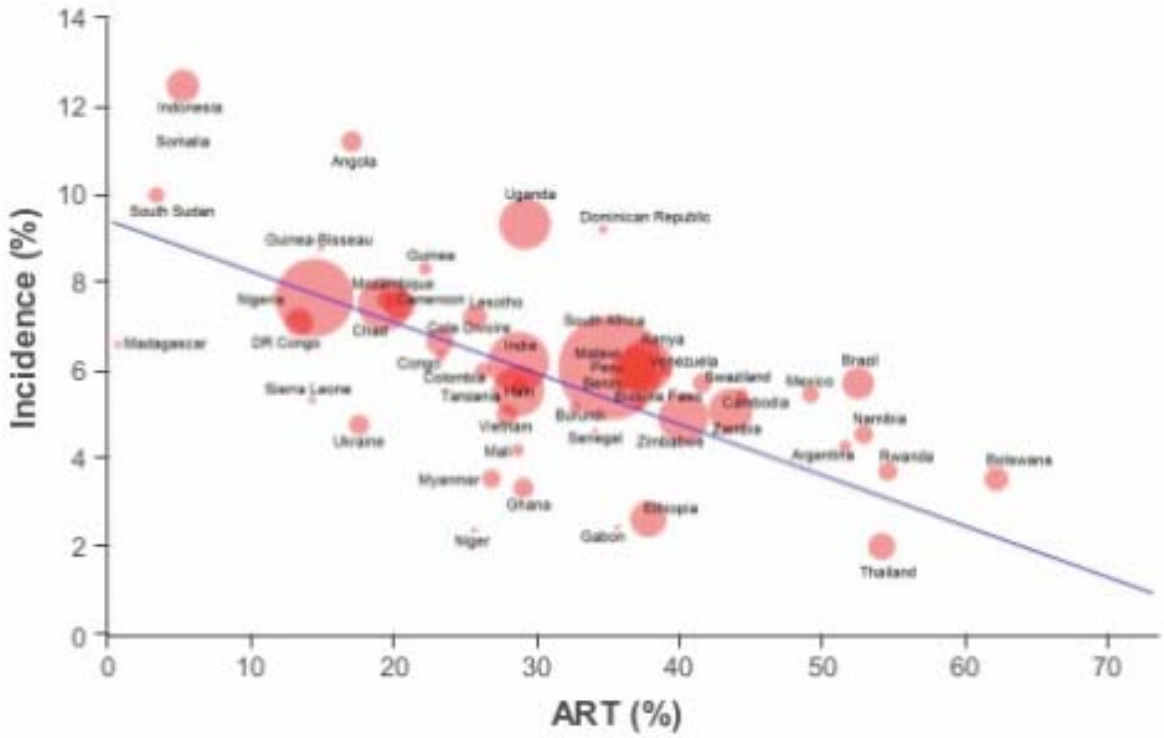
- Suivi 10031 person-years (partenaires 8509 py)
- 46 infections VIH liées: 3 vs 43 (Réduction de la transmission **-93%**)
- Pas d'infection VIH liée si CV indétectable

Cohen, n engl j med 375;9 , September 1, 2016

Corrélation couverture ARV et incidence

The Impact of TasP

New HIV infections (% growth) versus ART coverage in 51 countries



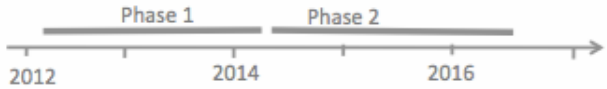
Hill et al. World AIDS Conference, July 2014, Melbourne, Australia [LBPE29]

ANRS 12249 TasP trial

- **Objective:** To evaluate the effect of early ART, initated irrespective of CD4 count criteria, on HIV incidence in the general population in the same setting
- **Design:** Cluster-randomized trial *(Iwuji et al. Trials 2013; Orne-Gliemann et al. BMC Public Health 2015)*

6-monthly rounds of home-based HIV-testing

Intervention	Control
Treat all HIV+ individuals regardless of CD4 count and clinical stage	Treat all HIV+ individuals according to South African guidelines *(≤350 CD4, WHO stage 3 or 4 until Dec 2014, ≤500 since Jan 2015)*



9

Trial procedures

Homestead identification (GPS)

Homestead visit every 6 months
1. Head of household verbal consent
2. Registration of individuals

Homestead procedures
1. Household assets questionnaire
2. Individual questionnaire
3. DBS sample, rapid HIV testing
4. TasP card

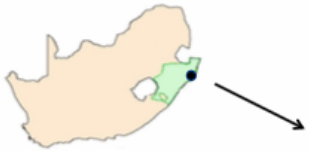
TasP clinic
- One per cluster (45 min walk max)
- HIV care and treatment according to arm
- Study questionnaires

HIV + → Referral to TasP clinics

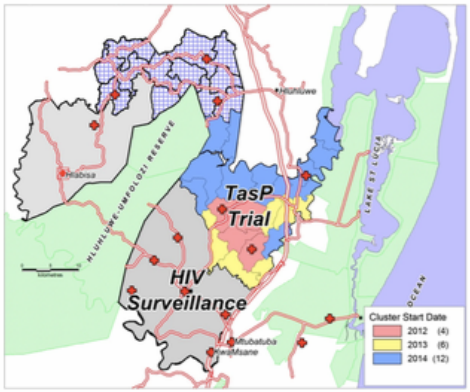
HIV - → Repeat HIV test 6 mths later

5

Trial area



Country: South Africa
Region: KwaZulu-Natal
Sub-district: Hlabisa
- 1 430 Km²
- 228,000 Zulu speaking people



4 clusters
+ 6 clusters
+ 12 clusters

Total of 22 clusters

10

ANRS 12249 TasP trial primary outcome

- Cumulative incidence of new HIV infections
  - Powered to detect a 34% reduction in incidence in intervention arm vs control arm
- Measured on longitudinal/repeat Dried Blood Spot (DBS) using HIV-ELISA
- Computed among those individuals with a first HIV-negative test
- Compared by Poisson regression taking into account cluster effect

F. Dabis, 2016

Description of trial population, HIV burden and ART coverage at the beginning of the trial

	Intervention	Control	Total
Socio-demographics at registration	(n=13,236)	(n=14,917)	(n=28,153)
Men	37%	38%	37%
Median age in years (IQR)	30 (22-50)	30 (22-49)	30 (22-50)
Baseline cluster characteristics			
Average HIV prevalence (95% CI) (DBS)	30% (29-31)	31% (30-32)	31% (30-31)
ART coverage*	31%	36%	34%

ANRS 12249 TasP: HIV incidence comparison

	Number of HIV-positive DBS tests	Person-years	Incidence for 100 person-years	95% CI
Control	268	11,787	2.27	2.00-2.55
Intervention	227	10,646	2.13	1.85-2.41
TOTAL	495	22,434	2.21	2.01-2.40

Adjusted risk ratio*

	aRR	95% CI	P-value
Intervention vs control	0.95	0.79-1.14	0.5821

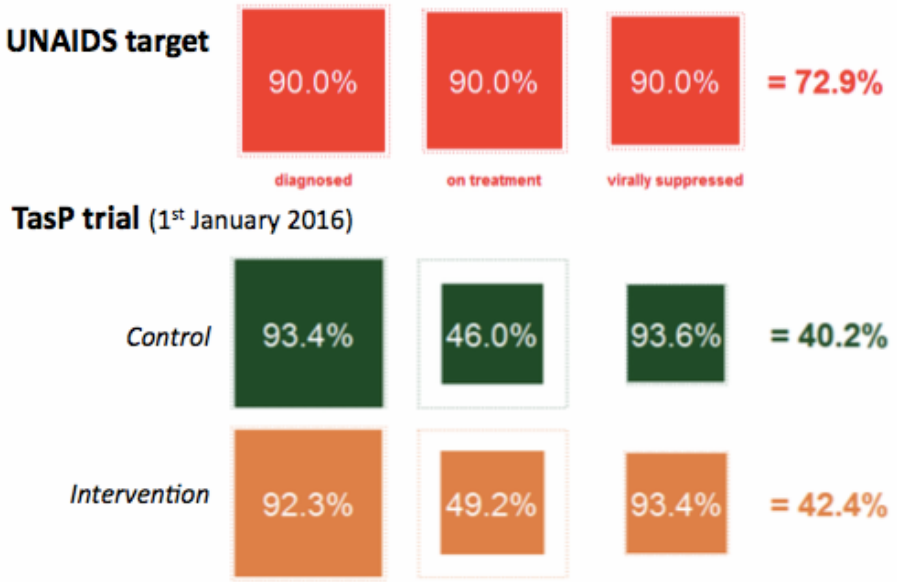
** Estimated with Poisson regression, adjusted on sex, age, change in national ART guidelines, baseline cluster HIV prevalence and ART coverage*

Trial process indicators

	Intervention	Control
Contact rate per survey round (range)	61% – 84%	66% – 90%
HIV ascertainment rate per survey round (range)	70% – 83%	77% – 88%
Entry into care among individuals not in care		
Within 3 months	28%	29%
Within 6 months	36%	37%
Within 12 months	47%	47%

	Intervention	Control
ART initiation within 3 months in TasP clinics among patients not on ART at first TasP clinic visit	91%	52%
Viral load <400 copies/ml among patients not on ART at first TasP clinic visit		
At month 6	93%	92%
At month 12	95%	95%
Estimated ART coverage* (as of 1st January 2016)	45%	43%
ART coverage improvement since baseline	+14	+7

ANRS 12249 TasP - Estimated cascade of care

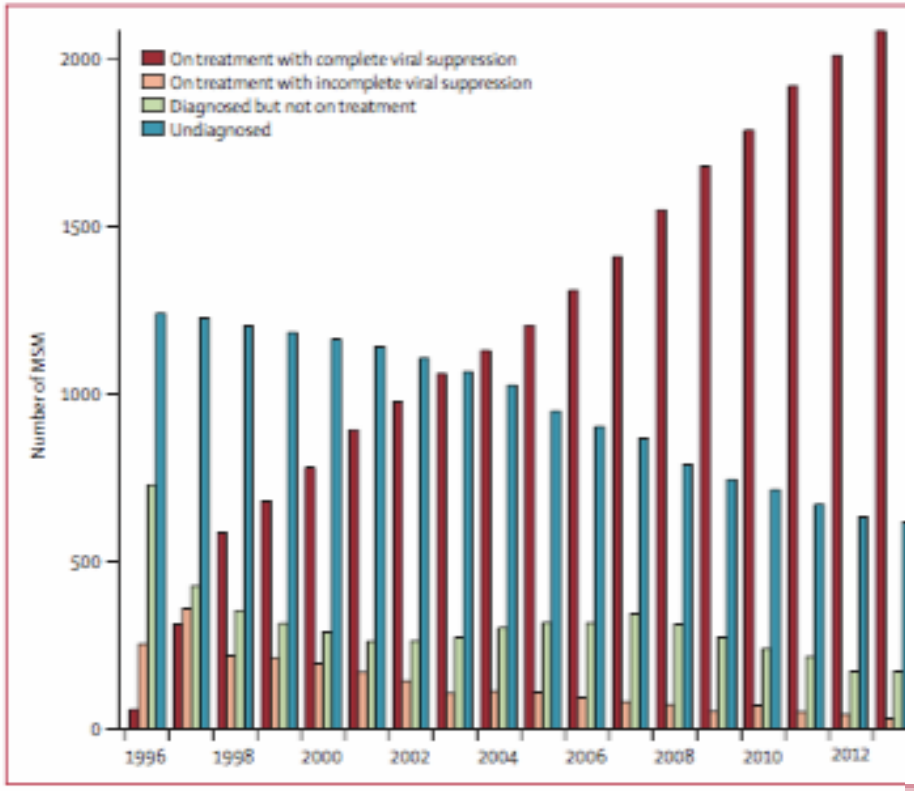


F. Dabis, 2016

Testing the hypothesis that treatment can eliminate HIV: a nationwide, population-based study of the Danish HIV epidemic in men who have sex with men

Justin T Okano, Danielle Robbins*, Laurence Palk, Jan Gerstoft, Niels Obel, Sally Blower*

Cohorte danoise: Diminution de l'incidence corrélée avec la proportion de patients sous traitement ARV



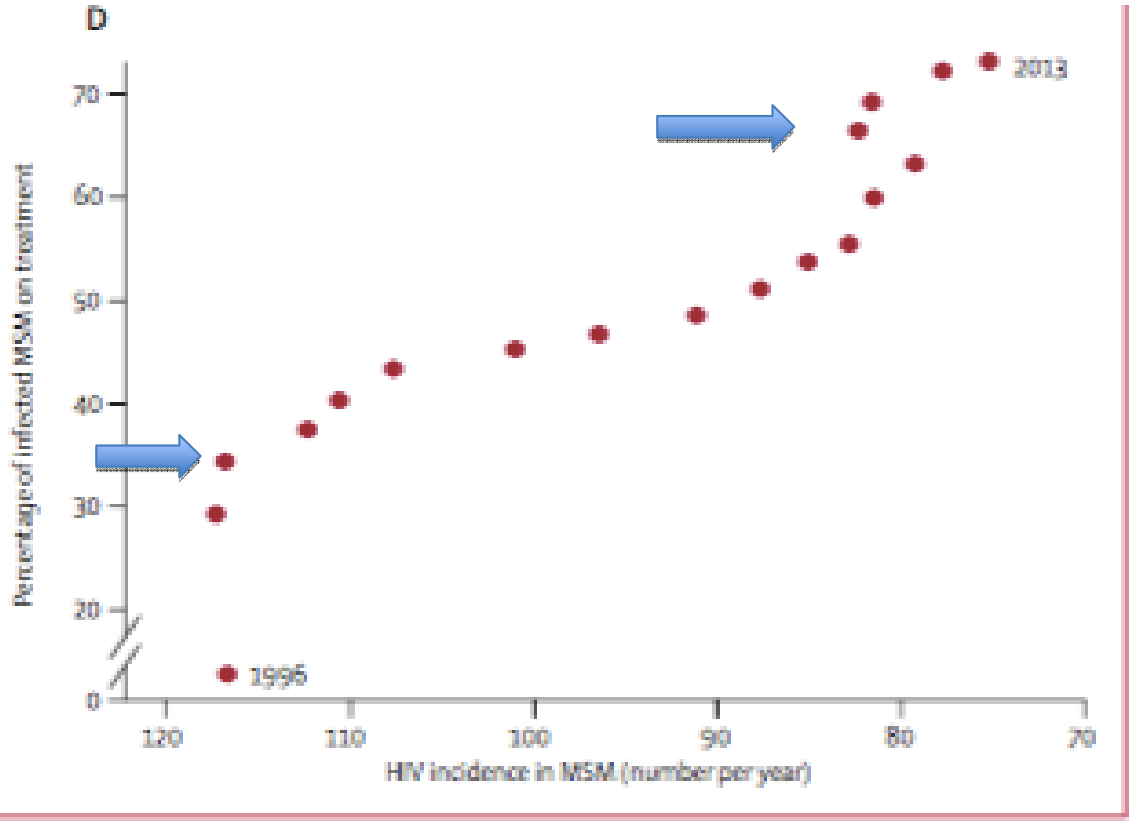


Figure 4: **Temporal changes in the HIV epidemic in MSM in Denmark after the introduction of combinatio therapies in 1996**

MSM=men who have sex with men. Danish HIV Cohort Study data show the total number of MSM in Denmark on treatment with complete viral suppression (viral load <200 copies per μL). Also shown are the numbers undiagnosed (estimates, median values), diagnosed but not on treatment, and on treatment with incomplete viral suppression.

J.T. Okano, www.thelancet.com/infection
Vol 16 July 2016

Evolution de la CV « populationnelle » et élimination de l'épidémie VIH : l'épidémie VIH chez les MSM au Danemark proche du seuil d'élimination

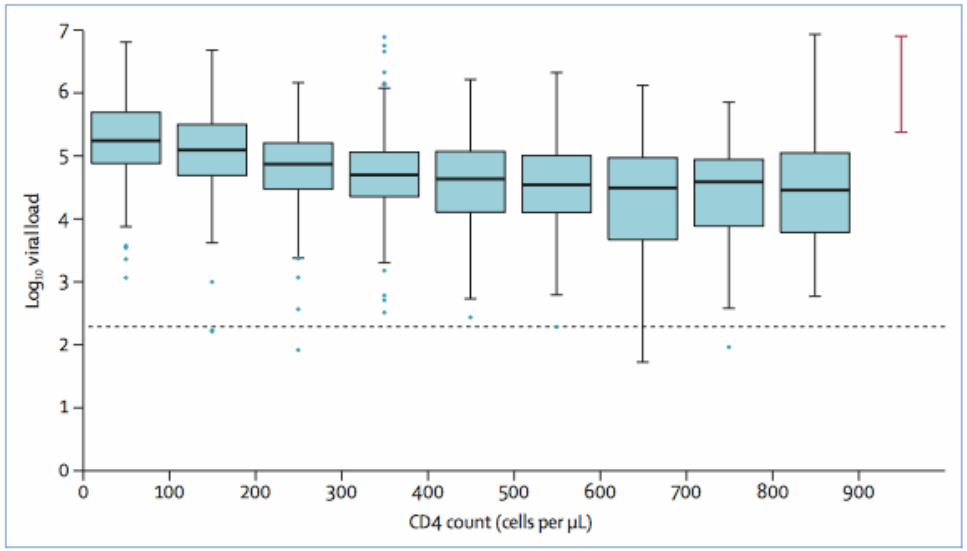


***Figure 1*: CD4-stratified viral load distributions**
Distributions were constructed with data collected from 1059 treatment-naive HIV-infected men who have sex with men who participated in the Danish HIV Cohort Study. The horizontal line in each box plot represents the median, blue dots show outliers, the dotted line denotes viral suppression (<200 copies per mL), and the red line shows the range of viral load estimates for acute infection.

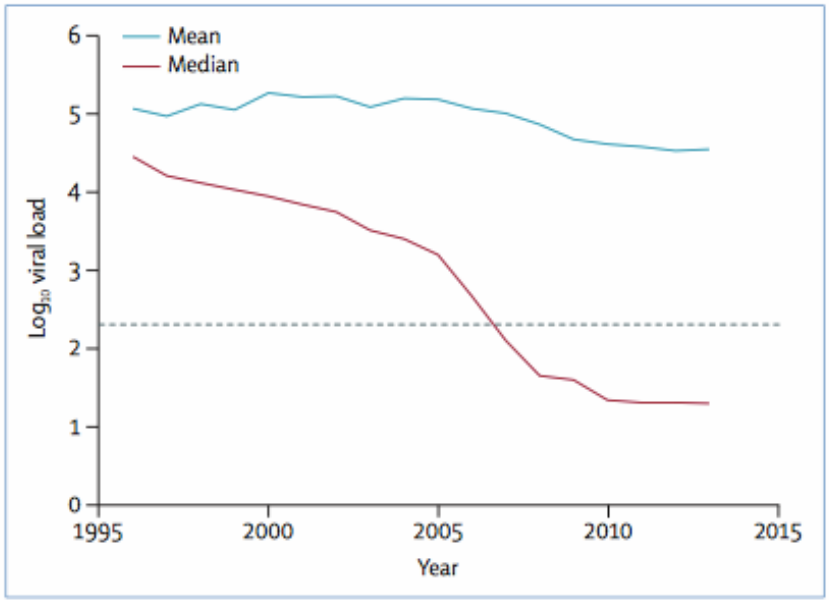


***Figure 2*: Temporal trends in values of the population viral load as the Danish HIV epidemic in men who have sex with men was driven to the brink of elimination**
Data are from the Danish HIV Cohort Study; the dotted line denotes viral suppression (<200 copies per mL).

By 2013, incidence was close to the elimination threshold: 1·4 (median, 95% Bayesian credible interval [BCI] 0·4–2·1) new HIV infections per 1000 MSM and there were only 617 (264–858) undiagnosed MSM.

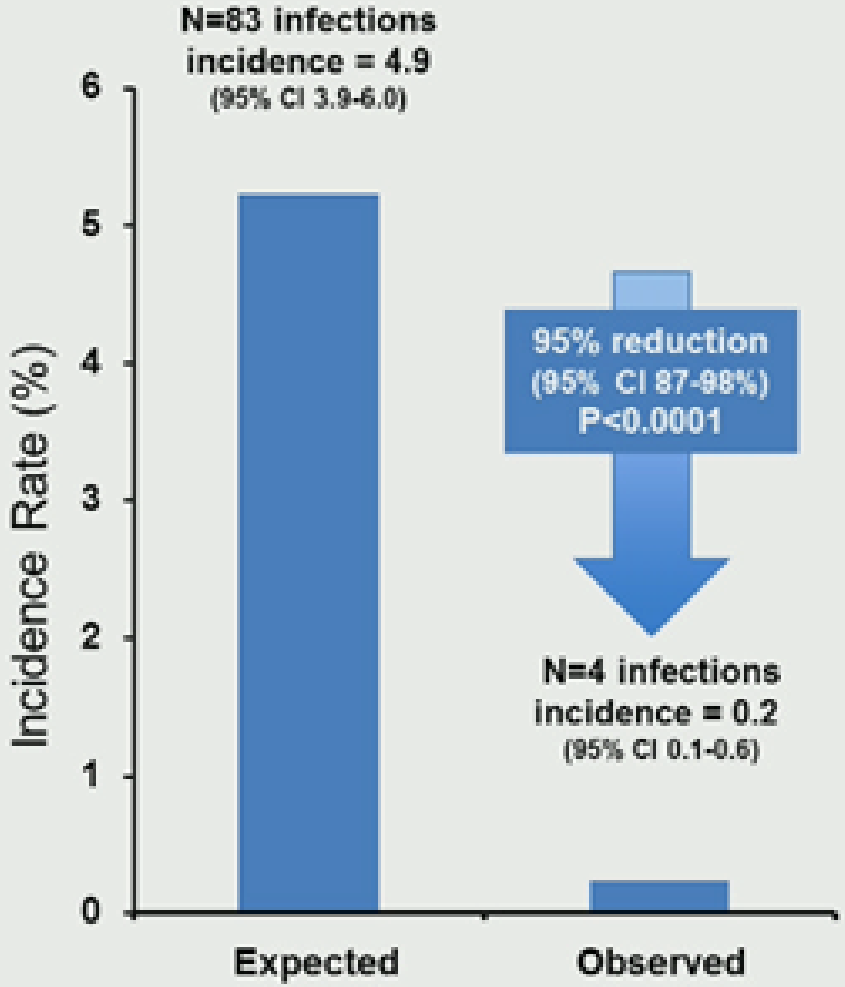
The average per act probability of transmitting HIV decreased from 0·0041 (2007) to 0·0027 (2013)

*Justin T Okano, Jan Gerstoft, Niels Obel,*Sally Blower*
www.thelancet.com/hiv **Vol3 November2016**

Combining ART and PrEP for HIV Discordant Couples in Africa

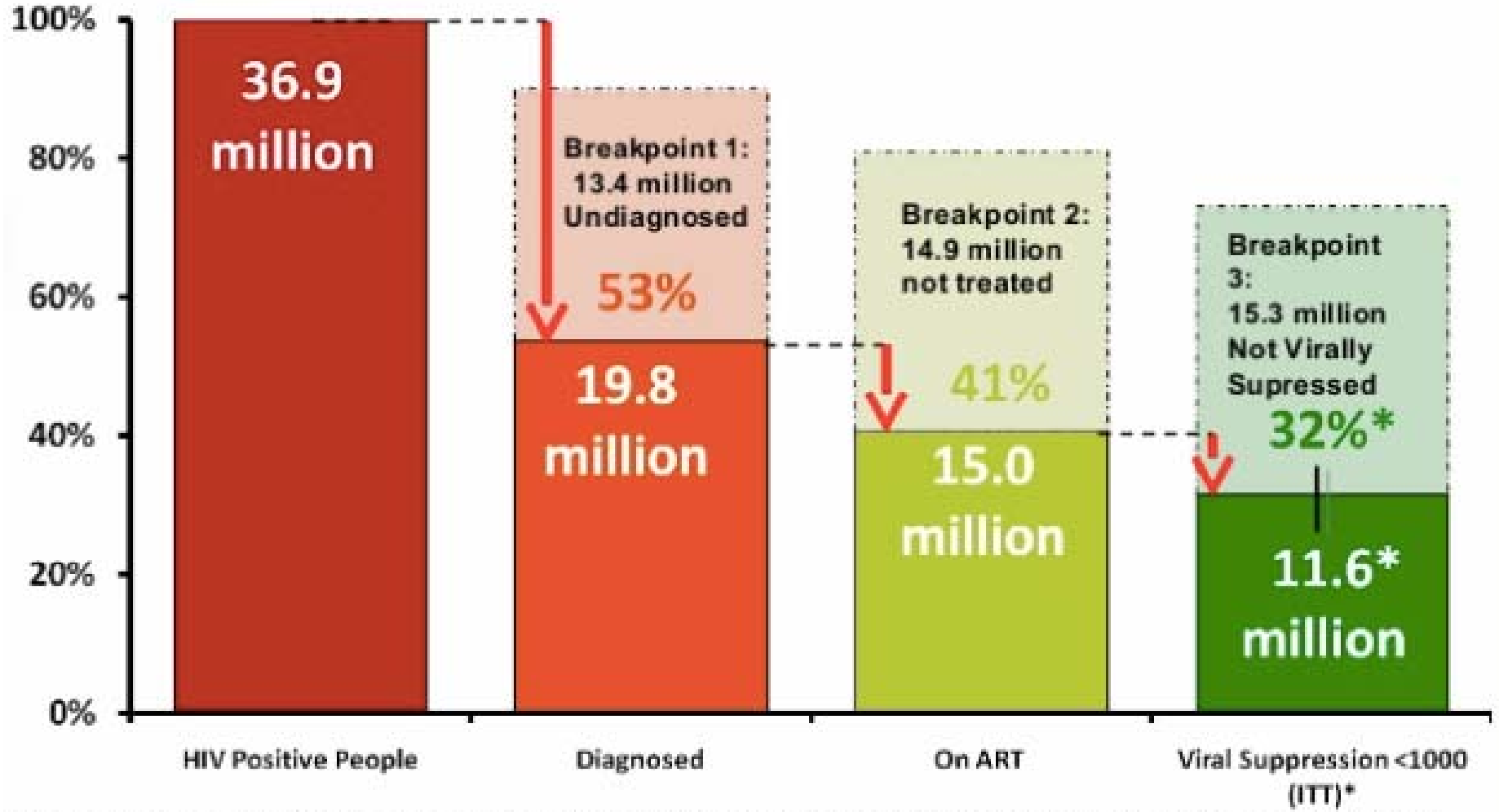
- For couples initiating ART at enrollment, PrEP was offered through 6 months, then stopped:

- For couples in which the infected partner delayed or declined ART, PrEP was continued until 6 months after ART initiation:



Baeten J, et al. AIDS 2016; Durban, South Africa; July 18-22, 2016; Abst. WEAC0105.

Global Estimates (2014-15) vs the Gap to reach 90-90-90 Targets



Ref: On ART = March 2015. How Aids Changed Everything. Fact Sheet. UNAIDS 2015. MDG 6: 15 YEARS, 15 LESSONS OF HOPE FROM THE AIDS RESPONSE July 2015. * Average viral suppression% Intention to Treat LMIC rate from a Systematic Review by McMahon J. et al. Viral suppression after 12 months of antiretroviral therapy in low-and middle-income countries: a systematic review." *Bulletin of the World Health Organization* 91.5 (2013): 377-385.

Merci


The Economist
The trap for Turkey
Wall Street's plumbing problem
Lady Gaga, Mother Teresa and profits
Brazil's boiling economy
The farce that is FIFA
The end of AIDS?
How 5 million lives have been saved, and a plague could now be defeated