JNI 17es Journées Nationales d'Infectiologie

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Lille Grand Palais

Lille
et l'interrégion Nord-Pas-de-Calais-Picardie

Best of en Infectiologie
Infection par le VIH/SIDA

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Hôpitaux Universitaires SAINT-LOUIS LARIBOISIÈRE FERNAND-WIDAL

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Déclaration d'intérêts de 2012 à 2015

- **Bourse de Recherche: Gilead Sciences, Merck**
- **Advisory Boards: Gilead Sciences, Merck, ViiV, BMS, Janssen**

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

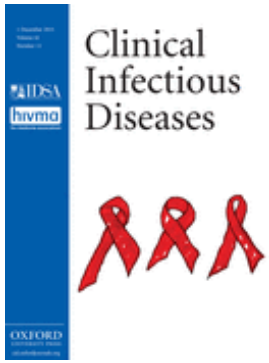
Laurent Mandelbrot,[1,2,5,8] Roland Tubiana,[9,10] Jerome Le Chenadec,[2] Catherine Dollfus,[11] Albert Faye,[5,12] Emmanuelle Pannier,[8,13] Sophie Matheron,[5,14] Marie-Aude Khuong,[17] Valerie Garrait,[18] Veronique Reliquet,[19] Alain Devidas,[20] Alain Berrebi,[21] Christine Allisy,[22] Christophe Elleau,[23] Cedric Arvieux,[24] Christine Rouzioux,[6,15] Josiane Warszawski,[2,3,4] and Stéphane Blanche[7,16]; for the ANRS-EPF Study Group[a]

Timing of Antiretroviral Treatment During Pregnancy in 8075 Women

Children Status	All Children No. (PT %)	Before Conception No. (PT %)	1st Trimester (< 14 GW) No. (PT %)	2nd Trimester (14-27 GW) No. (PT %)	3rd Trimester (> 27 GW) No. (PT %)
HIV-infected	56 (**0.7**)	10 (**0.2**)	3 (**0.4**)	22 (**0.8**)	21 (**2.1**)*
Not Infected	8019 (92.4)	3798 (92.8)	655 (91.9)	2597 (92.7)	969 (90.8)
Unknown	486 (5.6)	227 (5.5)	45 (6.3)	144 (5.1)	70 (6.5)

*P value < 0.001

Mandelbrot et al, CID 2015



Perinatal HIV Transmission Rate According to Timing of ART Initiation and Maternal Viral Load at Delivery

Maternal Plasma HIV RNA Level at Delivery	Before Conception		1st Trimester (< 14 GW)		2nd Trimester (14-27 GW)		3rd Trimester (> 27 GW)	
	No.PT/ Total	PT% (95% CI)	No.PT/ Total	PT% (95% CI)	No.PT/ Total	PT% (95% CI)	No. PT/ Total	PT% (95% CI)
> 400	5/230	2.2 (0.7-5)	1/69	1.5 (0.4-7.8)	7/291	2.4 (1.0-4.9)	10/228	4.4 (2.1-7.9)
50-400	1/301	0.3 (.01-1.8)	1/61	1.6 (0.4-8.8)	7/515	1.4 (.5-2.8)	9/297	3.0 (1.4-5.7)
< 50	0/2651	**0.0 (0-0.1)***	1/507	**0.2** (.01-1.1)	9/1735	**0.5** (0.2-1.0)	4/452	**0.9** (0.2-2.3)

* P value = 0.002

Elimination of Perinatal HIV transmission can be achieved in pregnant women who are tested for HIV, start ART before conception and maintain suppression of plasma VL.

Mandelbrot et al, CID 2015

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

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

HIV-negative Gay Men and transgender women reporting unprotected anal intercourse with a man in previous 90 days

Immediate Daily Oral TDT/FTC
(n = 275)

Deferred Daily TDF/FTC by 12 months
(n = 269)

- **Primary endpoint**: Time to accrual of 500 participants and retention
- **From June 2014**: HIV-infection in first 12 months
- **Other outcome measures**: safety, adherence, risk compensation
- All participants were offered a risk reduction package : regular HIV testing, diagnosis and treatment of STIs, support to reduce high risk behavior including condoms, PEP.

S. McCormack et al Lancet 2015

Incidence of HIV-Infection

Group	No. of infections	Follow-up (PY)	Incidence (per 100 PY)	90% CI
Overall	23	465	5.0	3.5–6.9
Immediate	3	243	**1.2**	0.4–2.9
Deferred	20	222	**9.0**	6.1–12.8

Efficacy = **86%** (90% CI: 64-96%)
P-value =0.0001

Number Needed to Treat =13 (90% CI: 9 – 23)

PEP use : 85 individuals (32%) in the deferred arm with 5 infections

S. McCormack et al Lancet 2015

Bacterial Sexually Transmitted Infections

	Immediate	Deferred	Unadjusted OR	Adjusted* OR	P-value
Any	152/265 (57%)	124/247 (50%)	1.33	**1.07**	0.74
Gonorrhoea	103/261 (39%)	89/242 (37%)	1.12	**0.86**	0.46
Chlamydia	77/261 (30%)	54/242 (22%)	1.46	**1.27**	0.27
Syphilis	30/263 (11%)	22/247 (9%)	1.32	**1.29**	0.39
Rectal Infection	93/258 (36%)	77/238 (32%)	1.18	**1.00**	0.99

*Adjusted for the number of screens for specific infections

S. McCormack et al Lancet 2015

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

Double-Blinded Randomized Placebo-Controlled Trial

- 400 HIV negative MSM
- Condomless anal sex with ≥ 2 partners within 6 m
- eGFR > 60 mL/mn

→ **Full prevention services* TDF/FTC before and after sex**

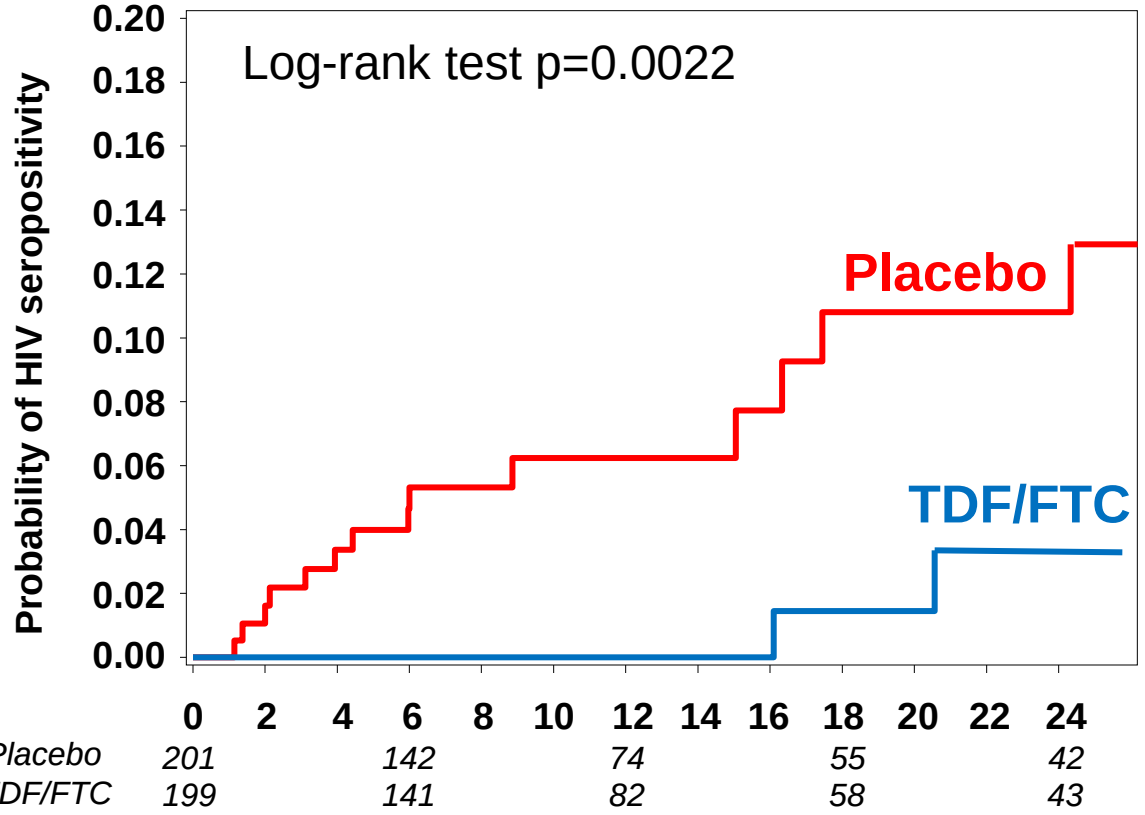
→ **Full prevention services* Placebo before and after sex**

* Counseling, condoms and gels, testing and treatment for STIs, vaccination for HBV and HAV, PEP

- Follow-up visits: month 1, 2 and every two months thereafter with 4th generation HIV ELISA assays (combined Ab/Ag detection) on serum

Molina JM et al. NEJM 2015

KM Estimates of the Probability of HIV-1 Infection



Mean follow-up of 13 months: 16 subjects infected

14 in placebo arm (incidence: 6.6 /100 PY) and **2 in TDF/FTC arm** (0.91 /100PY)

86% relative reduction in the incidence of HIV-1 (95% CI : 40-98, p=0.002)

Molina et al NEJM 2015

ipergay
ANRS
Intervention Préventive de l'Exposition aux Risques avec et pour les Gays

Adverse Events

Nb of Participants (%)	TDF/FTC n=199	Placebo n=201	P value
Any Serious AE	20 (10)	17 (8)	0.58
Any Grade 3 or 4 AE	19 (10)	15 (7)	0.45
Treatment D/C due to AE	1*(<1)	0	
Drug-Related GI AEs	28 (14)	10 (5)	0.002
Nausea/vomiting	16	2	
Abdominal pain	13	3	
Diarrhea	8	6	
Elevated Creatinine	35 (18)	20 (10)	0.03

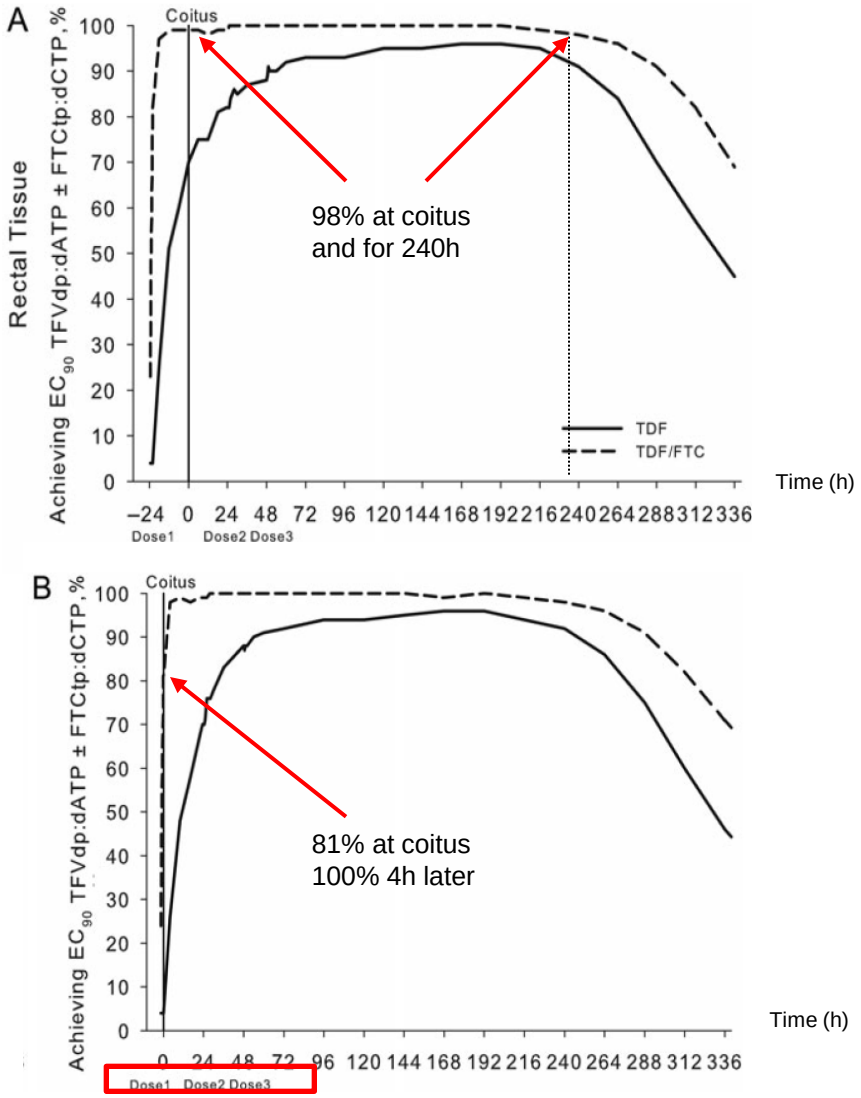
* deep veinous thrombosis with suspected DDI with dabigatran

Molina JM et al. NEJM 2015

A Translational Pharmacology Approach to Predicting Outcomes of Preexposure Prophylaxis Against HIV in Men and Women Using Tenofovir Disoproxil Fumarate With or Without Emtricitabine

Mackenzie L. Cottrell,[1] Kuo H. Yang,[2] Heather M. A. Prince,[3] Craig Sykes,[1] Nicole White,[1] Stephanie Malone,[1] Evan S. Dellon,[3] Ryan D. Madanick,[3] Nicholas J. Shaheen,[3] Michael G. Hudgens,[4] Jacob Wulff,[4] Kristine B. Patterson,[3] Julie A. E. Nelson,[5] and Angela D. M. Kashuba[1]

- 49 women received a single-dose of TDF (150 to 600 mg) or FTC (100 to 400 mg) with blood and rectal, cervical, and vaginal sampling over 48h.
- PK/PD model using tissue concentrations of TFV, FTC, TFV-DP and FTC-TP and competing endogenous nucleotides.
- Cell line (TZM-bl) and CD4 T-cells used to identify 90% Effective Concentration (EC_{90}) ratios of TVF-DP to dATP and FTC-TP to dCTP
- Percentage of the simulated population achieving the EC_{90} ratio for TDF or TDF/FTC over 14 days following a single coitus in <u>colorectal tissue</u> with the first dose given 24h (A) or 2 h (B) before coitus
- TDF+FTC achieved target exposure at the time of coitus in 81% (A) and 98% (B) of the population, and was sustained for 240h <u>(10 days) after coitus</u>



Cottrell ML et al. J Infect Dis 2016

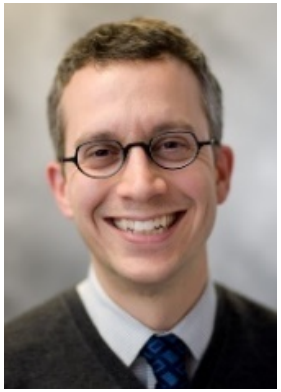
BRIEF REPORT HIV/AIDS

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

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

- All adults evaluated for PrEP from July 2012 through Feb 2015
- Patients surveyed by email about changes in sexual behavior.
- Among 801 individuals with at least one visit, 657 (82%) started PrEP.
- Mean duration of PrEP use: 7.2 months.
- Mean age was 37 years, 99% were MSM, 84% report multiple sex partners
- 187 (28%) were diagnosed with at least one STI during FU
- No HIV diagnoses during follow-up (97.5% CI: 0-1%)
- Nb sexual partners unchanged in 74%, decreased in 15%, increased in 11%
- Condom use unchanged in 56%, decreased in 41% and increased in 3%.
- How changes in sexual behavior may impact the risk for STIs in PrEP users.

Volk J. et al. CID 2015



ORIGINAL ARTICLE

Use of a Vaginal Ring Containing Dapivirine for HIV-1 Prevention in Women

- **ASPIRE Trial** (*A Study to Prevent Infection with a Ring for Extended use)*
  Phase 3 multicentric, randomized (1:1), double blinded, placebo controlled study of a vaginal ring containing Dapivirine for HIV prevention in women

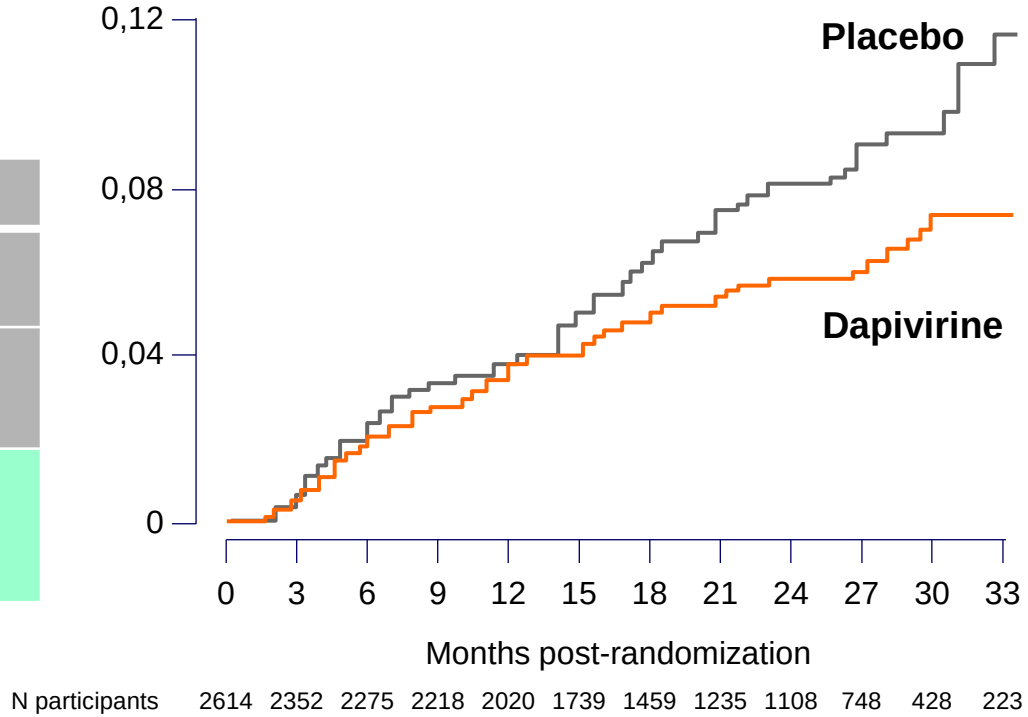
- **Methods**
  - Vaginal ring inserted every month at each monthly visit
  - « Counseling » for HIV prevention at each visit with free condoms
  - Women were tested monthly for pregnancy

- **Participants Characteristics**
  - 2 629 women enrolled from 2012 to 2015 in Africa (Malawi, South Africa, Uganda and Zimbabwe)
  - Median age: 26 years, 41 % married, and 17 % > 1 partner in past 3 months
  - Partner aware of ring use: 64%
  - 57 % reported condom use at last vaginal intercourse

Baeten JM et al. New Engl J Med 2016

Cumulative Incidence of HIV-1 Infection

	Dapivirine	PCB
HIV-1 infections	71	97
HIV-1 Incidence per 100 PY	3.3	4.5
Efficacy (95 %CI)	27 % (1 – 46) p = 0.05	

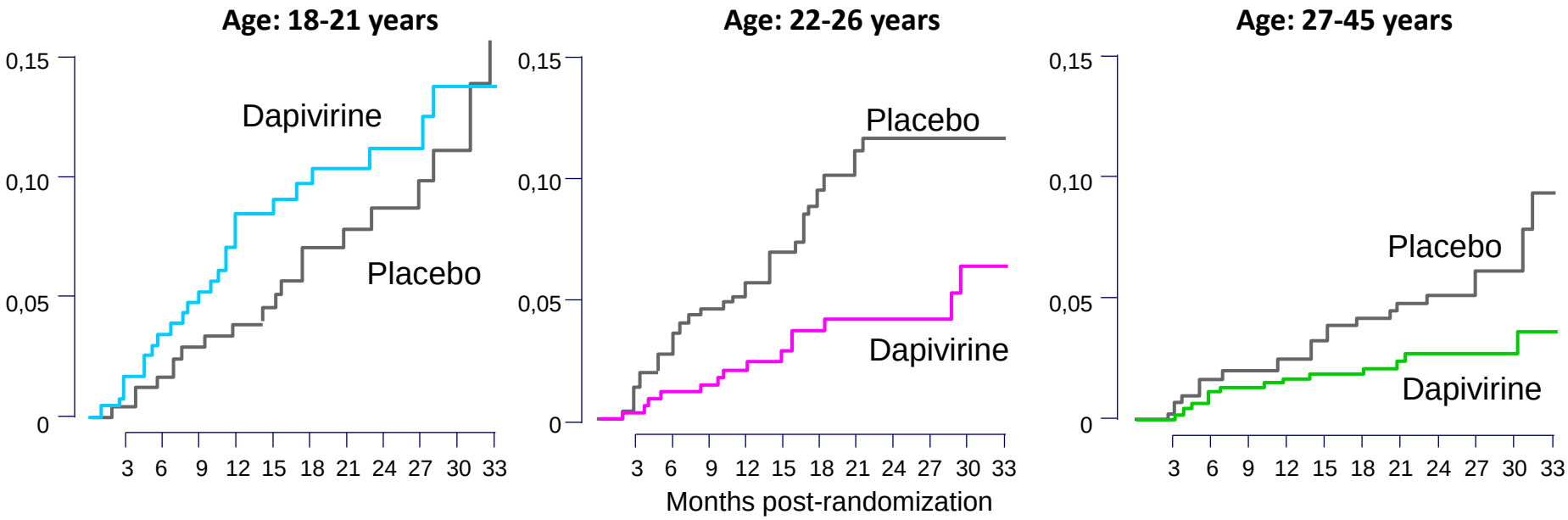


In women randomized in the dapivirine ring arm
the relative reduction of HIV incidence was 27% (95% CI: 1 to 46).

Baeten JM et al. New Engl J Med 2016

The NEW ENGLAND JOURNAL of MEDICINE

Cumulative Incidence of HIV-1 Infection According to Age at Enrollment



	18 - 21 years	22 - 26 years	27 - 45 years
HIV Incidence per year in placebo arm	5.4 %	6.1 %	3.0 %
Relative Efficacy of Dapivirine ring	- 27 % (- 133 - 31)	56 % (19 - 76)	51 % (8 - 74)

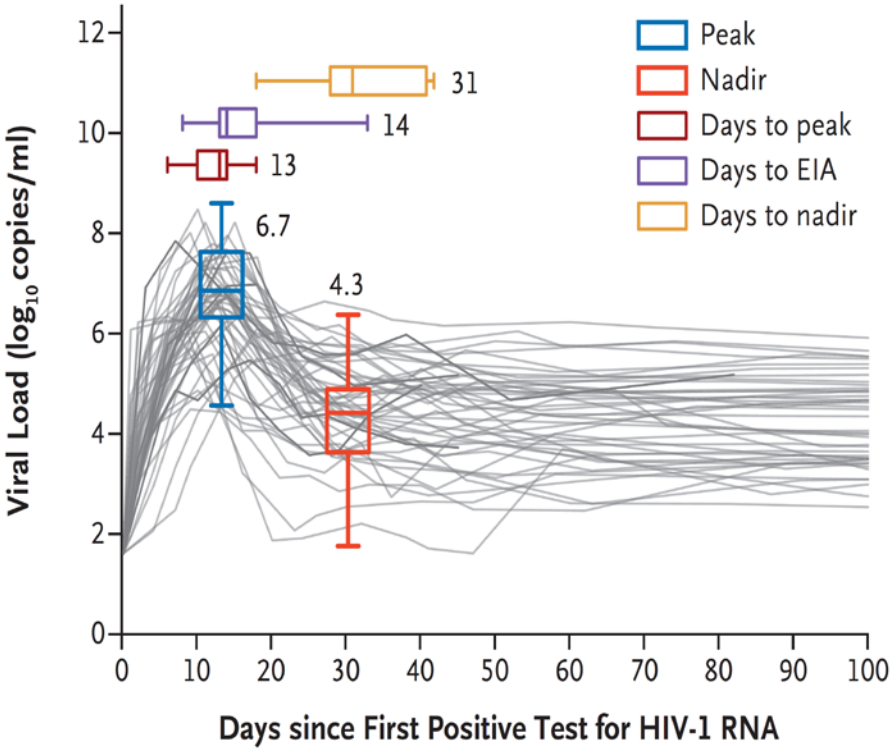
- No protection of Dapivirine ring in women ≤ 21 years vs. 56% in those > 21 years
- This difference was correlated with reduced adherence as assessed by dapivirine plasma levels

Baeten JM et al. New Engl J Med 2016

Prospective Study of Acute HIV-1 Infection in Adults in East Africa and Thailand

Merlin L. Robb, M.D., Leigh A. Eller, Ph.D., Hannah Kibuuka, M.B., Ch.B., Kathleen Rono, M.B., Ch.B., Lucas Maganga, M.B., Ch.B., Sorachai Nitayaphan, M.D., Eugene Kroon, M.D., Fred K. Sawe, M.B., Ch.B., Samuel Sinei, M.B., Ch.B.,

- RV 217 study: Prospective study in 2276 volunteers at high risk of HIV-infection in Sub-Saharan Africa and Thailand (twice weekly visits)
- 50 of 112 pts with acute HIV-infection had samples collected before HIV-1 Ab detected
  - Median peak viremia: 13 days after first sample positive on RNA testing
  - Nadir viremia at 31 days and equivalent to the viral load set point
  - EIA reactivity after a median of 14 days
- Clinical symptoms rare:
  - 50% reported neither symptoms nor signs
  - Just before and at the time of peak viremia
- High level of HIV RNA in asymptomatic patients with acute infection and no detectable HIV antibodies may limit the effect of test and treat strategies on HIV transmission



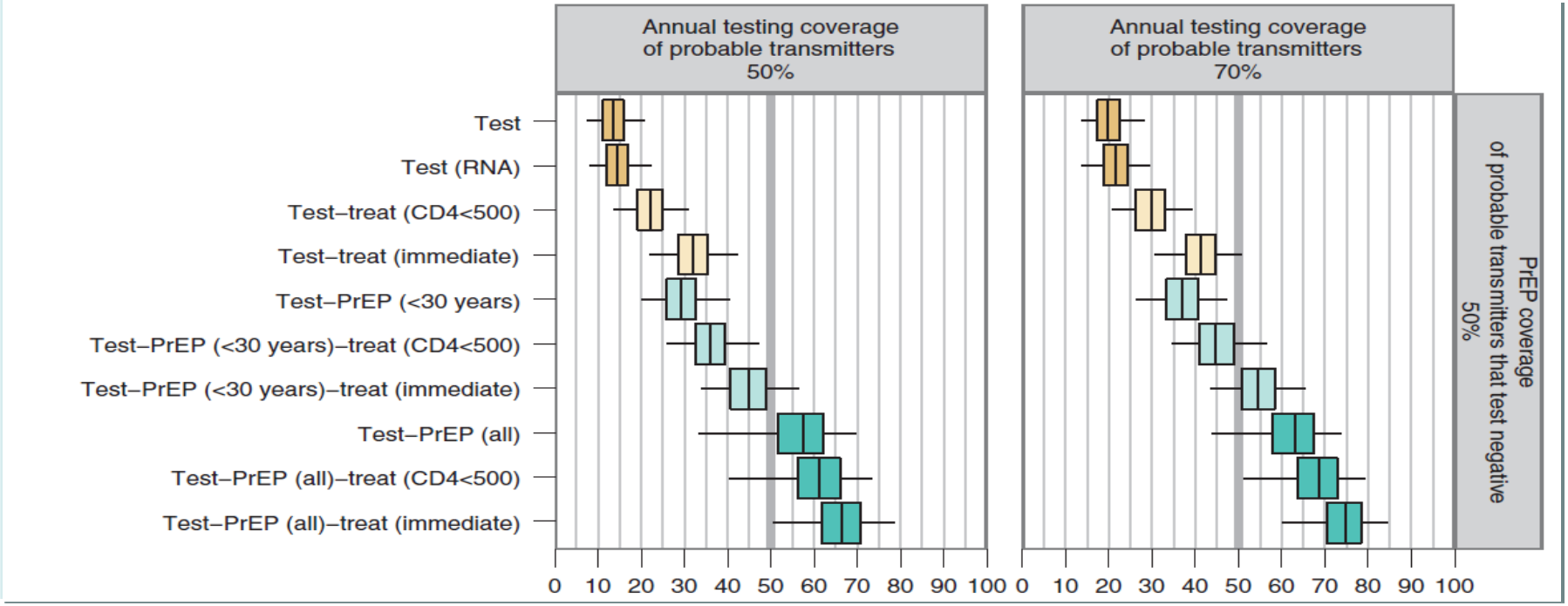
Robb ML et al NEJM 2016

RESEARCH ARTICLE

HIV

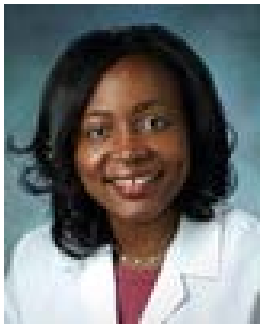
Sources of HIV infection among men having sex with men and implications for prevention

Oliver Ratmann,[1]* Ard van Sighem,[2] Daniela Bezemer,[2] Alexandra Gavryushkina,[3] Suzanne Jurriaans,[4] Annemarie Wensing,[5] Frank de Wolf,[1] Peter Reiss,[2,6] Christophe Fraser,[1] ATHENA observational cohort



- 617 infections in MSM: **71% of transmissions from undiagnosed men, 6% from men on ART**
- **Annual Testing + Immediate ART + PrEP** could prevent up **to 66% of HIV infections**

Ratmann O, et al. Sci Transl Med. 2016 Jan 6;8(320):320ra2



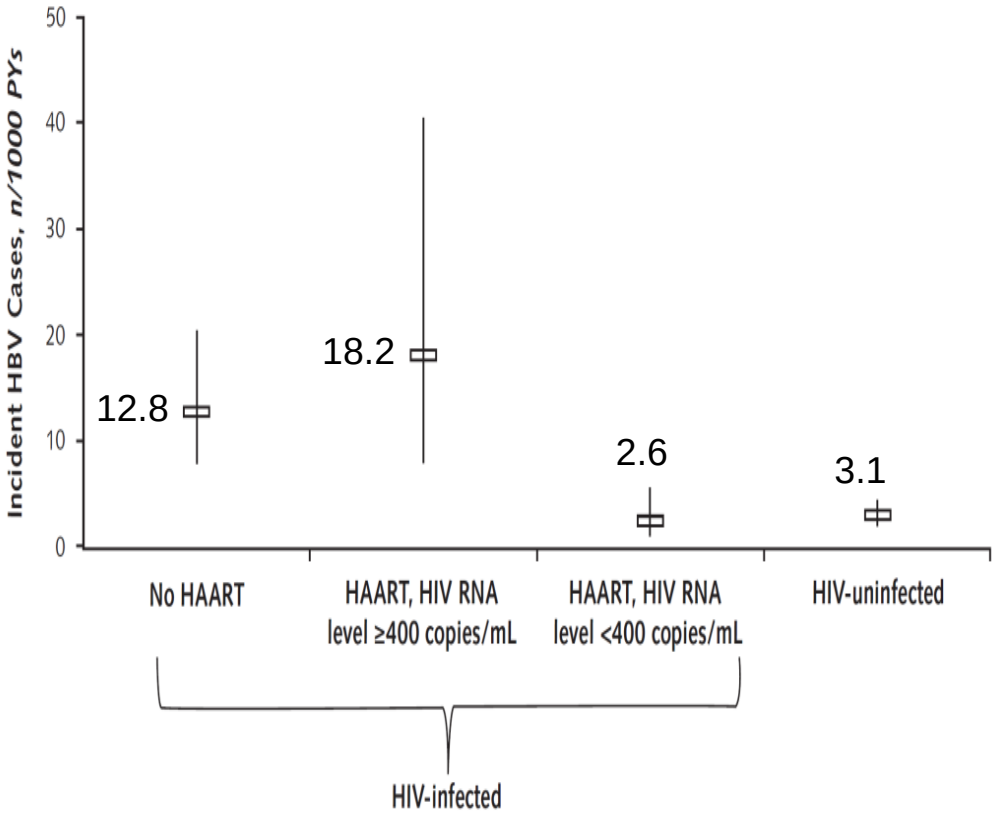
Annals of Internal Medicine ORIGINAL RESEARCH

Incident Hepatitis B Virus Infection in HIV-Infected and HIV-Uninfected Men Who Have Sex With Men From Pre-HAART to HAART Periods

A Cohort Study

Oluwaseun Falade-Nwulia, MD, MPH; Eric C. Seaberg, PhD; Anna E. Snider; Charles R. Rinaldo, PhD; John Phair, MD; Mallory D. Witt, MD; Chloe L. Thio, MD

- 2375 MSM enrolled in the multicenter AIDS cohort study from 1994 to 2003 with no HBV infection.
- Median follow-up: 9.5 years with 244 HBV infections: incidence rate of 9.6 per 1000 PYs (100 fold higher than in the general population).
- Effective ART was associated with reduced rates of incident HBV infection
- 6 of 262 men receiving ART regimens with an HBV-active drug (3TC/FTC or TDF) who had an HIV RNA level < 400 cp/ml developed HBV infection, with an incidence rate of 2.6 per 1000 PYs
- Receiving ≥1 dose of the HBV vaccine decreased the risk of HBV infection by 70%
- **There is an urgent need for HBV vaccination in MSM**



Falade-Nwulia et al. Ann Inter Med 2015

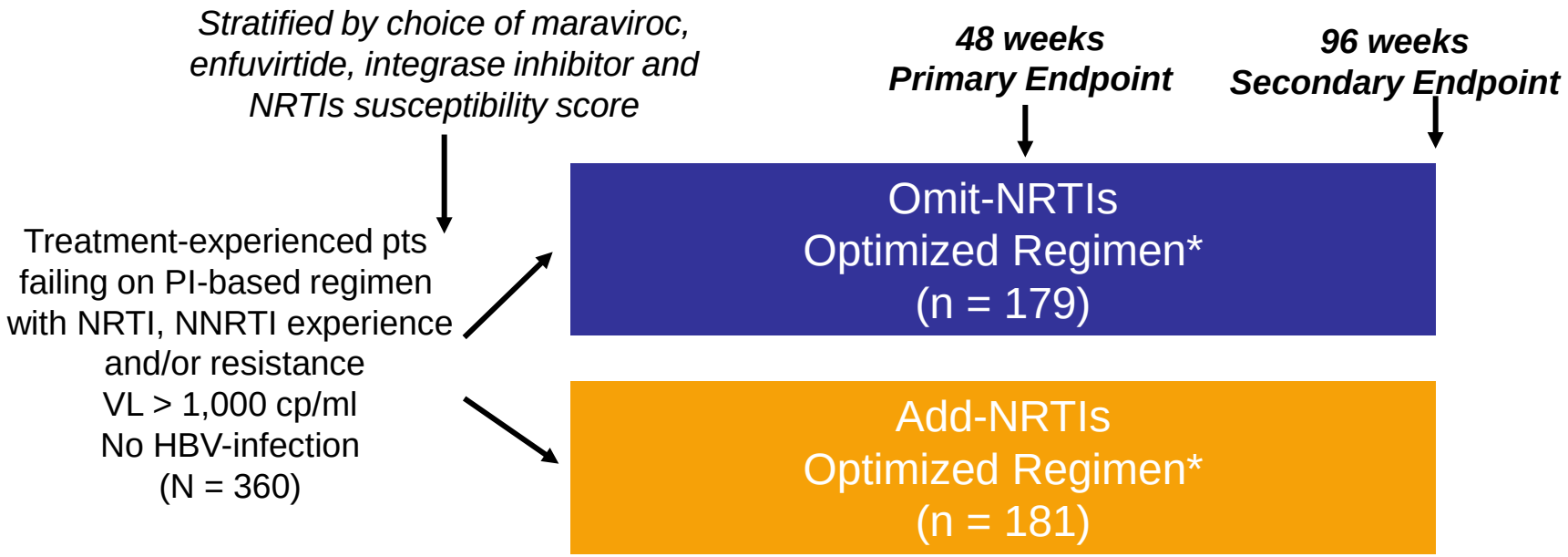
Annals of Internal Medicine ORIGINAL RESEARCH

HIV Salvage Therapy Does Not Require Nucleoside Reverse Transcriptase Inhibitors

A Randomized, Controlled Trial

Karen T. Tashima, MD; Laura M. Smeaton, MS; Carl J. Fichtenbaum, MD; Adriana Andrade, MD, MPH; Joseph J. Eron, MD; Rajesh T. Gandhi, MD; Victoria A. Johnson, MD; Karin L. Klingman, MD; Justin Ritz, MS; Sally Hodder, MD; Jorge L. Santana, MD; Timothy Wilkin, MD; and Richard H. Haubrich, MD, on behalf of the A5241 Study Team

- Randomized, non-inferiority, multicenter trial (OPTION - ACTG A5241)
  - Primary endpoint: regimen failure (VF or discontinue NRTI assignment)

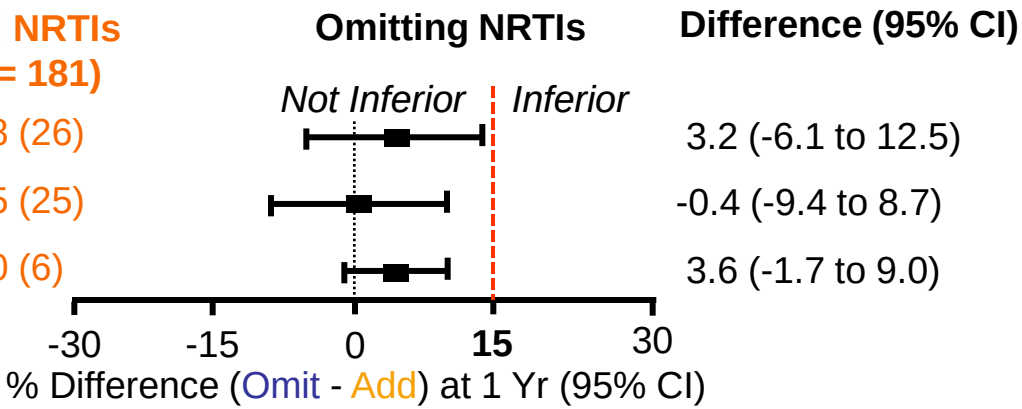


*choice based on treatment history, prior intolerance and genotypic and phenotypic viral resistance tests to construct a salvage regimen with a phenotypic susceptibility score > 2.

Tashima K, et al. Annals Intern Med 2015

Primary Outcome of Regimen Failure and Its Components

Outcome, n (%)	Omit NRTIs (n = 179)	Add NRTIs (n = 181)	Difference (95% CI)
Regimen failure	53 (30)	48 (26)	3.2 (-6.1 to 12.5)
Virologic failure	44 (25)	45 (25)	-0.4 (-9.4 to 8.7)
Stop NRTI assignment	19 (8)	10 (6)	3.6 (-1.7 to 9.0)



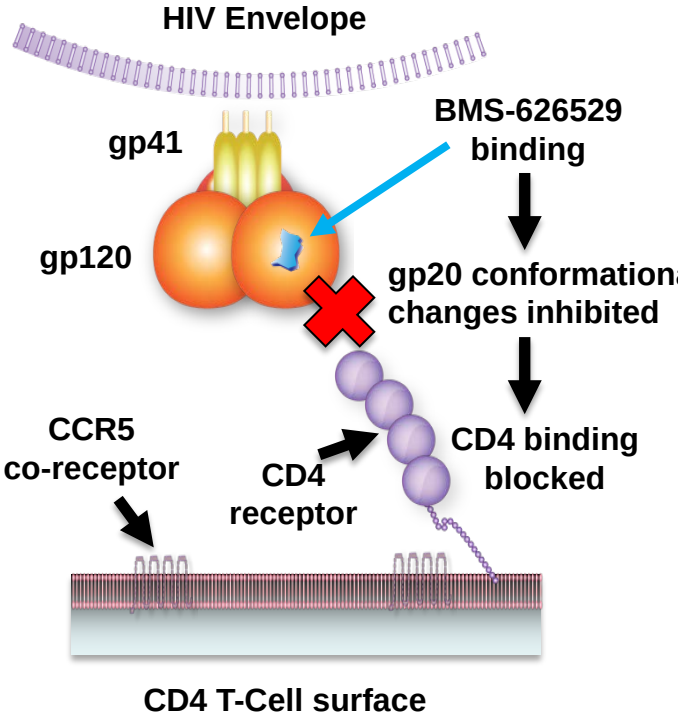
- Most common salvage ARV regimen used: DRV/r + raltegravir + either etravirine or maraviroc (86%) and most common NRTIs used: TDF+ FTC or 3TC (81%)
- Similar virologic suppression (HIV-1 RNA < 50 c/mL) in each arm (~ 65%) and similar CD4+ cell count increases in each arm (90-106 cells/mm^3)
- No significant difference in any safety outcome when globally evaluating symptoms and laboratory abnormalities, however:
  - Significant increase in non-HDL cholesterol in the omit-NRTIs arm
  - However, more deaths in add-NRTIs arm

Tashima KT, et al. Annals Intern Med 2015

Safety and efficacy of the HIV-1 attachment inhibitor prodrug BMS-663068 in treatment-experienced individuals: 24 week results of AI438011, a phase 2b, randomised controlled trial

Jacob P Lalezari, Gulam H Latiff, Cynthia Brinson, Juan Echevarría, Sandra Treviño-Pérez, Johannes R Bogner, Melanie Thompson, Jan Fourie, Otto A Sussmann Pena, Fernando C Mendo Urbina, Marcelo Martins, Iulian G Diaconescu, David A Stock, Samit R Joshi, George J Hanna, Max Lataillade, for the AI438011 study team

- Randomized, open-label, 96-week, Phase 2b study
  - Primary endpoints: proportion of patients with an HIV-1 RNA <50 cp/ml at week 24 and frequency of SAEs and AEs leading to discontinuation



Stratified by baseline AI IC_{50}
(25% not assessable - 6% not susceptible)

24 weeks Primary Endpoint

Treatment-experienced pts failing on 1st or 2nd line ART
VL > 1,000 cp/ml
> 50 CD4
No TDF, ATV or RAL resistance
AI IC_{50} < 100 nmol/L
(N = 254)

BMS-66068 400 to 1200 mg
TDF + Raltegravir
(n = 203)

Atazanavir/ritonavir
TDF + Raltegravir
(n = 51)

Antiviral Activity of the HIV-1 Attachment Inhibitor in Treatment-Experienced Patients

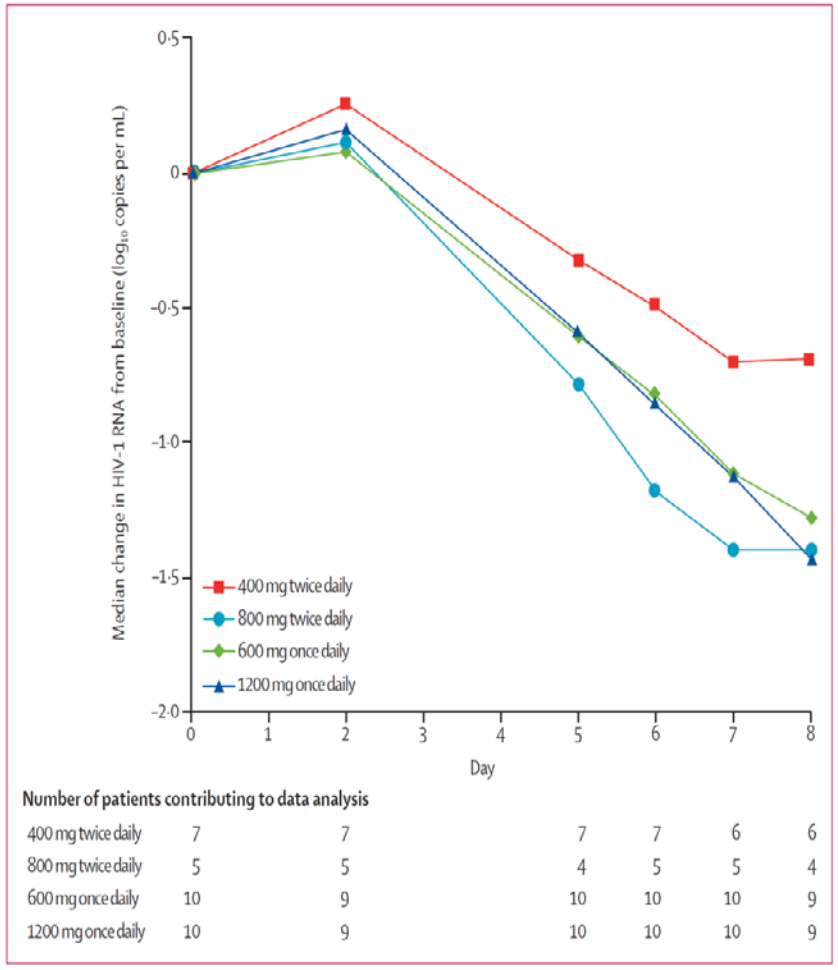


Figure 2: Median change in HIV-1 RNA viral load from baseline for patients participating in the BMS-663068 monotherapy substudy

	BMS-663068 + TDF + RAL				ATV/r + TDF + RAL n = 51
	400 mg BID 50	800 mg BID 49	600 mg QD 51	1200 mg QD 50	
HIV-1 RNA <50 c/mL	**80%**	**69%**	**76%**	**72%**	75%
HIV-1 RNA ≥50 c/mL %	16.%	20%	22%	26%	18%
Discontinued due to AE or death, n (%)	1 2%	2 4%	0	1 2%	2 4%
HIV-1 RNA <400 c/mL, %	92%	80%	90%	80%	82%

- No patients who met criteria for resistance testing in the ATV/R developed drug resistance
- 40% of patients (8/19) who failed in the AI arm had virus with a 3-fold increase in IC_{50} from baseline and 4/8 also developed raltegravir resistance

Lalezari et al. Lancet HIV 2015

Empirical tuberculosis therapy versus isoniazid in adult outpatients with advanced HIV initiating antiretroviral therapy (REMEMBER): a multicountry open-label randomised controlled trial

Lancet 2016; 387: 1198–209
See Editorial page 1134
See Comment page 1141
*Contributed equally

Mina C Hosseinipour, Gregory P Bisson*, Sachiko Miyahara, Xin Sun, Agnes Moses, Cynthia Riviere, Fredrick K Kirui, Sharlaa Badal-Faesen, David Lagat, Mulinda Nyirenda, Kogieleum Naidoo, James Hakim, Peter Mugyenyi, German Henostroza, Paul D Leger, Javier R Lama, Lerato Mohapi, Jorge Alave, Vidya Mave, Valdilea G Veloso, Sandy Pillay, Nagalingeswaran Kumarasamy, Jing Bao, Evelyn Hogg, Lynne Jones, Andrew Zolopa, Johnstone Kumwenda, Amita Gupta, for the Adult AIDS Clinical Trials Group A5274 (REMEMBER) Study Team†*

Stratified by CD4 counts (> or < 25) and prognosis factors (BMI, anemia, hospital admission)

24 weeks
Primary Endpoint

96 weeks
End of Follow-up

Treatment-naive pts
TB excluded
(symptoms screen, chest X-ray sputum smears using GeneXpert) and cultures)
CD4 < 50 cells/mm^3
ALT < 2.5 ULN
(N = 850)

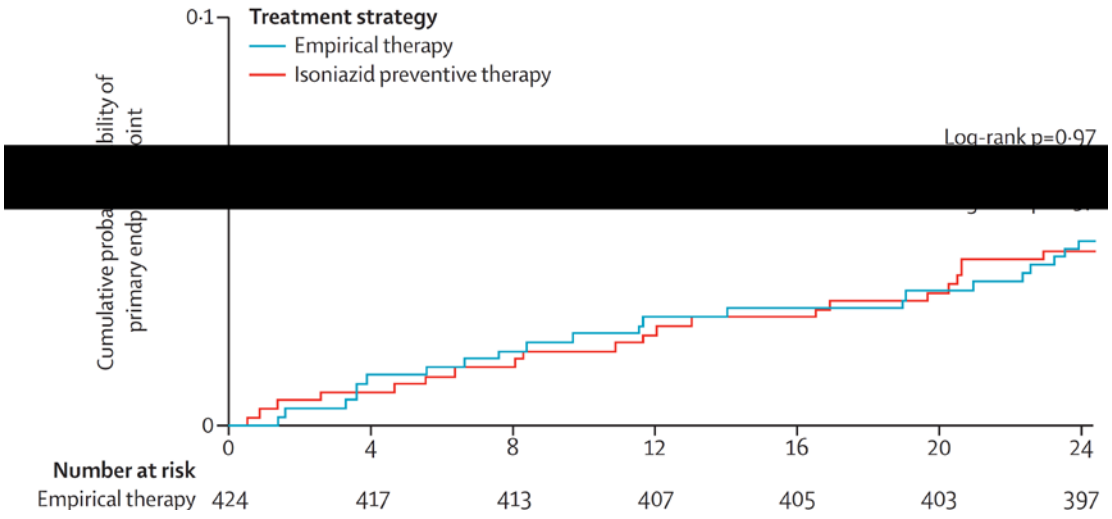
TB treatment
+ EFV-containing ART (n = 424)

INH Therapy
+ EFV-containing ART (n = 426)

Primary endpoint: survival (death or unknwon status)
Study powered to detect a 7.5% difference in death rate

Hosseinipour M et al. Lancet 2016

Cumulative Probability of Time to Death or Probable or confirmed TB



- At week 24, 5% of participants from each group died or were of unknown status: absolute risk difference of -0·06% (95% CI -3·05 to 2·94).
- Higher rate of TB in the empirical arm (31 vs 18 in the INH group) with more Rx discontinuations (11% vs 4%)
- Grade 3 or 4 signs or symptoms occurred in 12% in the empirical group and 11% in the INH arm.
- Grade 3 or 4 lab abnormalities occurred in 23% of participants in both arms.
- TB drug resistance in 3 patients per arm
- No benefit in rate of bacterial infections (9% vs 12%, p = 0.095)

Hosseinipour M et al. Lancet 2016