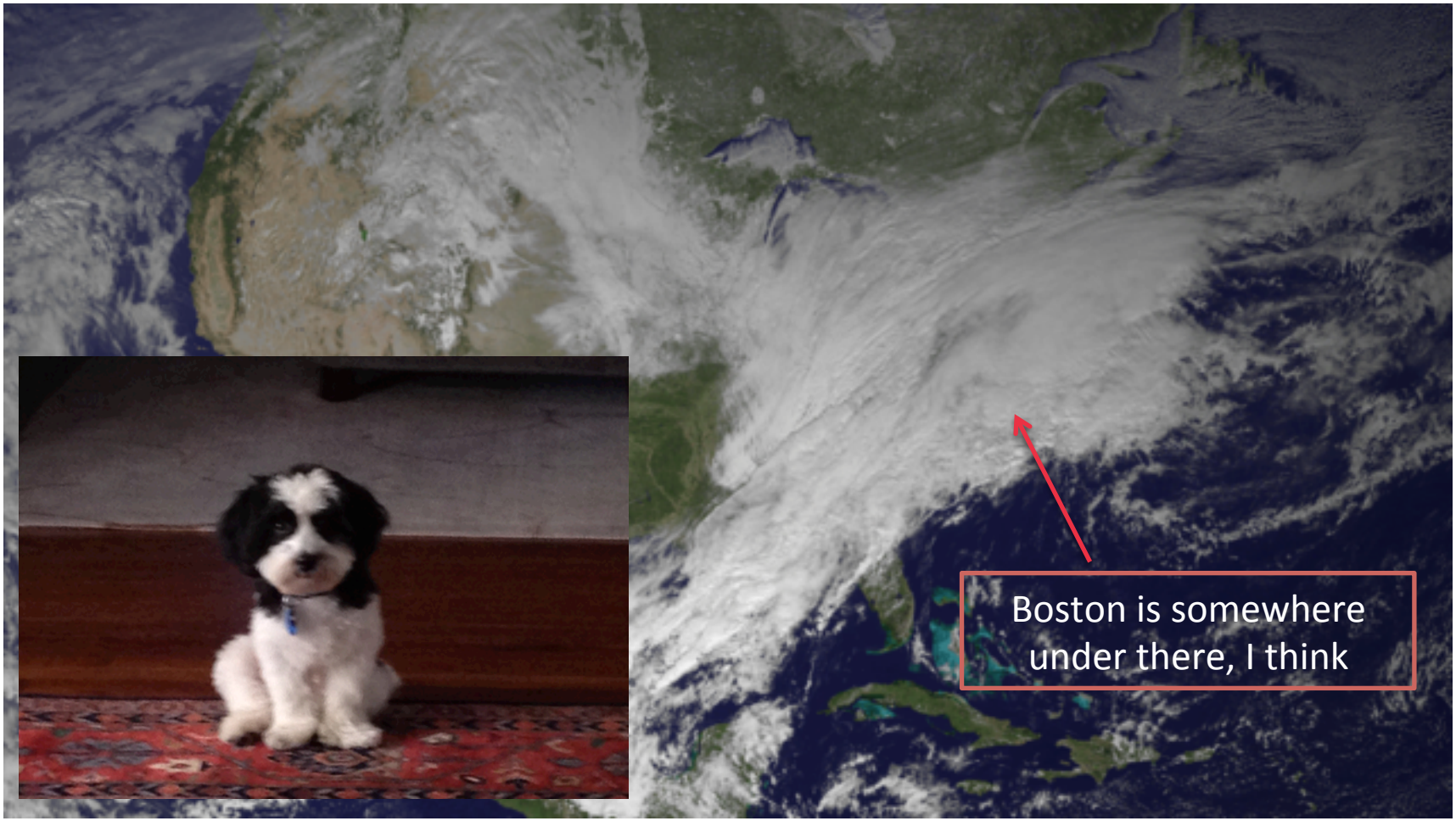
The Most Important Studies in HIV Medicine in the Past Year, and Why

Paul E. Sax, M.D.
Clinical Director, Division of Infectious Diseases
Brigham and Women's Hospital
Professor of Medicine
Harvard Medical School

Delighted to be in LA



Most Important Studies: The Rules

- Focus on prevention and treatment
- Presented, published, or released in past 12 months
- Will influence policy, research agenda, or clinical care
- No basic science – no gels
- Apologies for:
  - Omitting your favorites
  - Being biased toward my co-investigators and colleagues

Prevention

Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial

Kachit Choopanya, Michael Martin, Pravan Suntharasamai, Udomsak Sangkum, Philip A Mock, Manoj Leethochawalit, Sithisat Chiamwongpaet, Praphan Kitisin, Pitinan Natrujirote, Somyot Kittimunkong, Rutt Chuachoowong, Roman J Gvetadze, Janet M McNicholl, Lynn A Paxton, Marcel E Curlin, Craig W Hendrix, Suphak Vanichseni, for the Bangkok Tenofovir Study Group

- Randomized clinical trial of tenofovir vs placebo to prevent HIV
- DOT option based on investigator discretion
- n = 2413; median age 31, 80% men; < 10% injected daily, 18% shared needles

Choopanya K, et al. Lancet 2013.

PrEP for IDUs: Results

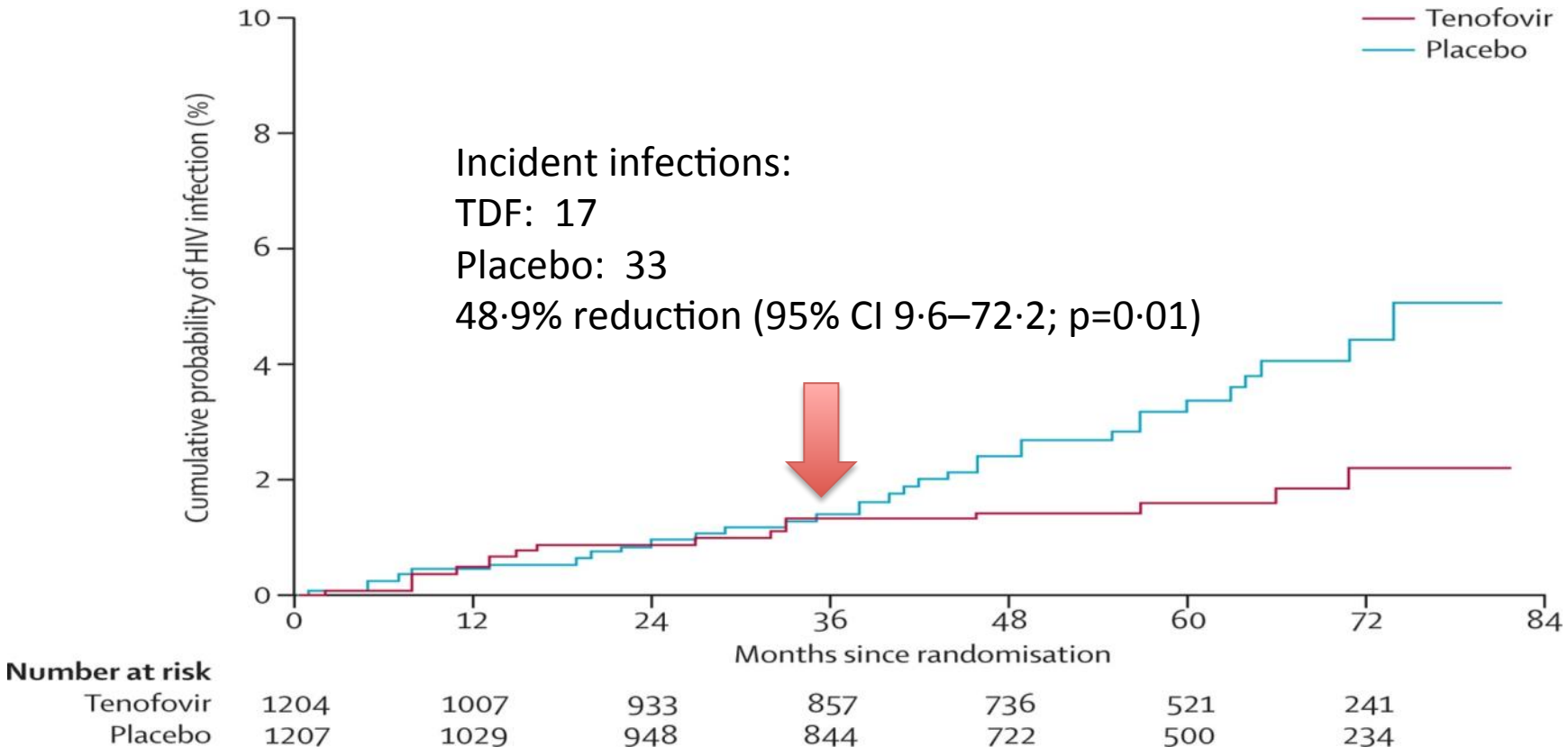


Figure 2 Kaplan-Meier estimates of time to HIV infection in the modified intention-to-treat population

Choopanya K, et al. Lancet 2013.

PrEP for IDUs: Other Findings

- Incidence much lower than anticipated
- Efficacy increased with adherence – 74% reduction in risk for those with detectable drug levels
- Higher adherence in women and those older than 40
- More nausea in TDF group; no renal toxicity
- No incident resistance detected

Morbidity and Mortality Weekly Report

Update to Interim Guidance for Preexposure Prophylaxis (PrEP) for the Prevention of HIV Infection: PrEP for Injecting Drug Users

- Issued concurrently with publication of paper
- Recommendations
  - Consider for those at "very high risk", meaning: sharing of equipment, injecting daily, using cocaine or crystal meth
  - Critical to exclude HIV first
  - Use TDF/FTC (not tenofovir)

MMWR June 14 2013.

PrEP in IDUs: Questions and Implications

- Why was the incidence so low?
- Why did efficacy not become apparent until year 3?
- Was the CDC guidance appropriate? Was it needed?
- Can these findings be broadened to highest risk regions (e.g., Vietnam, Eastern Europe)?

The New York Times

U.S.

WORLD | U.S. | N.Y. / REGION | BUSINESS | TECHNOLOGY | SCIENCE | HEALTH | SPORTS | OPINION

POLITICS | EDUCATION | TEXAS

Heroin in New England, More Abundant and Deadly

Cheryl Senter for The New York Times

A Deadly Dance: In Maine, a surge in heroin use is contributing to a rash of fatal overdoses.

New York Times, July 2013.

VOICE: PrEP not Effective Due to Poor Adherence

N=5029 HIV- Women: Primary Efficacy Results (mITT)

	TDF	Oral Placebo	FTC/TDF	Oral Placebo	TFV Gel	Gel Placebo
Person-years	823	837	1285	1306	1026	1030
No. of HIV Infections	52	35	61	60	61	70
HIV incidence per 100 p-y	6.3 (4.7, 8.3)	4.2 (2.9, 5.8)	4.7 (3.6, 6.1)	4.6 (3.5, 5.9)	5.9 (4.5, 7.6)	6.8 (5.3, 8.6)
% samples with TFV detected	30%		29%		25%	
% women with no TFV detected ever	58%		50%		55%	

Marrazzo J, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 26LB.

A Resisted Pill to Prevent H.I.V.

Chester Higgins Jr./The New York Times

Damon Jacobs, a New York psychotherapist, began taking Truvada after a breakup. He said he was not using a condom as consistently as he had been, "and that scared me greatly."

By DAVID TULLER
Published: December 30, 2013

New York Times, Dec 30 2013.

ORIGINAL ARTICLE

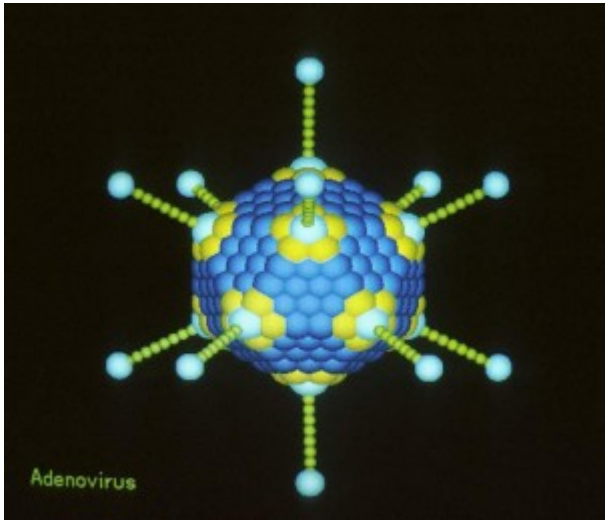
Efficacy Trial of a DNA/rAd5 HIV-1 Preventive Vaccine

Scott M. Hammer, M.D., Magdalena E. Sobieszczyk, M.D., M.P.H., Holly Janes, Ph.D., Shelly T. Karuna, M.D., Mark J. Mulligan, M.D., Doug Grove, M.S., Beryl A. Koblin, Ph.D., Susan P. Buchbinder, M.D., Michael C. Keefer, M.D., Georgia D. Tomaras, Ph.D., Nicole Frahm, Ph.D., John Hural, Ph.D., Chuka Anude, M.D., Ph.D., Barney S. Graham, M.D., Ph.D., Mary E. Enama, M.A., P.A.-C., Elizabeth Adams, M.D., Edwin DeJesus, M.D., Richard M. Novak, M.D., Ian Frank, M.D., Carter Bentley, Ph.D., Shelly Ramirez, M.A., Rong Fu, M.S., Richard A. Koup, M.D., John R. Mascola, M.D., Gary J. Nabel, M.D., Ph.D., David C. Montefiori, Ph.D., James Kublin, M.D., M.P.H., M. Juliana McElrath, M.D., Ph.D., Lawrence Corey, M.D., and Peter B. Gilbert, Ph.D., for the HVTN 505 Study Team*

Hammer SM, et al. N Engl J Med 2013.

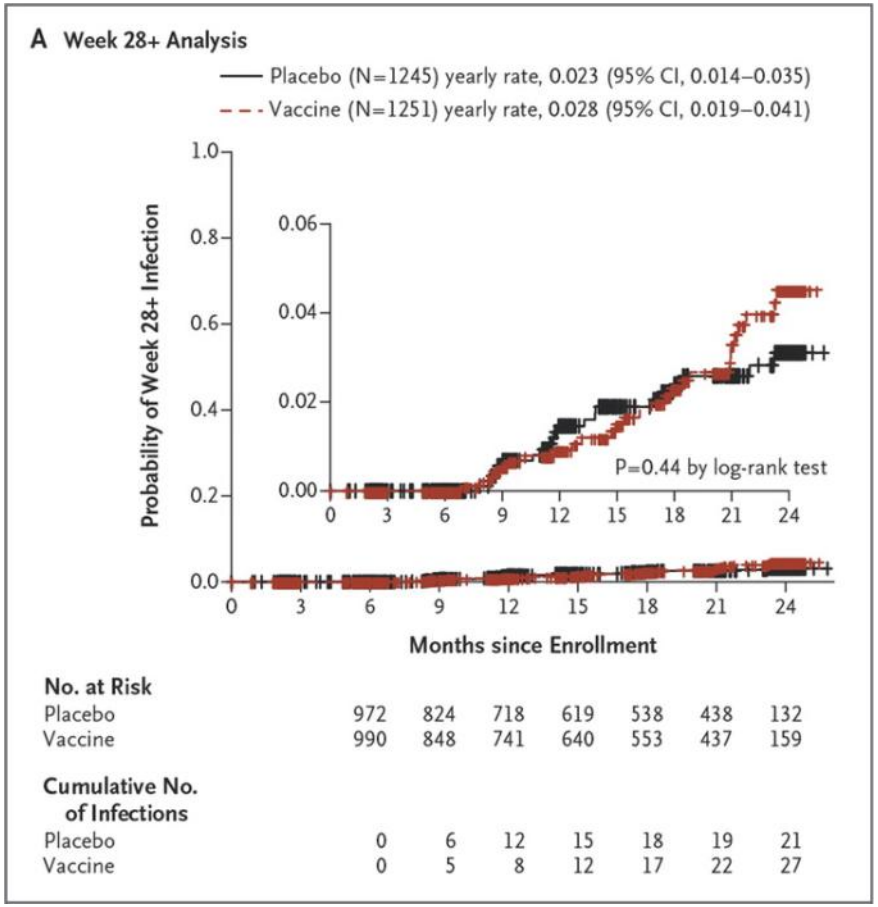
HVTN 505: DNA/rAd5 Vaccine Study

- Randomized, double-blind, placebo-controlled trial in HIV negative, high-risk MSM or transgender women seronegative for Ad5
- Intervention: "Multigene, multiclade DNA prime–recombinant adenovirus type 5 vector boost (DNA/rAd5) vaccine" vs placebo
- n = 2499; 70% white, median age 29
- Primary endpoints: 1) incidence of HIV; 2) HIV RNA set point



HVTN 505: Results

- Study stopped early for futility
- Infections after week 24:
  - Vaccine: 28
  - Placebo: 21
- No beneficial effect of vaccine on set-point
- Some immune responses detected – not associated with protection



Hammer SM, et al. N Engl J Med 2013.

The HIV Vaccine Effort to Date

- Billions of dollars (nearly 1 billion annually) invested in research effort – basic and clinical
- Six efficacy studies
  - 1 slightly effective
  - 1 (and possibly 2) *increased* infection risk
  - 3 did nothing
- In the context of effective treatment and other prevention strategies, how important is continued high-level research funding?

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Cost-Effectiveness of HIV Treatment as Prevention in Serodiscordant Couples

Rochelle P. Walensky, M.D., M.P.H., Eric L. Ross, B.A., Nagalingeswaran Kumarasamy, M.B., B.S., Ph.D., Robin Wood, D.Sc., Farzad Noubary, Ph.D., A. David Paltiel, Ph.D., M.B.A., Yoriko M. Nakamura, B.A., Sheela V. Godbole, M.D., Ravindre Panchia, M.B., B.Ch., Ian Sanne, M.B., B.Ch., D.T.M.&H., Milton C. Weinstein, Ph.D., Elena Losina, Ph.D., Kenneth H. Mayer, M.D., Ying Q. Chen, Ph.D., Lei Wang, Ph.D., Marybeth McCauley, M.P.H., Theresa Gamble, Ph.D., George R. Seage III, D.Sc., M.P.H., Myron S. Cohen, M.D., and Kenneth A. Freedberg, M.D.

Walensky RW, et al. N Engl J Med 2013.

What does it mean if something is "cost effective"?

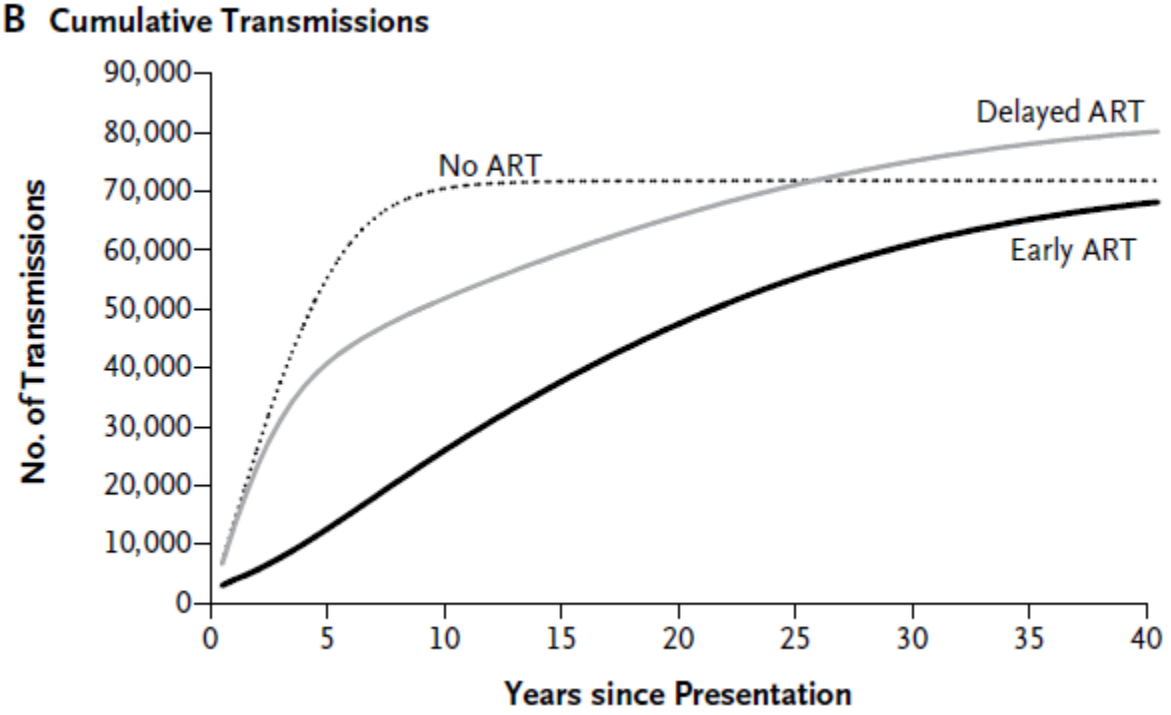
- Think of it as "good value for money spent"
- It does NOT mean that money is saved – very few interventions are cost-saving
  - One notable cost-saving example: childhood immunizations
- The key metric is how much is spent for a health benefit – often expressed as "dollars/ year of life saved" or "dollars/case prevented"

Cost-effectiveness of Early ART

- Collaboration between CEPAC group and HPTN 052 study team
- Comparison of early vs delayed ART for serodiscordant couples in South Africa and India
- Data from 052 used to populate model
- Both clinical and transmission outcomes considered

Walensky RW, et al. N Engl J Med 2013.

Cost-effectiveness of Early ART: Results



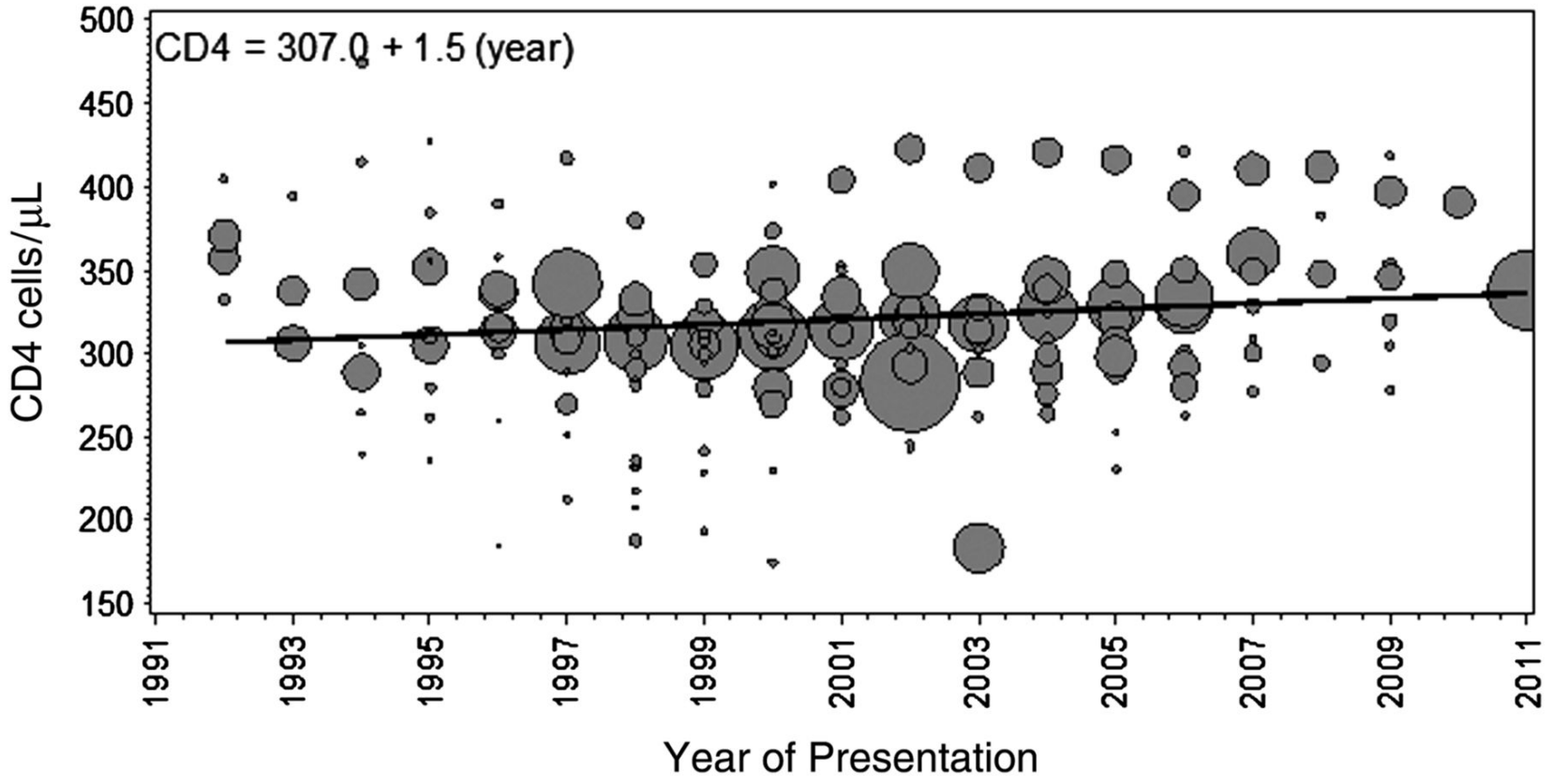
- Early ART prolonged survival and prevented transmissions
- In the first 5 years, it was cost-saving in South Africa; it was highly cost-effective over the lifetime of the patient in both countries
- Results stable through numerous sensitivity analyses

CEA of Early ART: Policy Implications

- Early treatment of HIV in South Africa will initially *save money*
  - Savings from prevention of HIV-related complications and reduced transmissions
- In both countries, it is highly cost-effective
- For policy-makers, this should be a fastball down the middle of the plate

Walensky RW, et al. N Engl J Med 2013.

Mean CD4 at Presentation – A Figure with a Depressingly Flat Slope



Lesko C R et al. Clin Infect Dis. 2013;57:1027-1037

Clinical Infectious Diseases

INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY SEPTEMBER 2013, VOL. 34, NO. 9

US PUBLIC HEALTH SERVICE GUIDELINE

Updated US Public Health Service Guidelines for the Management of Occupational Exposures to Human Immunodeficiency Virus and Recommendations for Postexposure Prophylaxis

David T. Kuhar, MD;[1] David K. Henderson, MD;[2] Kimberly A. Struble, PharmD;[3] Walid Heneine, PhD;[4] Vasavi Thomas, RPh, MPH;[4] Laura W. Cheever, MD, ScM;[5] Ahmed Gomaa, MD, ScD, MSPH;[6] Adelisa L. Panlilio, MD;[1] for the US Public Health Service Working Group

- Quiz: Prior to this version, when were these guidelines previously updated?

A. 2005
B. 2007
C. 2009
D. 2011

Kuhar DT, et al. Inf Cont Hosp Epi 2013.

Revised Guidelines for Occupational PEP

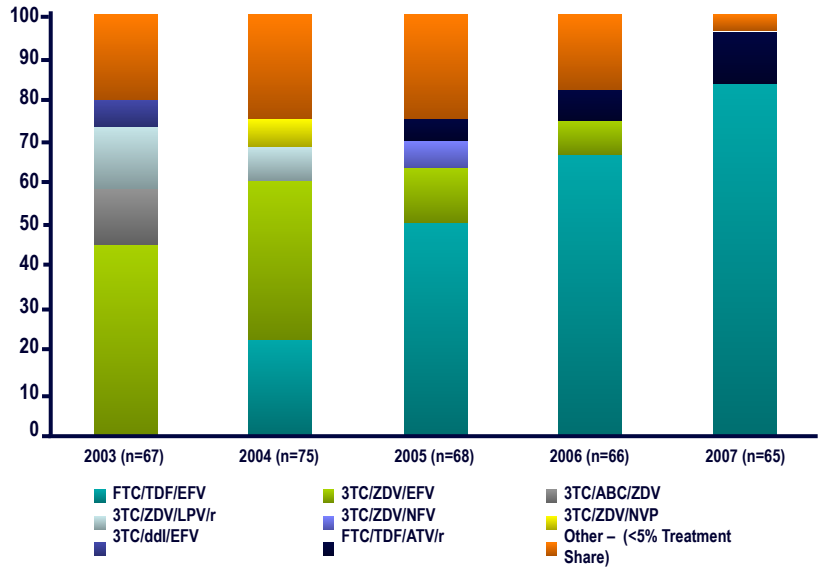
- First choice: TDF/FTC, raltegravir x 28 days
  - Numerous alternatives, including TDF/FTC/EVG/COBI
- No two-drug options for low-risk exposures
- No need to r/o window period in source patient
- "Expert consultation" recommended for complex cases
- Follow-up shortened to 4 months if 4th generation Ag/Ab combination test is used
  - NY State Guidelines: only 3 months needed

Kuhar DT, et al. Inf Cont Hosp Epi 2013; www.hivguidelines.org

Treatment

A Slide of Historical Interest

Convergence of First-Line Regimens: Alabama



In 2007, 95% started either TDF/FTC/EFV (85%) or TDF/ FTC + ATV/r (10%).

McKinnell J, et al. 48th ICAAC/46th IDSA; Washington, DC; October 25-28. Abst. H-1260

Slide presented here October, 2009.

What a Year for Integrase Inhibitors (in particular dolutegravir)

- The following studies all presented and/or published in past year
  - SPRING-2
  - SINGLE
  - FLAMINGO
  - SAILING
- TDF/FTC/EVG/Cobi: no new cases of renal tubulopathy in long-term f/u

Once-daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study

Francois Raffi, Anita Rachlis, Hans-Jürgen Stellbrink, W David Hardy, Carlo Torti, Chloe Orkin, Mark Bloch, Daniel Podzamczer, Vadim Pokrovsky, Federico Pulido, Steve Almond, David Margolis, Clare Brennan, Sherene Min, on behalf of the SPRING-2 study group

Sharon L. Walmsle… Dan Duicules… Laurent Hocque… Catherine Gra… Sherene Min, M.…

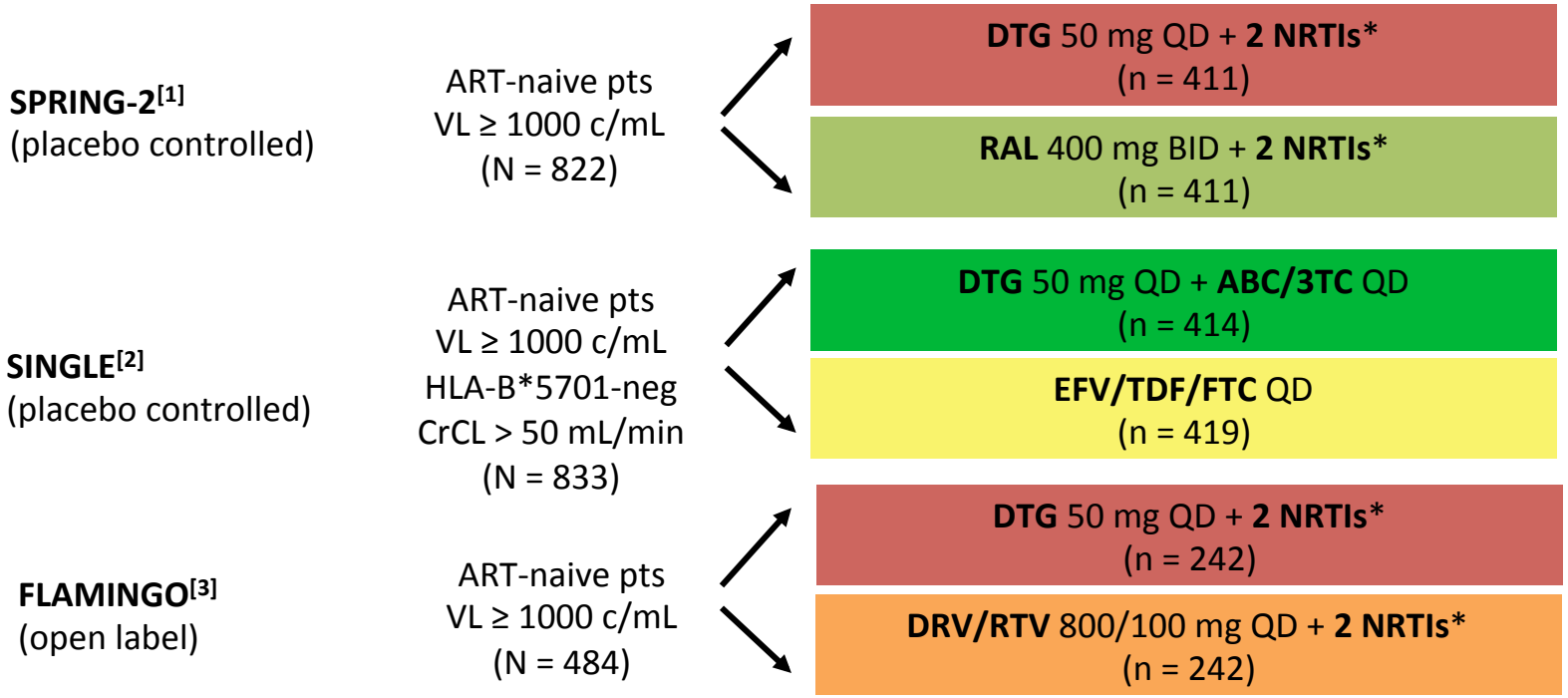
…than Clumeck, M.D., …Gutiérrez, M.D., … Sandkovsky, M.D., …an Wynne, M.D., …IGLE Investigators*

Dolutegravir versus raltegravir in antiretroviral-experienced, integrase-inhibitor-naive adults with HIV: week 48 results from the randomised, double-blind, non-inferiority SAILING study

Pedro Cahn, Anton L Pozniak, Horacio Mingrone, Andrey Shuldyakov, Carlos Brites, Jaime F Andrade-Villanueva, Gary Richmond, Carlos Beltran Buendia, Jan Fourie, Moti Ramgopal, Debbie Hagins, Franco Felizarta, Jose Madruga, Tania Reuter, Tamara Newman, Catherine B Small, John Lombaard, Beatriz Grinsztejn, David Dorey, Mark Underwood, Sandy Griffith, Sherene Min, on behalf of the extended SAILING Study Team

Dolutegravir vs Currently "Preferred" Regimens in Treatment-Naive Pts

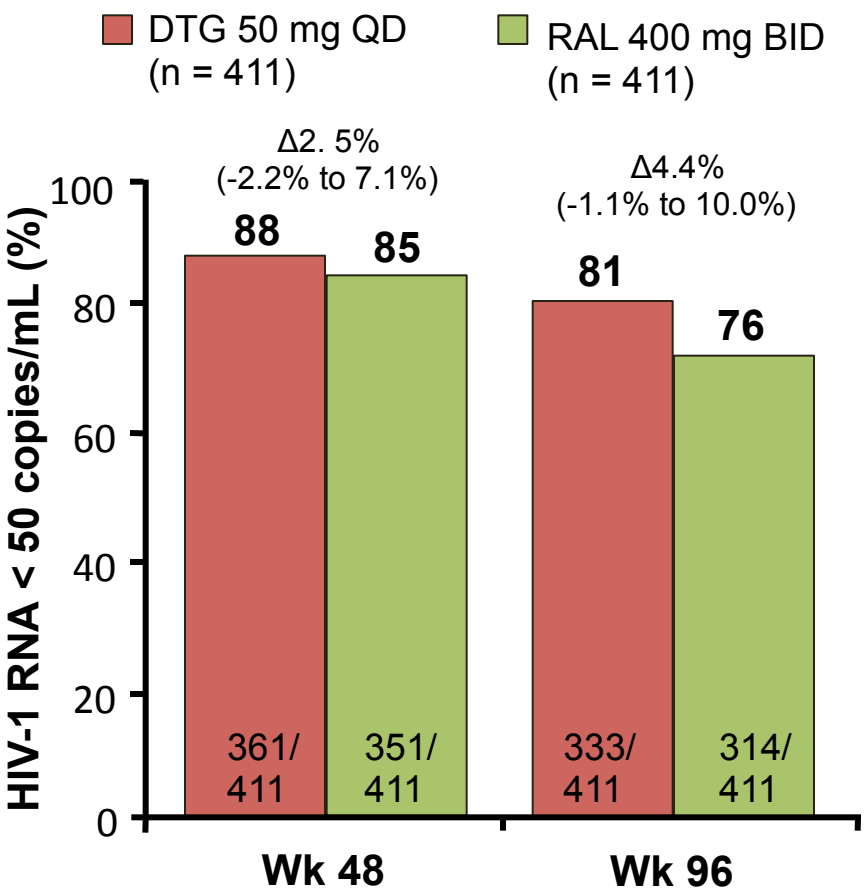
- Randomized, noninferiority phase III studies
- Primary endpoint: HIV-1 RNA < 50 c/mL at Wk 48



*Investigator-selected NRTI backbone: either TDF/FTC or ABC/3TC.

1. Raffi F, et al. Lancet. 2013;381:735-743. 2. Walmsley S, et al. N Engl J Med 2013;
3. Feinberg J, et al. ICAAC 2013. Abstract H1464a.

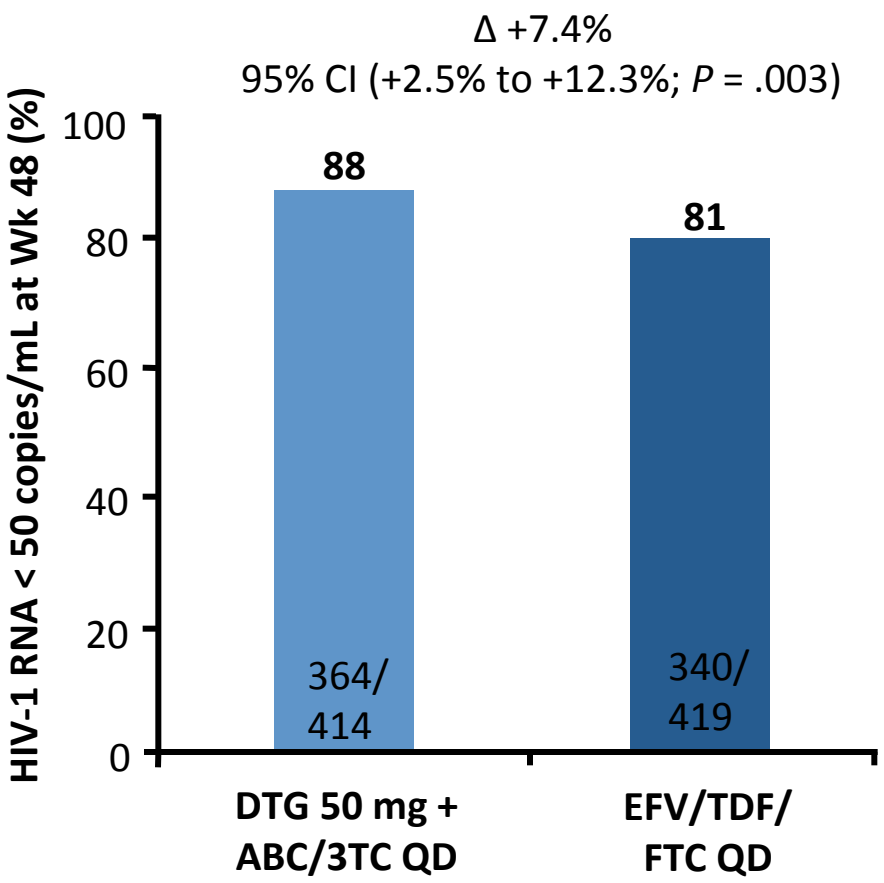
SPRING-2: Raltegravir vs Dolutegravir



- DTG noninferior to RAL at both Wk 48 primary endpoint[1] and Wk 96[2]
- Treatment-related study d/c: 2% in each arm at Wk 96
- VF at Wk 96[2]: 5% (22/411) in DTG arm and 7% (29/411) in RAL arm
- CD4+ cell count increase at Wk 96 similar:
  - +276 cells/mm^3 (DTG) vs +264 cells/mm^3 (RAL)
- No DTG resistance

1. Raffi F, et al. Lancet. 2013;381:735-743. 2. Raffi F, et al. IAS 2013. Abstract TULBPE17.

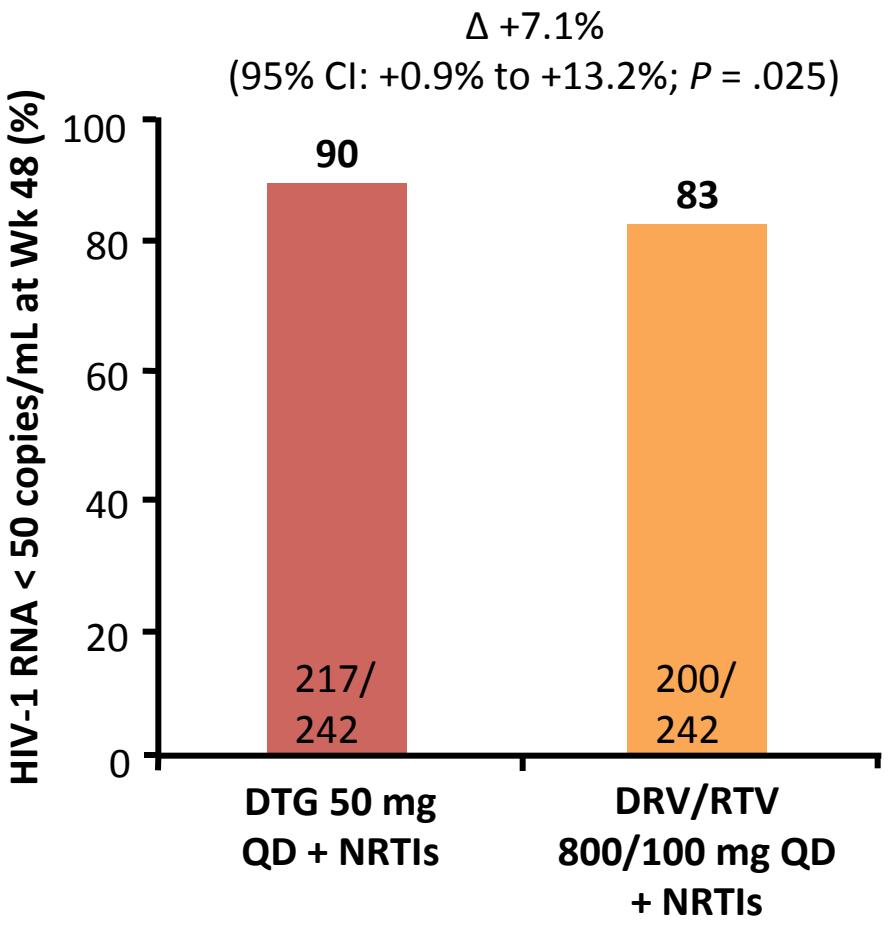
SINGLE: DTG + ABC/3TC vs EFV/TDF/FTC



- DTG superior to EFV at Wk 48
- Treatment-related study d/c: 2% in DTG vs 10% in EFV arm
- VF at Wk 48: 4% (18/414) in DTG arm and 4% (17/419) in EFV arm
- CD4+ cell count increase at Wk 48 greater with DTG:
  - +267 cells/mm^3 (DTG) vs
  - +208 cells/mm^3 (EFV) ($P < .001$)
- No DTG resistance

Walmsley S, et al. N Engl J Med 2013.

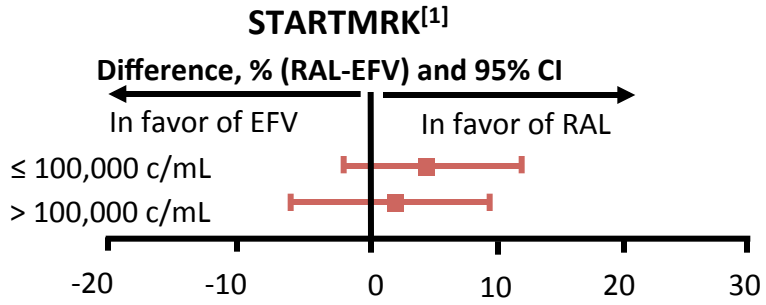
FLAMINGO: DTG vs DRV/RTV

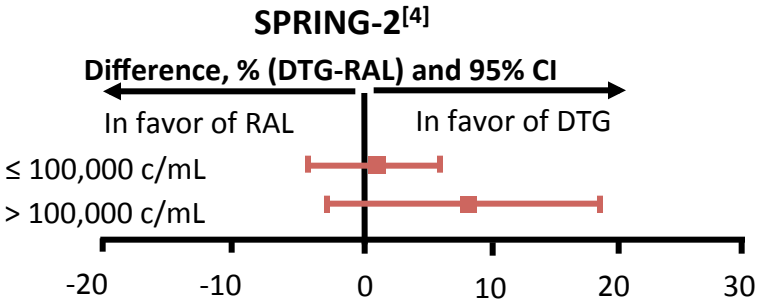


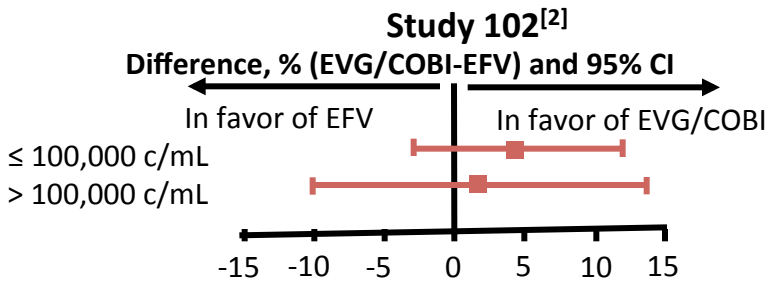
- DTG superior to DRV/RTV at Wk 48 primary efficacy endpoint
  - Treatment-related study d/c: 2% in DTG arm vs 4% in DRV/RTV arm
- VF at Wk 48: < 1% (n = 2) in each arm
- CD4+ cell count increase at Wk 48 similar:
  - +210 cells/mm^3 in each arm
- No DTG resistance

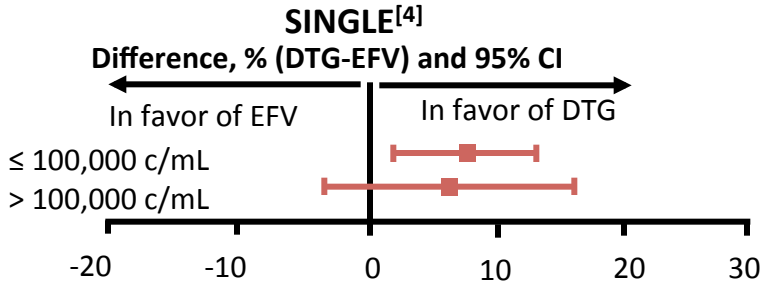
Feinberg J, et al. ICAAC 2013. Abstract H1464a.

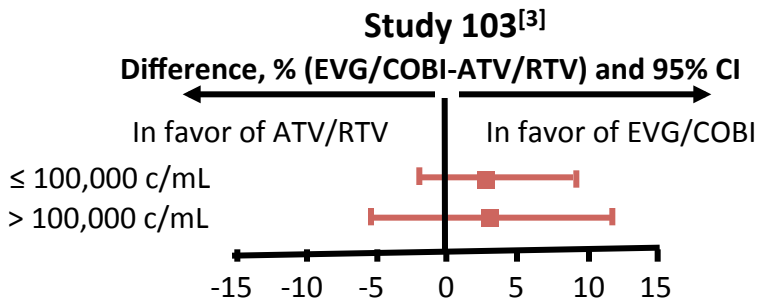
Activity of Integrase-based Therapies Maintained at High HIV RNA

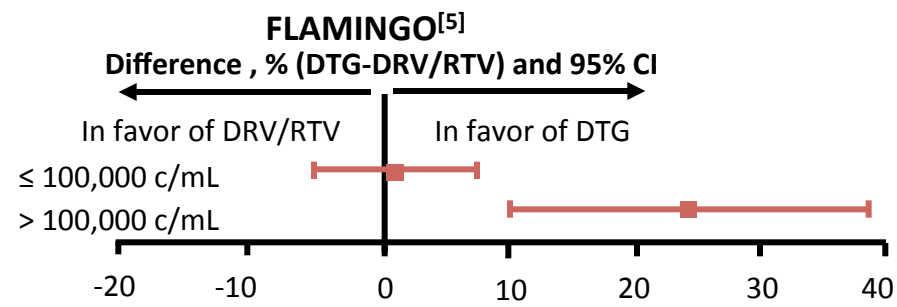












1. Lennox J, et al. Lancet. 2009;374:796-806. 2. Sax PE, et al. Lancet. 2012;379:2439-2448. 3. De Jesus E, et al. Lancet. 2012;379:2429-2438. 4. Brinson C, et al. CROI 2013. Abstract 554. 5. Feinberg J, et al. ICAAC 2013. Abstract H1464a.

DHHS 2013: What to Start

	Preferred Regimens	Alternative Regimens
NNRTI	▪ EFV/TDF/FTC	▪ EFV + ABC/3TC ▪ RPV/TDF/FTC or RPV + ABC/3TC
Boosted PI	▪ ATV/RTV + TDF/FTC ▪ DRV/RTV + TDF/FTC	▪ ATV/RTV + ABC/3TC ▪ DRV/RTV + ABC/3TC ▪ FPV/RTV + (TDF/FTC or ABC/3TC) ▪ LPV/RTV + (TDF/FTC or ABC/3TC)
INSTI	▪ RAL + TDF/FTC ▪ EVG/COBI/TDF/FTC ▪ DTG + ABC/3TC ▪ DTG + TDF/FTC	▪ RAL + ABC/3TC

- Are integrase-based regimens now our best initial options?

DHHS Guidelines. February 2013. DHHS Recommendation on INSTIs. October 2013.

Another Slide of Historical Interest

Many "3rd Drug" Potential Choices – Influence of Recent Data

- NNRTI
  - **Efavirenz**
  - Nevirapine
- Ritonavir-boosted PIs
  - **Atazanavir**
  - **Darunavir**
  - Fosamprenavir
  - Lopinavir
  - Saquinavir
- Integrase inhibitor
  - **Raltegravir**

Compared in ACTG 5257 – *enrolling now!*

Slide presented here October, 2009.

Efficacy of Initial Therapy: The Flat Part of an Asymptotic Function

- Premise: Current initial HIV therapy cannot be improved virologically
- Novel treatments must offer safety, tolerability or economic benefits – or they must be curative
- The following studies should be viewed in this context

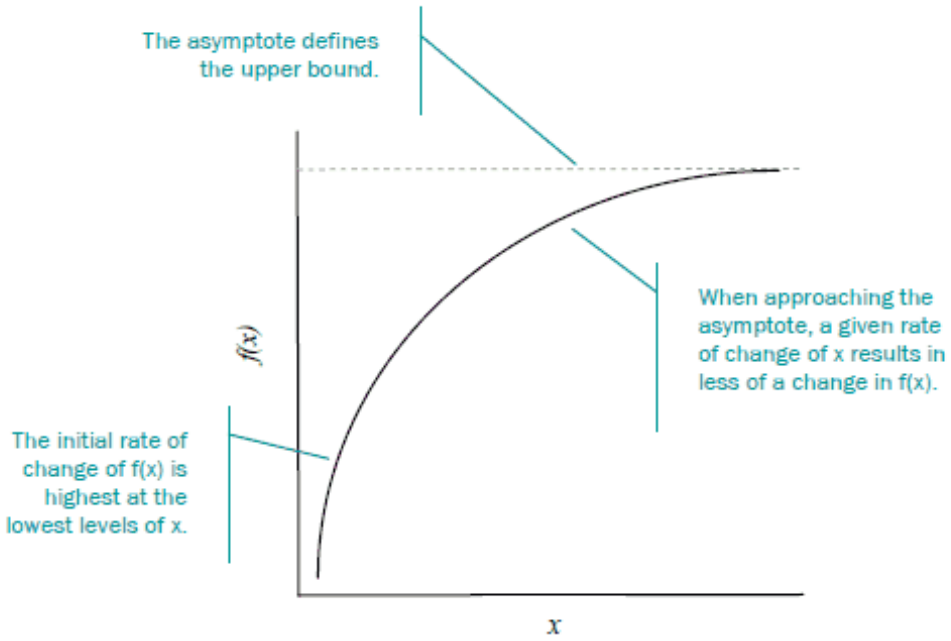
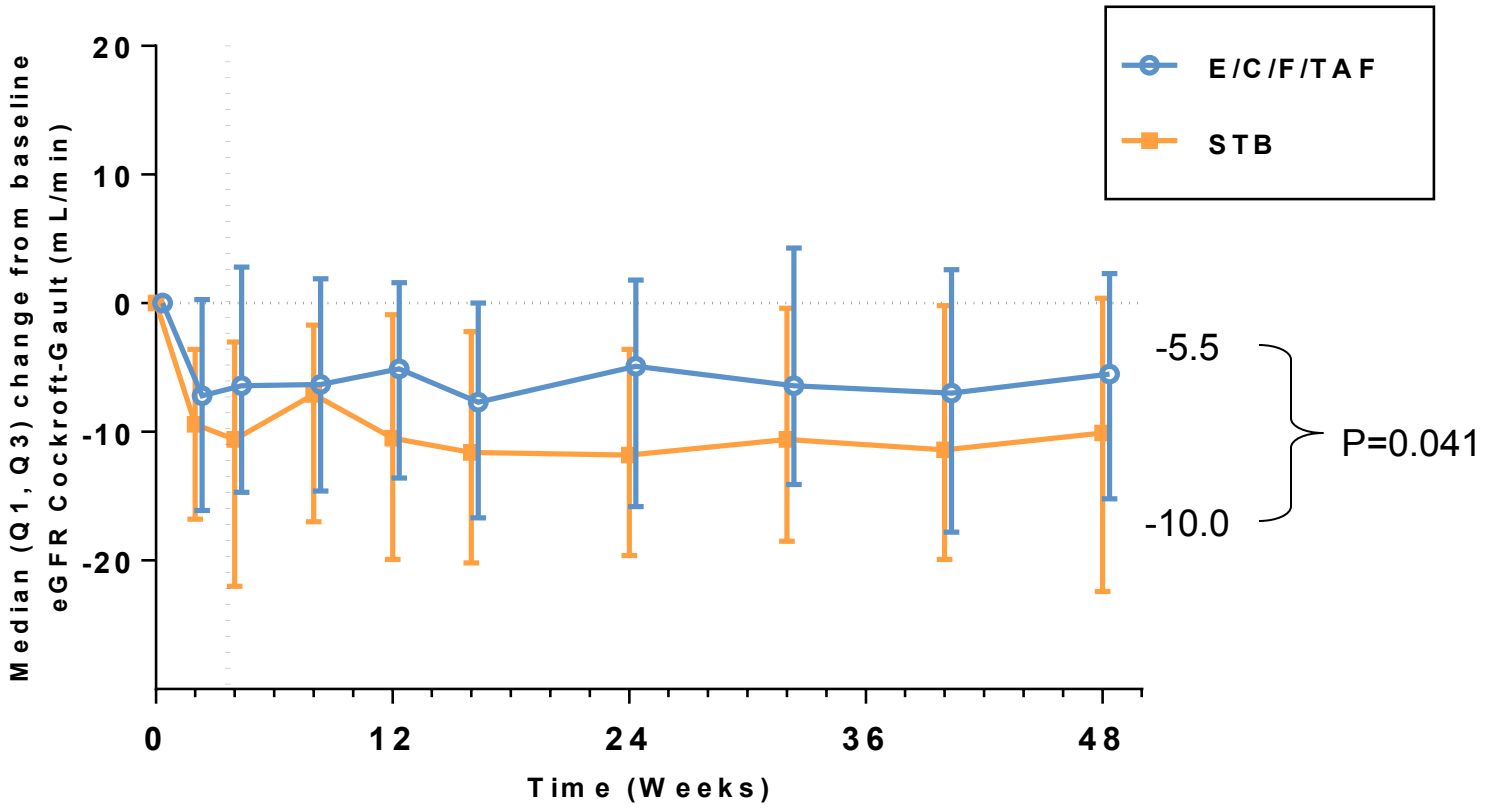


Figure 2-3 — General Asymptotic Function

Tenofovir Alafenamide (TAF): Pro-drug of Tenofovir

- Achieves 5x higher intracellular concentrations with 90% lower plasma levels
- Potential benefits
  - Reduced renal and bone toxicity
  - Much smaller dose allows smaller pill, novel coformulations
  - Activity vs some TDF-resistant strains
  - Reduced cost of production
- Phase III studies fully enrolled

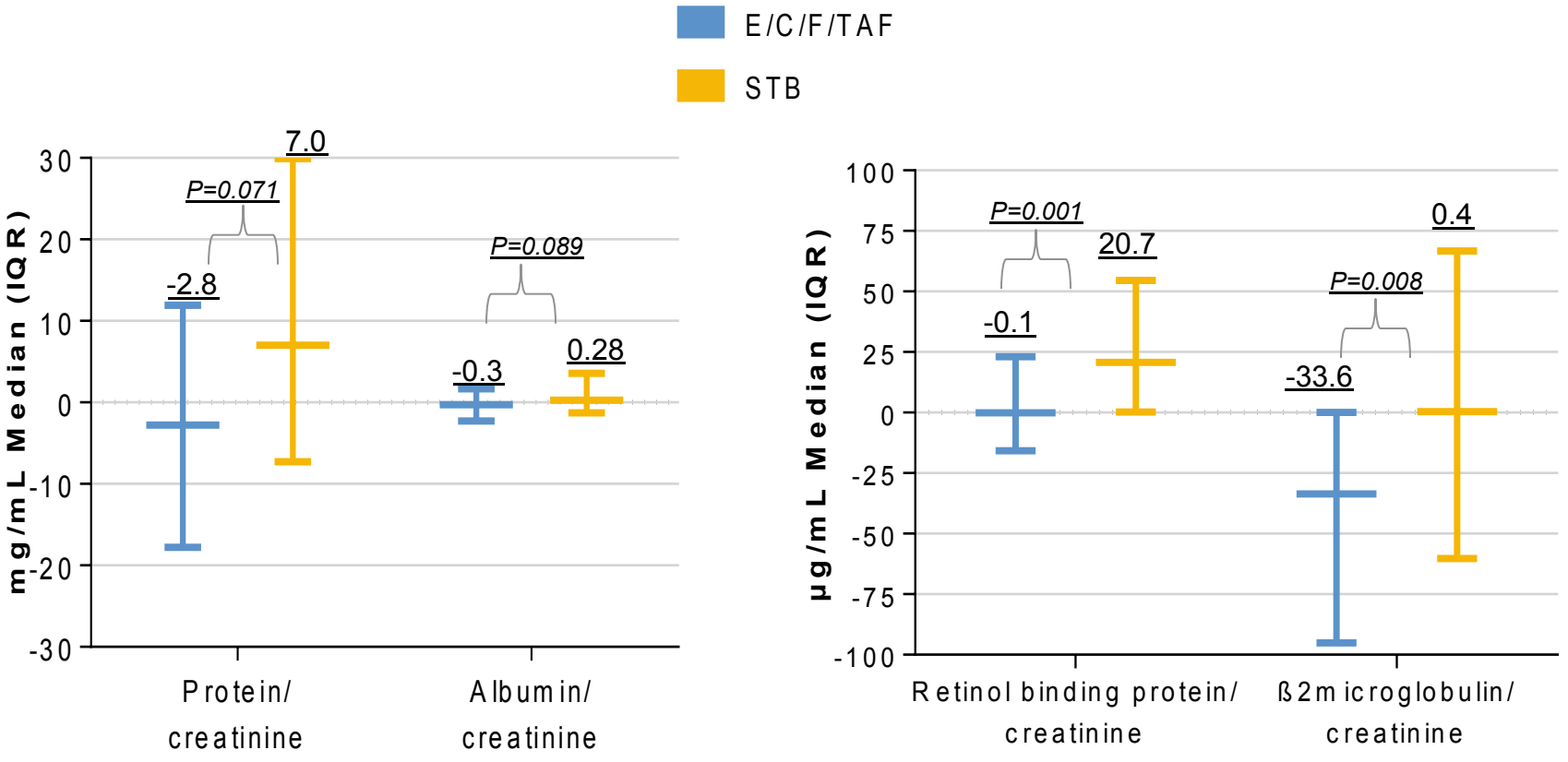
TAF vs TDF Phase II: Change in Estimated GFR Over Time



P. Sax, et al., ICAAC 2013; Paper H-1464d

TAF vs TDF Phase II: Urine Tubular Protein Markers

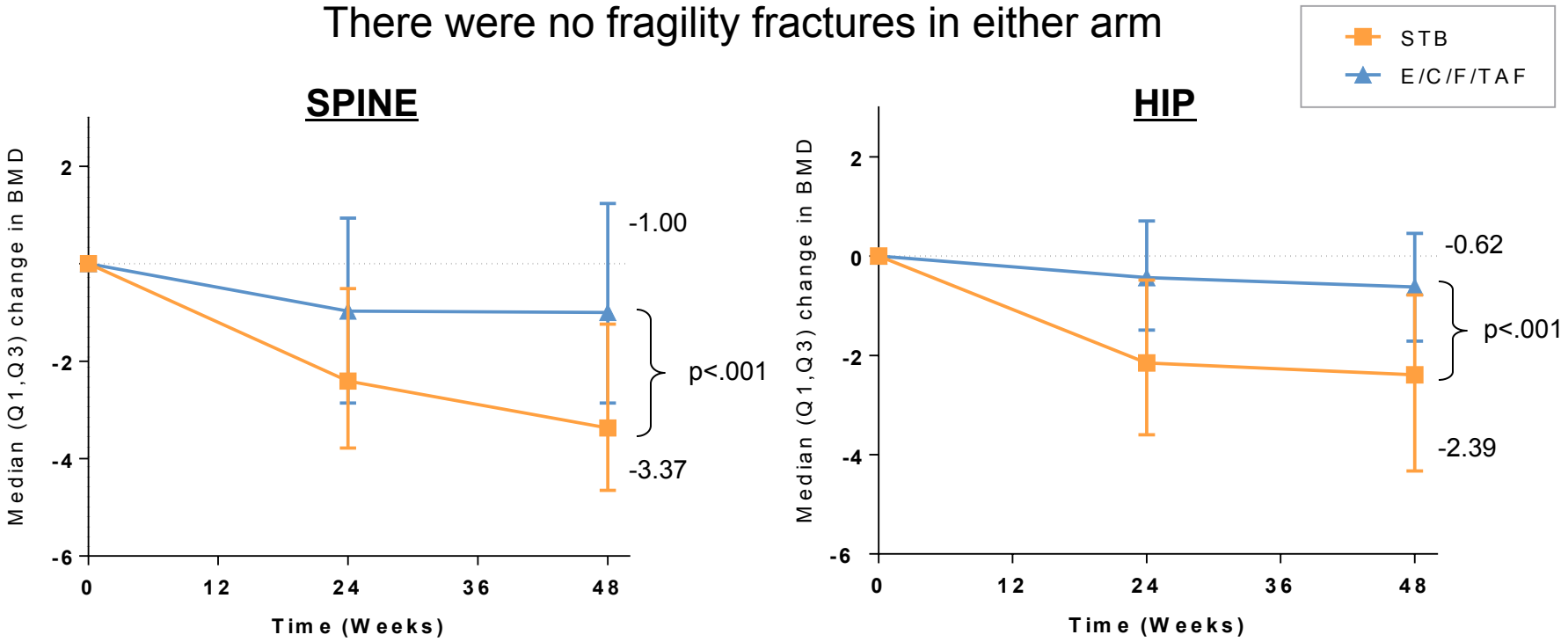
Median change from BL Value



P. Sax, et al., ICAAC 2013; Paper H-1464d

TAF vs TDF Phase II: Percent Change in Spine and Hip BMD (DEXA)

There were no fragility fractures in either arm



No decrease in hip BMD: 32% E/C/F/TAF vs 7% STB (p<.001)

W48 Median Value of Bone Biomarkers as % of Baseline: E/C/F/TAF vs. STB

Procollagen Type 1 N-terminal propeptide (P1NP):	109% vs 169% (p<0.001)
C-terminal telopeptide (CTx):	119% vs. 178% (p<0.001)

P. Sax, et al., ICAAC 2013; Paper H-1464d

Theoretically, Our Best Future Regimen

A single-tablet formulation of TAF + emtricitabine + dolutegravir

14th EUROPEAN AIDS CONFERENCE
OCTOBER 16–19, 2013
BRUSSELS, BELGIUM

GARDEL
GLOBAL ARV DESIGN ENCOMPASSING LOPINAVIR/RITONAVIR AND LAMIVUDINE VS LOPINAVIR/RITONAVIR BASED STANDARD THERAPY

Dual therapy with Lopinavir/ Ritonavir (LPV/r) and Lamivudine (3TC) is non-inferior to standard triple drug therapy in Naïve HIV-1 infected subjects : 48-week results of the GARDEL Study.

ClinicalTrials.gov : # NCT01237444

Pedro Cahn on behalf of the GARDEL study group

FUNDACION HUESPED
en acción contra el sida

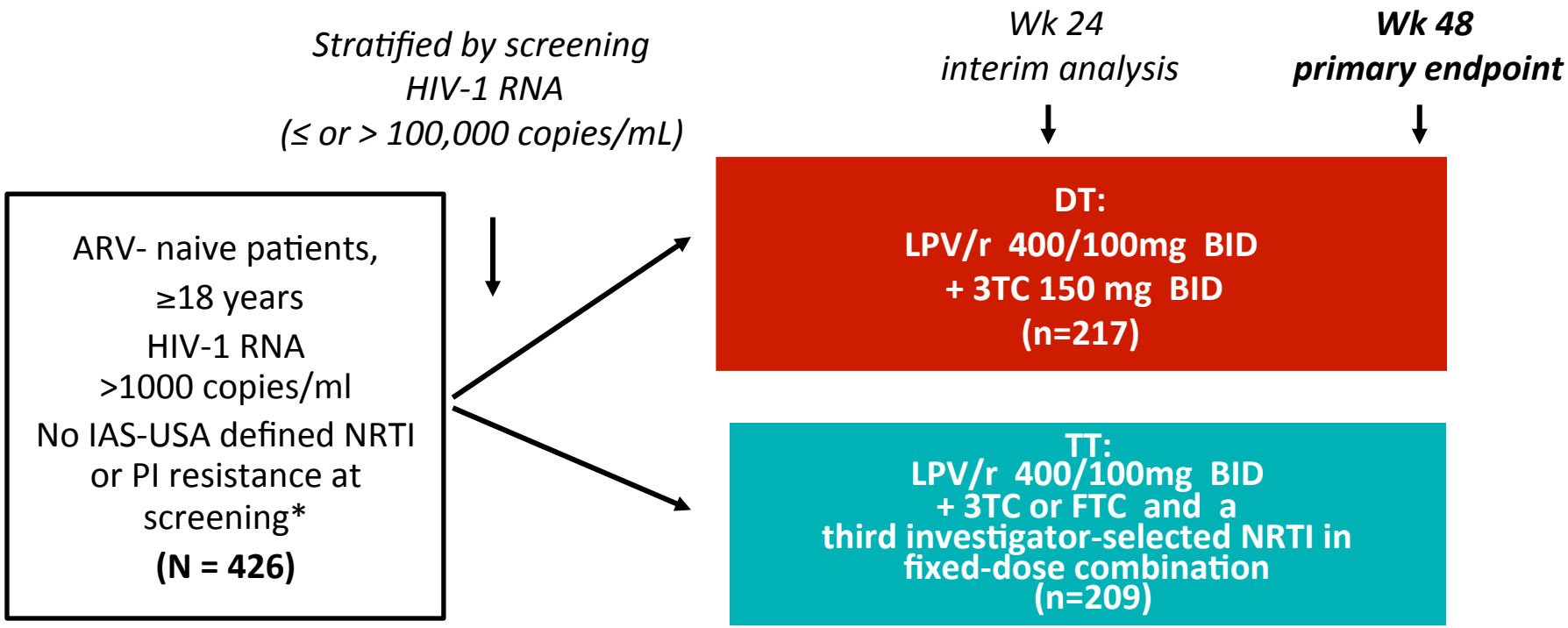
GARDEL: Background

- Virologic suppression no longer a challenge with current regimens
- Can it be done with safer, less costly initial treatment?
- Can it be done with fewer than three active drugs?
- GARDEL tested a two-active drug regimen (3TC + LPV/r, dual therapy, DT) vs a three-active drug regimen (2NRTIs + LPV/r, triple therapy, TT)

Study Design

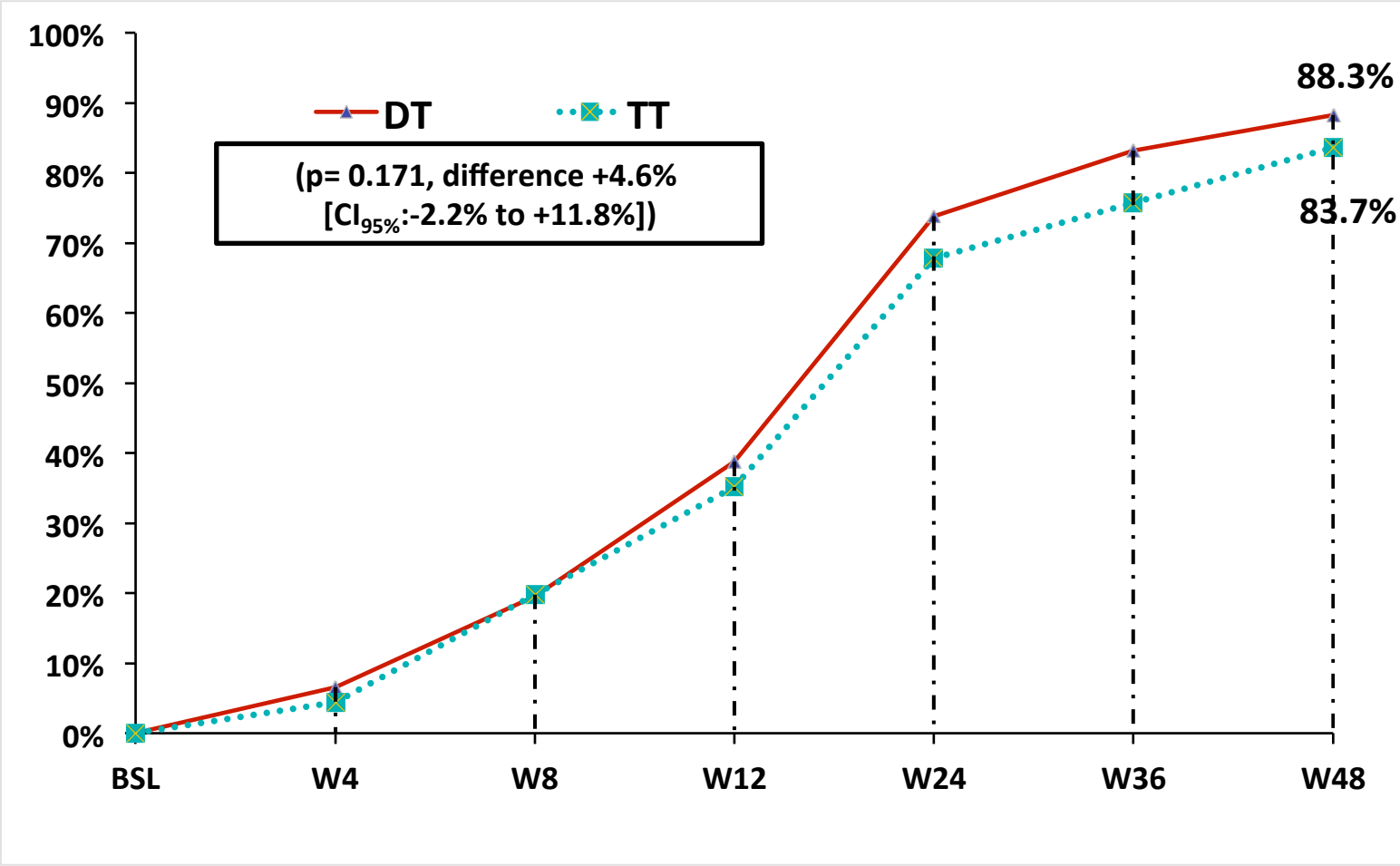
Phase III, randomized, international , controlled, open-label study

- Study included adult patients from Argentina, Chile, Mexico, Peru, Spain, US.



*Defined as ≥ 1 major or ≥ 2 minor LPV/r mutations)
LPV major mutations include the following mutations: V32I; I47V/A; L76V; V82A/F/T/S

GARDEL: Double Therapy Non-Inferior to Triple



GARDEL Study: Conclusions

- Dual therapy with 3TC + LPV/r non-inferior to 2NRTIs + LPV/r
  - No decreased efficacy at high HIV RNA
  - Tended to be better tolerated
- Questions
  - Why did this work but RAL and MVC + PI regimens have not? "Magic" of 3TC/FTC?
  - Would it work with QD 3TC? QD ATV/r or DRV/r?
  - Implications for current initial therapy?
  - Implications for maintenance therapy?

Question

- I have been asked at least once by a payor to split up a coformulated HIV treatment.

1. True
2. False

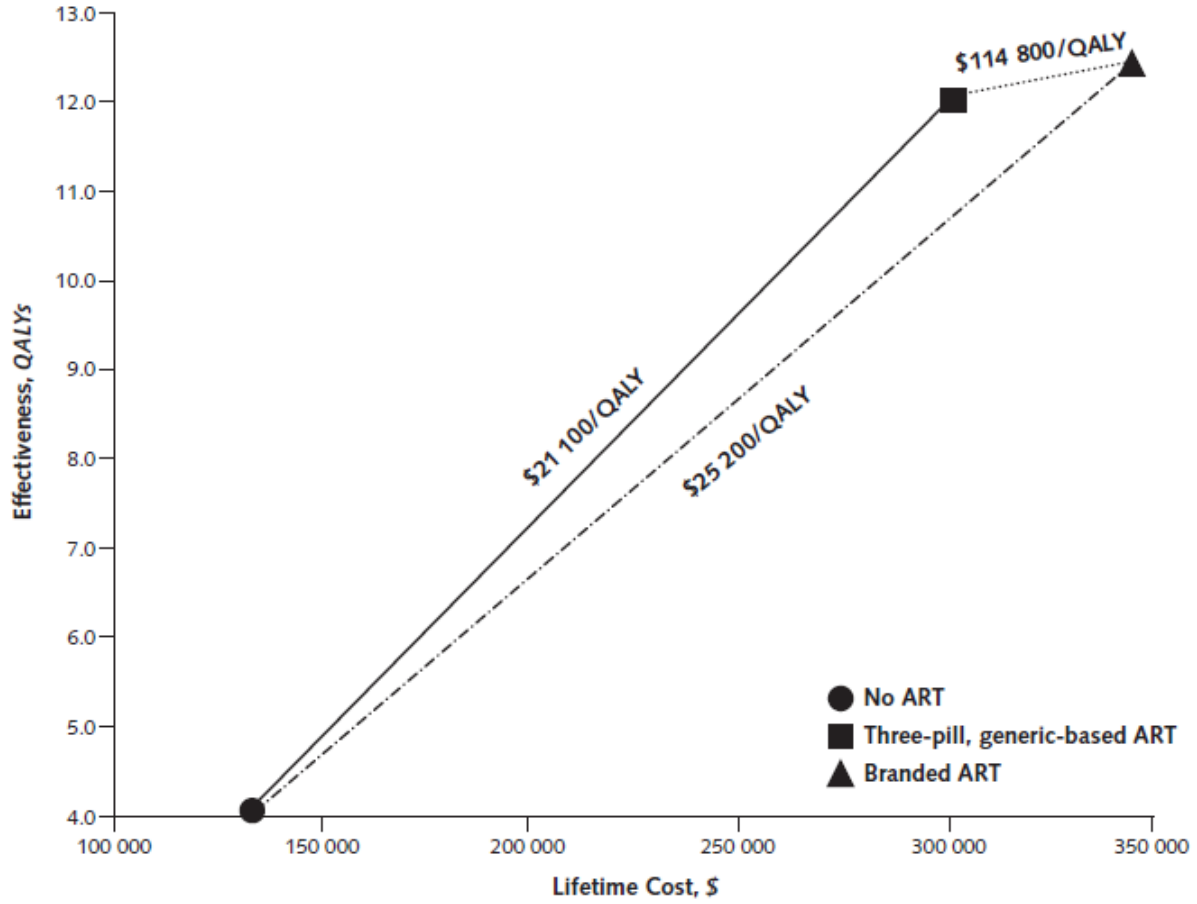
Economic Savings Versus Health Losses: The Cost-Effectiveness of Generic Antiretroviral Therapy in the United States

Rochelle P. Walensky, MD, MPH; Paul E. Sax, MD; Yoriko M. Nakamura, BA; Milton C. Weinstein, PhD; Pamela P. Pei, PhD; Kenneth A. Freedberg, MD, MSc; A. David Paltiel, PhD; and Bruce R. Schackman, PhD

- Mathematical simulation of HIV disease
- Branded TDF/FTC/EFV compared to separate TDF, 3TC, EFV
  - Annual cost: $15300 vs $9200
  - Slight reduction in efficacy of generics projected due to separate pills, FTC vs 3TC
  - All assumptions varied widely in sensitivity analyses

Walensky RW, et al. Annals Int Med 2013.

Projected Clinical and Economic Outcomes of Generic vs Branded ART



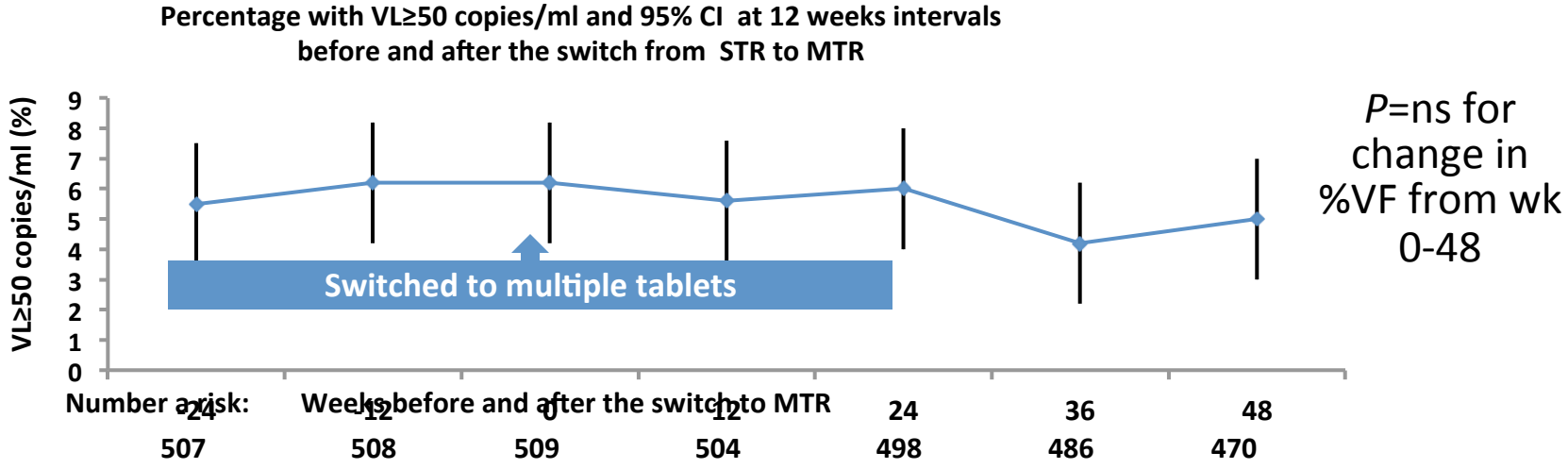
Per-person lifetime costs are on the x-axis, and life expectancy in QALYs is on the y-axis. The dotted-and-dashed line indicates the anticipated incremental cost-effectiveness ratio of branded ART compared with no ART in the absence of a generic alternative

Walensky RW, et al. Annals Int Med 2013.

Change from Single Tablet to Multiple Tablets After Virologic Suppression

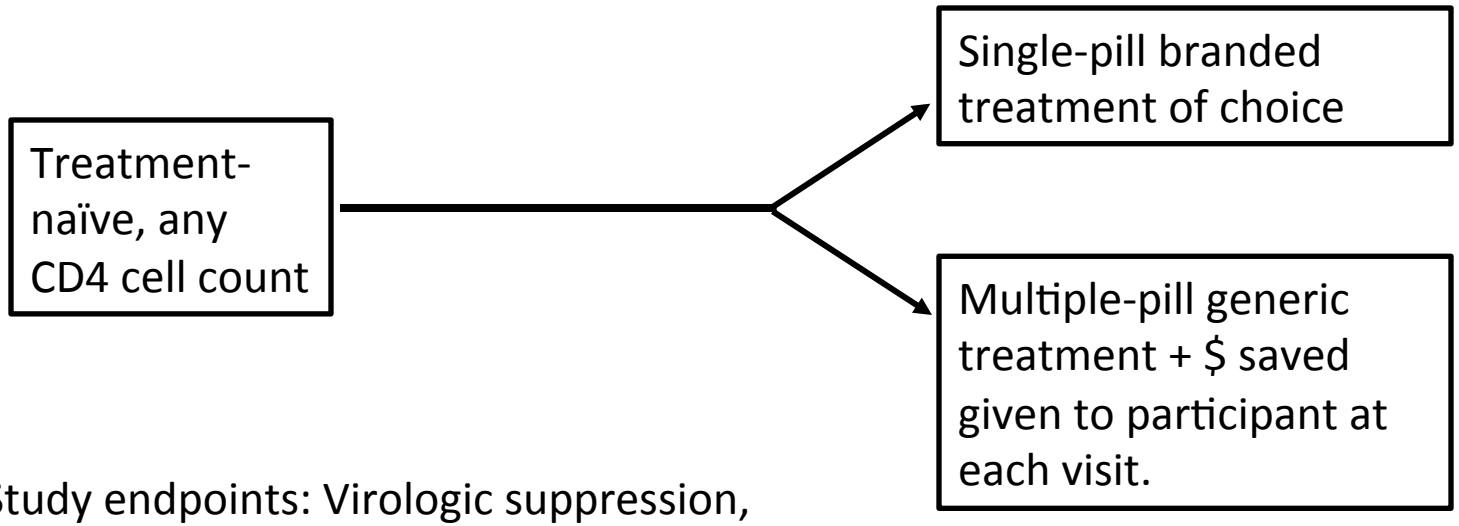
509 patients in Denmark on TDF/FTC/EFV; 478 (94%) switched to TDF + 3TC + EFV

Eligibility
- STR - first cART regimen in 215 (42%)
- On TDF/FTC/EFV ≥ 1 year prior to the change to multiple tablets
- No known compliance problems



Engsig F, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 579.

A Proposed Randomized Clinical Trial That Will Never Happen



Study endpoints: Virologic suppression, adherence (complete and partial), health care utilization, patient satisfaction, and overall costs.

HARVARD
School of Public Health

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

Suicidality in Patients Randomly Assigned to Efavirenz for Initial Treatment of HIV-1

Katie Mollan, MS

University of North Carolina at Chapel Hill, Center for AIDS Research
Harvard School of Public Health, Center for Biostatistics in AIDS Research

Collaborators:

Camlin Tierney, PhD, Marlene Smurzynski, PhD,
Joseph Eron, MD, Eric Daar, MD, Thomas Campbell, MD
Paul Sax, MD, Roy Gulick, MD, Lumine Na, MS
Lauren O'Keefe, BS, Kevin R. Robertson, PhD

ACTG
AIDS CLINICAL TRIALS GROUP

Key Objectives

- Estimate the incidence of suicidality and
- Compare time to suicidality in treatment naïve HIV infected adults who were randomly assigned an EFV-containing or EFV-free regimen
- Evaluate associations between baseline patient characteristics and time to suicidality

Included ARV-naïve Studies

Study	Enrollment Period	Efavirenz-containing Regimens (n=3241)	Efavirenz-free Regimens (n=2091)	Median Follow-up Weeks EFV	Median Follow-up Weeks EFV free
A5095	2001-2002	EFV+ ZDV/3TC/ABC EFV+ ZDV/3TC	ZDV/3TC/ABC	145 (48*)	144 (48*)
A5142	2003-2004	EFV + 3TC + NRTI EFV + LPV/r	LPV/r + 3TC + NRTI	112	112
A5175	2005-2007	EFV + 3TC/ZDV EFV + FTC/TDF	ATV + ddI-EC + FTC	184 (87*)	184 (87*)
A5202	2005-2007	EFV + FTC/TDF EFV + 3TC/ABC	ATV/r + FTC/TDF ATV/r + 3TC/ABC	137	138

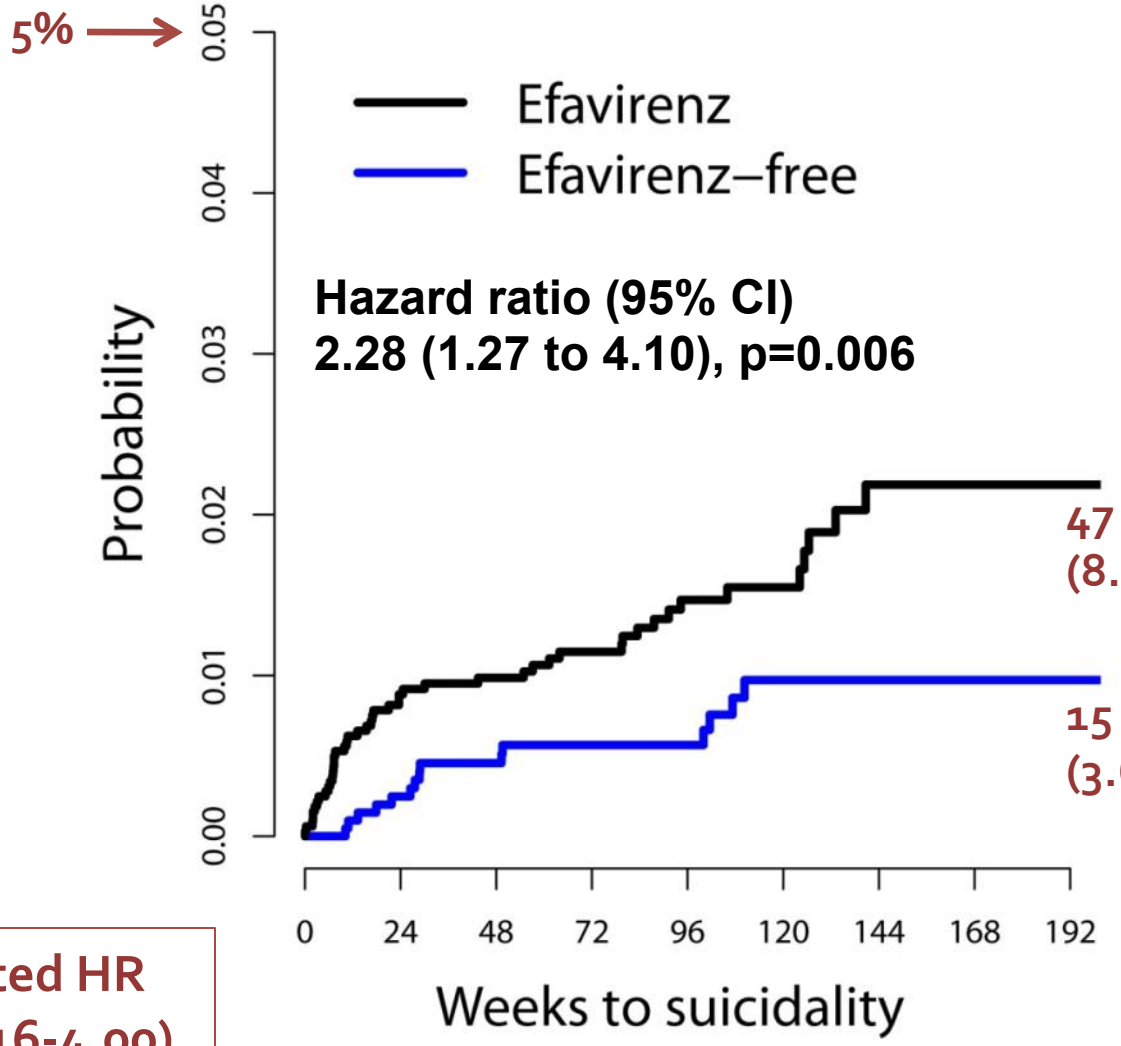
*Prior to release of DSMB recommendations

Baseline Characteristics

Characteristic	Efavirenz (n=3241)	Efavirenz-free (n=2091)
United States (US) Multinational	72% 28%	78% 22%
Male	73%	74%
US Race/Ethnicity White non-Hispanic Black non-Hispanic Hispanic	(n=2,324) 39% 36% 22%	(n=1,627) 39% 35% 22%
Age (years) , median(IQR)	36 (30, 43)	37 (30, 43)
AIDS Event History (Yes)	15%	16%
Injection Drug History (Yes)	8%	7%
Psychiatric History or Psychoactive Rx (Yes)	31%	33%
Antidepressant Rx (Yes)	10%	10%

Balanced within each study

Time to Suicidality, primary analysis



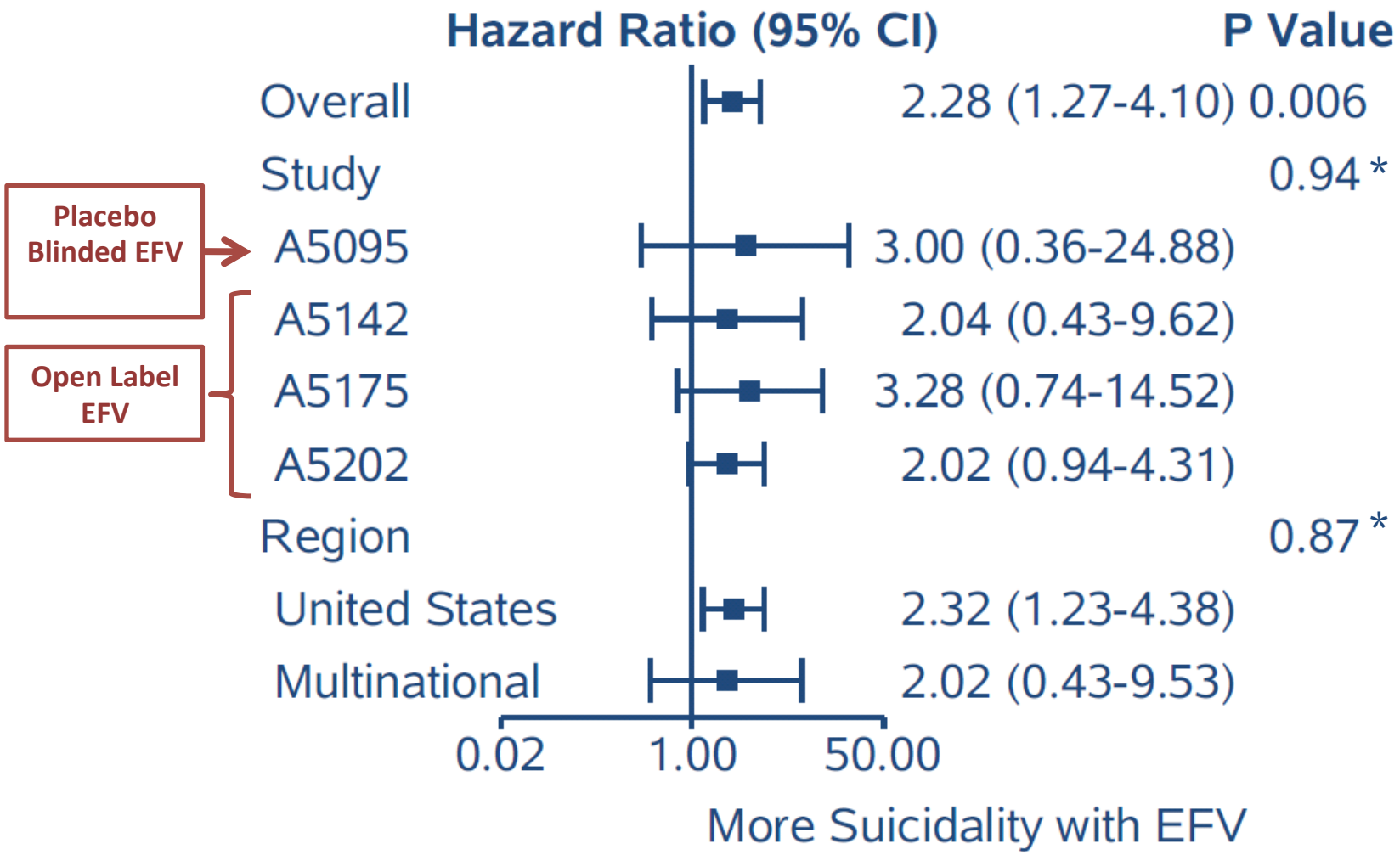
47 events/5817 PY*
(8.08/ 1000 PY)

15 events/4099 PY*
(3.66/1000 PY)

*Person Years, sum of at-risk follow-up

As-treated HR
2.16 (1.16-4.00)

Suicidality by study and region



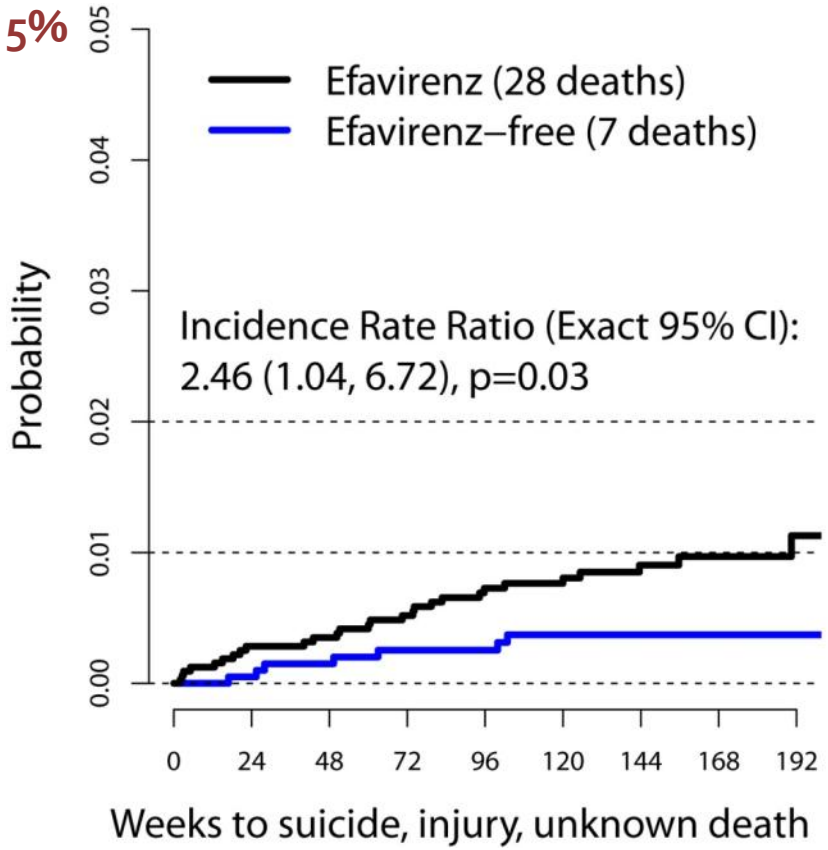
*interaction test

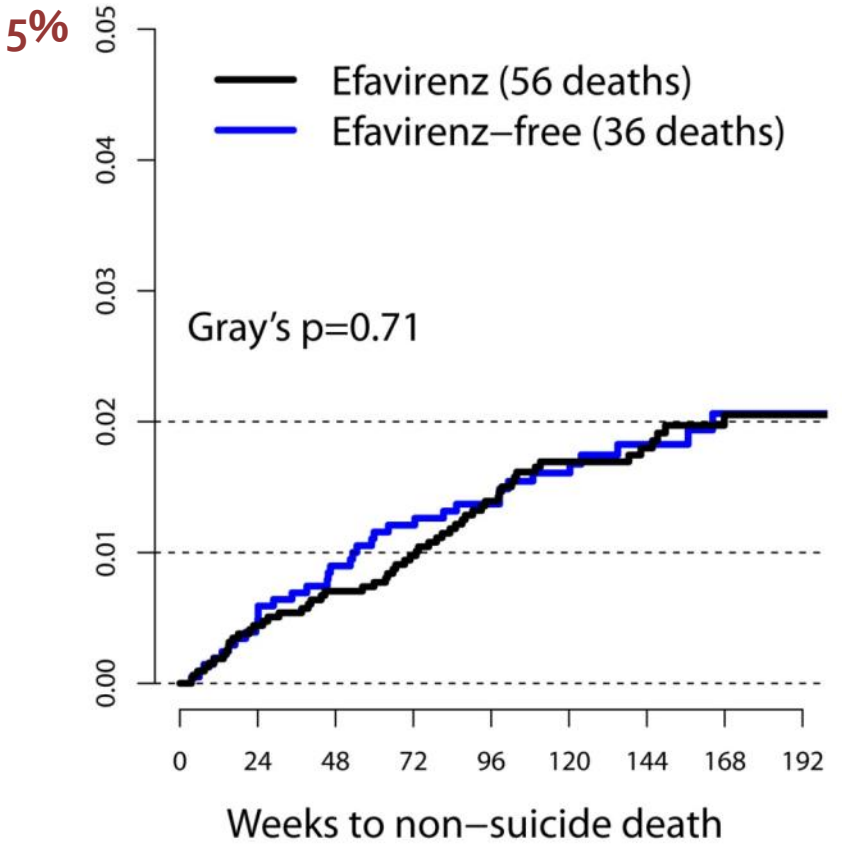
Factors Associated with Suicidality

Variable	Hazard Ratio (95% CI)	P-value
Randomly assigned efavirenz	2.15 (1.20 to 3.87)	0.01
Age category <30 30-44 ≥ 45 years	 2.82 (1.25 to 6.34) 1.69 (0.81 to 3.55) 1.00 (reference)	0.04
Injection drug history	2.18 (1.11 to 4.30)	0.02
Psychiatric History or Psychoactive Rx	3.90 (2.23 to 6.82)	<0.001

- Multivariable (adjusted) Cox model, EFV, younger age, IDU history, and psychiatric history associated with higher risk of suicidality
- Also adjusted for: sex (p=0.3), CD4 count category (p=0.11), and AIDS event history (p=0.08)

Time to death, ITT post-hoc analysis*





Causes: suicide, accident, substance abuse, homicide, unknown

All other causes: e.g. infections, cancer, organ failure

* Death categories were pre-specified, analysis was post-hoc

Strengths

- Potential confounders balanced by random assignment of efavirenz
- Large sample (n=5,332) with median follow-up of nearly 3 years
- A5095 EFV placebo-blinded
- Consistent results across ITT, as-treated, and sensitivity analyses

Limitations

- Retrospective study with no standardized questionnaire regarding suicidality
- Potential undisclosed or underreported suicidality
- 3 of 4 studies were open-label
- Some EFV-free regimens no longer recommended

Efavirenz and Suicidality

- Randomization to EFV conferred a 2-fold increased risk of suicidality
  - Estimated NNH = 217
  - Overall suicidality was uncommon; actual suicide attempts did not differ significantly
  - Deaths from violence/accidents/unexplained also increased in EFV group
- Implications
  - Should EFV be prescribed to patients with psychiatric histories? Should it be prescribed at all?
  - Should those on EFV with depression be switched?
  - What impact will this have internationally?

Question

- I have had completely stable patients with no side effects on ART ask about whether they could undergo a bone marrow transplant for HIV cure.

1. True
2. False

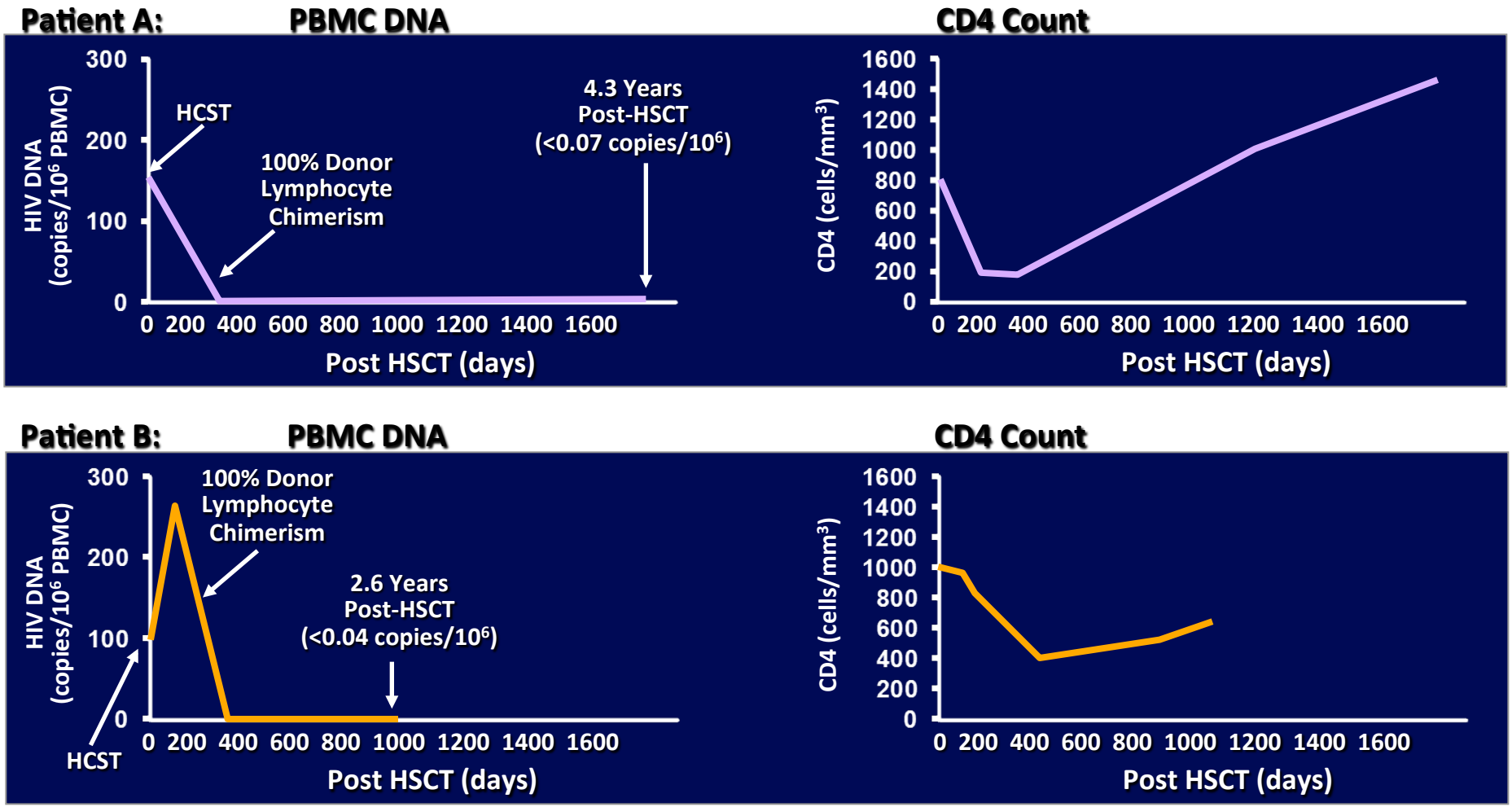
Absence of Detectable HIV-1 Viremia after Treatment Cessation in an Infant

Deborah Persaud, M.D., Hannah Gay, M.D., Carrie Ziemniak, M.S., Ya Hui Chen, B.A., Michael Piatak, Jr., Ph.D., Tae-Wook Chun, Ph.D., Matthew Strain, M.D., Ph.D., Douglas Richman, M.D., and Katherine Luzuriaga, M.D.

- Baby born in Mississippi to HIV+ mom not on ART (HIV RNA 2423)
  - Started on combination therapy 30 hours after birth when HIV RNA 20,000
  - Continued suppressive Rx for 18 months, then stopped
- Low-level HIV RNA detected at 24 but not 26 months; no HIV DNA in resting CD4 cells

Persaud D, et al. N Engl J Med 2013.

Reduction in Viral Reservoir after Allogeneic Stem Cell Transplant



HSCT: hematopoietic stem cell transplantation.

Henrich T, et al. 7th IAS Conference. Kuala Lumpur, 2013. Abstract WeLBA05.

Initial Results After Treatment Interruption

Additional/Ongoing Results		
	Patient A	Patient B
Post-HSCT Highly sensitive PCR-based chimerism	Host cells: 0.00041% to 0.00081% of PBMCs	Host cells: 0.00035% to 0.00096%of PBMCs
Immune response HIV-specific (INF-γ ELISpot) Other	None None	None CMV/EBV/ Influenza
ART stopped HIV plasma RNA PBMC DNA SCA Proviral DNA	7 weeks Not detectable Not detectable -- --	15 weeks Not detectable Not detectable Not detectable Not detectable

Henrich T, et al. 7th IAS Conference. Kuala Lumpur, 2013. Abstract WeLBA05.

HIV virus returns after cure hope rose

2 Boston patients had transplants of marrow, halted powerful drugs

By Kay Lazar | GLOBE STAFF DECEMBER 06, 2013

- Virologic rebound detected in both patients
- Have resumed ART and achieved virologic suppression
- Full details of cases not yet in public domain

Boston Globe, Dec 6 2013

Almost Made It

- SECOND-LINE Study: LPV/r plus NRTIs or RAL are similar. *Lancet* 2013.
- SAILING: DTG superior to RAL in treatment-experienced. Cahn P, *Lancet* 2013.
- CD4 monitoring of little utility in stable patients. Gale HD, *Clin Infect Dis* 2013.
- Sofosbuvir + ledipasvir cures 90%+ genotype 1 HCV. Lawetz E, *Lancet* 2013.
- Clindamycin and TMP-SMX are similar for outpatient SSTIs. Miller L, IDSA 2013.

Top Studies: Conclusions

- HIV remains a very active area of clinical research
- Prevention and treatment arenas both amenable to significant progress
- Have an interesting study? Please submit to the new IDSA journal, *Open Forum Infectious Diseases*, accepting papers now!

Thank you, Raphy L and Judy C (one image for both of you)!