Top 10 Research Papers of the Last 30 Years

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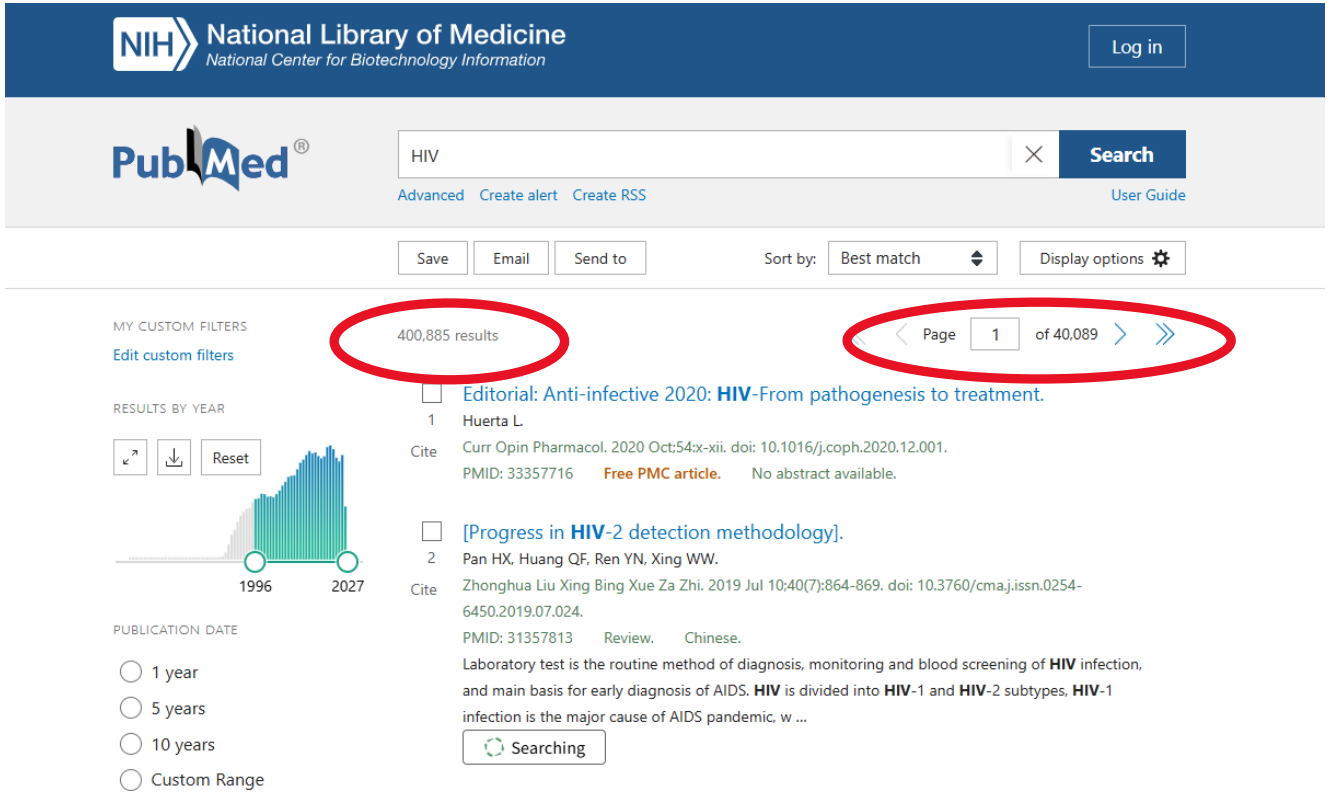
Conflict of Interest

In relation to this presentation I declare that I have no conflict of interest

Picking 10 research papers from the last 30 years



Note: Older papers are not written in Person-First Language

Timeline

1995
First PI
Saquinavir

1996
First NNRTI
Nevirapine

2006
First once daily single tablet regimen

2007
First INSTI
Raltegravir

2008
Berlin patient

2012
First ARV combination for prevention
Truvada

2014
First results from the PARTNER study

2015
Results from START study

2021
First LAI
Cabotegravir/ rilpivirine

2023
REPRIEVE study

2025
Lenacapavir approved for PrEP

1990s

1996
First NNRTI
Nevirapine

1996
Combination therapy

1996
Treatment to prevent vertical transmission

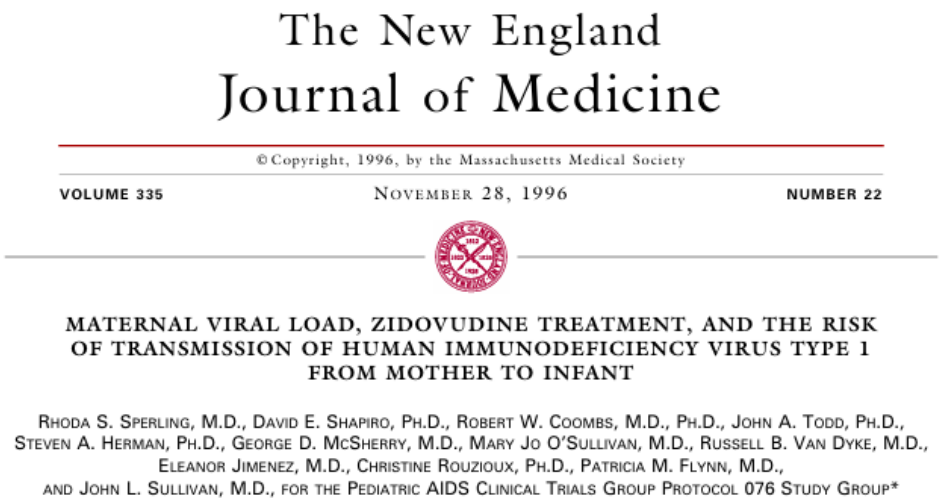
1999
NNRTI
Efavirenz

1997
Death of Princess Diana

1998
Good Friday Agreement

1999
Britney Spears
Baby one more time

Vertical transmission prevention



The New England
Journal of Medicine

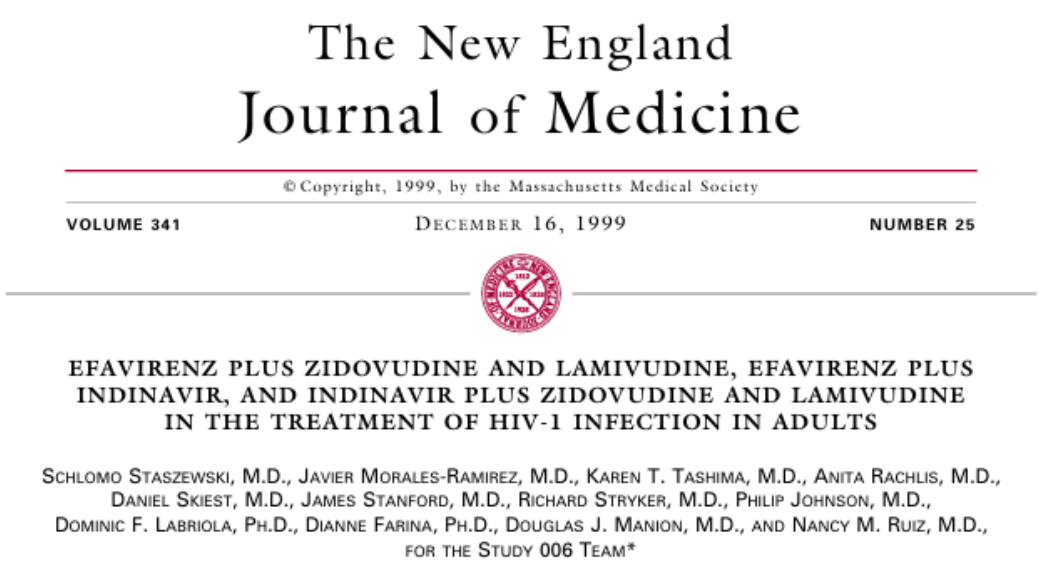
VOLUME 335 NOVEMBER 28, 1996 NUMBER 22

MATERNAL VIRAL LOAD, ZIDOVUDINE TREATMENT, AND THE RISK OF TRANSMISSION OF HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 FROM MOTHER TO INFANT

RHODA S. SPERLING, M.D., DAVID E. SHAPIRO, PH.D., ROBERT W. COOMBS, M.D., PH.D., JOHN A. TODD, PH.D., STEVEN A. HERMAN, PH.D., GEORGE D. MCSHERRY, M.D., MARY JO O'SULLIVAN, M.D., RUSSELL B. VAN DYKE, M.D., ELEANOR JIMENEZ, M.D., CHRISTINE ROUZIOUX, PH.D., PATRICIA M. FLYNN, M.D., AND JOHN L. SULLIVAN, M.D., FOR THE PEDIATRIC AIDS CLINICAL TRIALS GROUP PROTOCOL 076 STUDY GROUP*

- 1996
- RCT of AZT versus placebo during pregnancy, delivery and for newborn infant (6 weeks)
- Showed how treatment lowers risk of vertical transmission

EFV versus IDV combination therapy



The New England
Journal of Medicine

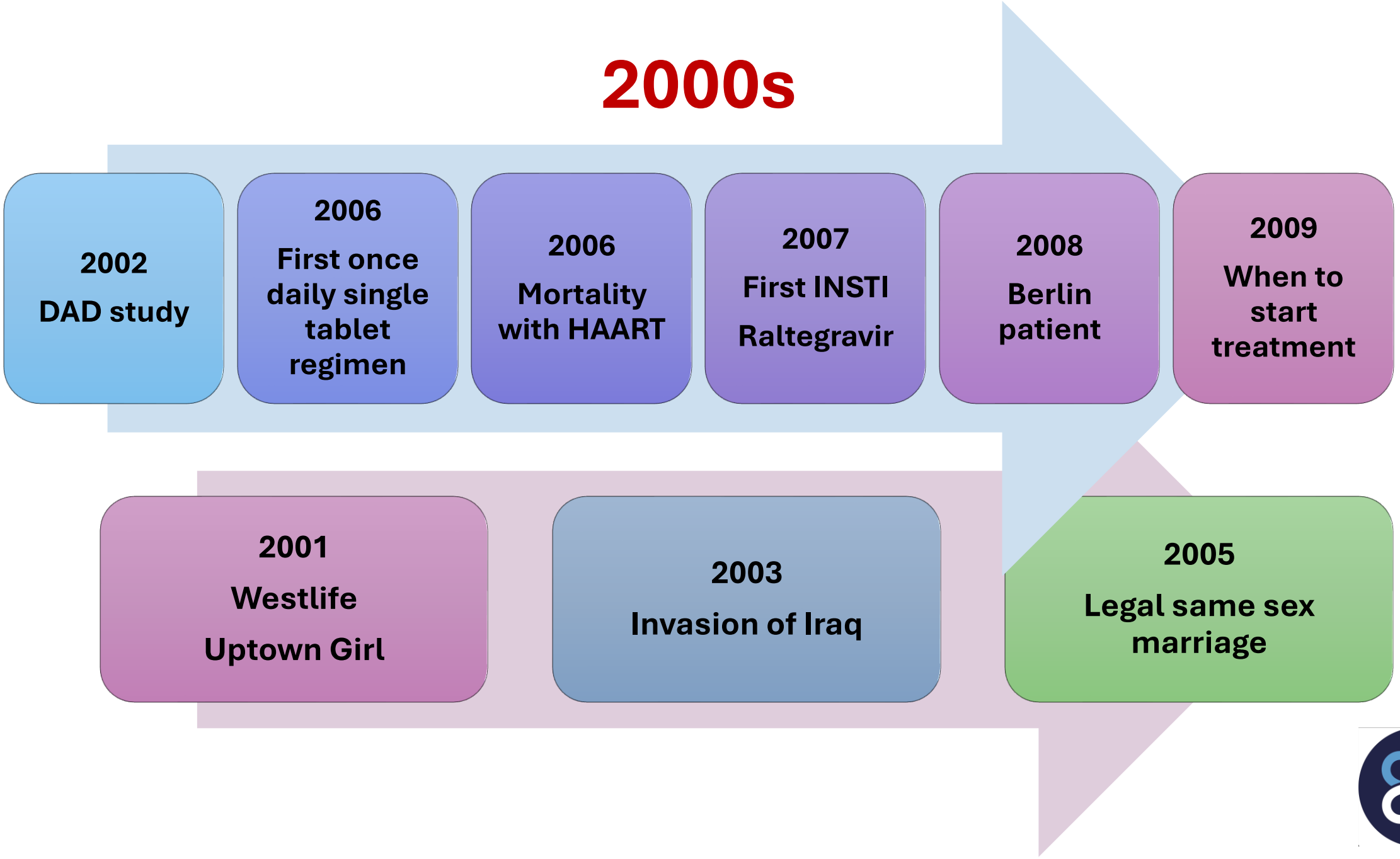
VOLUME 341 DECEMBER 16, 1999 NUMBER 25

EFAVIRENZ PLUS ZIDOVUDINE AND LAMIVUDINE, EFAVIRENZ PLUS INDINAVIR, AND INDINAVIR PLUS ZIDOVUDINE AND LAMIVUDINE IN THE TREATMENT OF HIV-1 INFECTION IN ADULTS

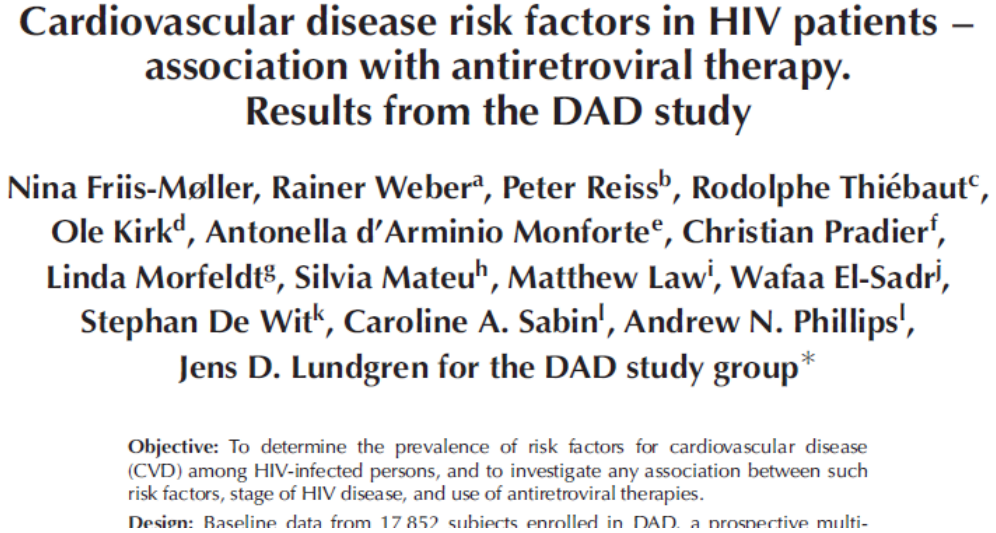
SCHLOMO STASZEWSKI, M.D., JAVIER MORALES-RAMIREZ, M.D., KAREN T. TASHIMA, M.D., ANITA RACHLIS, M.D., DANIEL SKIEST, M.D., JAMES STANFORD, M.D., RICHARD STRYKER, M.D., PHILIP JOHNSON, M.D., DOMINIC F. LABRIOLA, PH.D., DIANNE FARINA, PH.D., DOUGLAS J. MANION, M.D., AND NANCY M. RUIZ, M.D., FOR THE STUDY 006 TEAM*

- 1999
- Comparison of 3 regimens in 450 participants
  - EFV + AZT + 3TC
  - EFV + IDV
  - IDV + AZT
- EFV + AZT + 3TC more effective and better tolerability
- EFV became standard of care

2000s


2002
DAD study
2006
First once daily single tablet regimen
2006
Mortality with HAART
2007
First INSTI
Raltegravir
2008
Berlin patient
2009
When to start treatment
2001
Westlife
Uptown Girl
2003
Invasion of Iraq
2005
Legal same sex marriage

Cardiovascular risk with ART



Cardiovascular disease risk factors in HIV patients – association with antiretroviral therapy. Results from the DAD study

Nina Friis-Møller, Rainer Weber[a], Peter Reiss[b], Rodolphe Thiébaut[c], Ole Kirk[d], Antonella d'Arminio Monforte[e], Christian Pradier[f], Linda Morfeldt[g], Silvia Mateu[h], Matthew Law[i], Wafaa El-Sadr[j], Stephan De Wit[k], Caroline A. Sabin[l], Andrew N. Phillips[l], Jens D. Lundgren for the DAD study group*

Objective: To determine the prevalence of risk factors for cardiovascular disease (CVD) among HIV-infected persons, and to investigate any association between such risk factors, stage of HIV disease, and use of antiretroviral therapies.

Design: Baseline data from 17 852 subjects enrolled in DAD, a prospective multi-

- 2003
- DAD study
- Aim to determine CVD risk factors and effect of HIV disease and ART
- High prevalence of CVD risk factors
- NNRTIs and PIs increase risk of CHD

Effect of ART on mortality

CLINICAL SCIENCE

Mortality in the Highly Active Antiretroviral Therapy Era

Changing Causes of Death and Disease in the HIV Outpatient Study

Frank J. Palella, Jr., MD, Rose K. Baker, MA,† Anne C. Moorman, BSN, MPH,‡ Joan S. Chmiel, PhD,* Kathleen C. Wood, BSN,† John T. Brooks, MD,‡ Scott D. Holmberg, MD, MPH,‡ and HIV Outpatient Study Investigators*

Background: AIDS-related death and disease rates have declined in the highly active antiretroviral therapy (HAART) era and remain low; however, current causes of death in HAART-treated patients remain ill defined.

Objective: To describe mortality trends and causes of death among HIV-infected patients in the HAART era.

Conclusions: Although overall death rates remained low through 2004, the proportion of deaths attributable to non-AIDS diseases increased and prominently included hepatic, cardiovascular, and pulmonary diseases, as well as non-AIDS malignancies. Longer time spent receiving HAART and higher CD4 cell counts at HAART initiation were associated with death from non-AIDS causes. CD4 cell count at time of death increased over time.

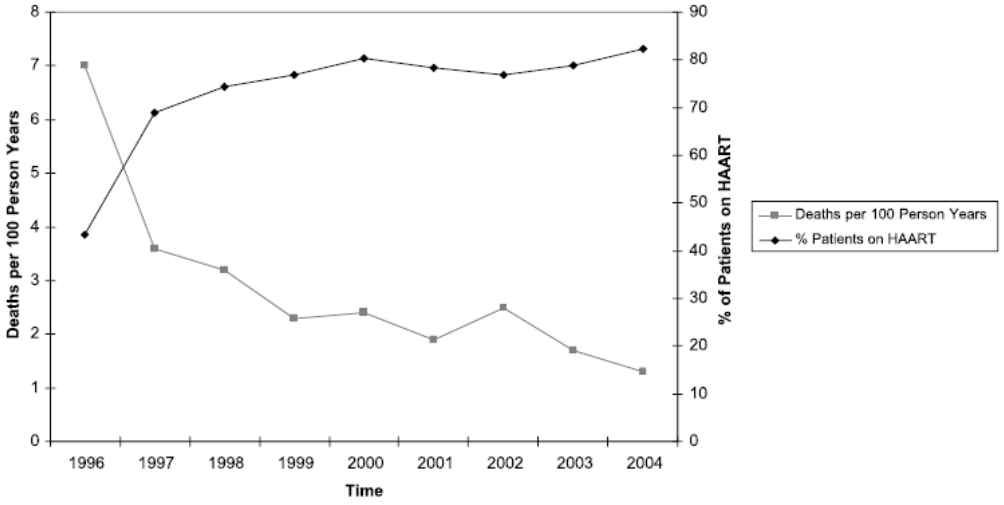
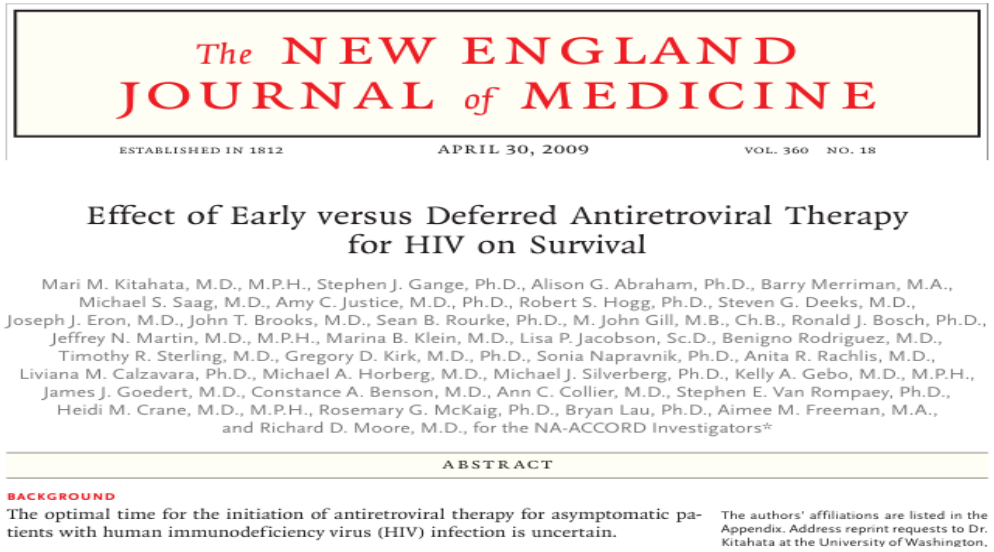


FIGURE 1. Mortality and HAART use over time.

- 2006
- HIV Outpatient Study (HOPS 1996 – 2004)
- Decline in death with use of ART
- Death due to non-AIDS related illness (hepatic, pulmonary, cardiovascular)

Early versus Deferred ART



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 30, 2009 VOL. 360 NO. 18

Effect of Early versus Deferred Antiretroviral Therapy for HIV on Survival

Mari M. Kitahata, M.D., M.P.H., Stephen J. Gange, Ph.D., Alison G. Abraham, Ph.D., Barry Merriman, M.A., Michael S. Saag, M.D., Amy C. Justice, M.D., Ph.D., Robert S. Hogg, Ph.D., Steven G. Deeks, M.D., Joseph J. Eron, M.D., John T. Brooks, M.D., Sean B. Rourke, Ph.D., M. John Gill, M.B., Ch.B., Ronald J. Bosch, Ph.D., Jeffrey N. Martin, M.D., M.P.H., Marina B. Klein, M.D., Lisa P. Jacobson, Sc.D., Benigno Rodriguez, M.D., Timothy R. Sterling, M.D., Gregory D. Kirk, M.D., Ph.D., Sonia Napravnik, Ph.D., Anita R. Rachlis, M.D., Liviana M. Calzavara, Ph.D., Michael A. Horberg, M.D., Michael J. Silverberg, Ph.D., Kelly A. Gebo, M.D., M.P.H., James J. Goedert, M.D., Constance A. Benson, M.D., Ann C. Collier, M.D., Stephen E. Van Rompaey, Ph.D., Heidi M. Crane, M.D., M.P.H., Rosemary G. McKaig, Ph.D., Bryan Lau, Ph.D., Aimee M. Freeman, M.A., and Richard D. Moore, M.D., for the NA-ACCORD Investigators*

ABSTRACT

BACKGROUND

The optimal time for the initiation of antiretroviral therapy for asymptomatic patients with human immunodeficiency virus (HIV) infection is uncertain.

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Kitahata at the University of Washington,

- 2009
- NA-ACCORD study group
- Compared starting ART early to deferring until CD4+ counts
- Starting ART early improves survival

First Integrase Inhibitor

Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial

Jeffrey L Lennox, Edwin DeJesus, Adriano Lazzarin, Richard B Pollard, Jose Valdez Ramalho Madruga, Daniel S Berger, Jing Zhao, Xia Xu, Angela Williams-Diaz, Anthony J Rodgers, Richard J O Barnard, Michael D Miller, Mark J DiNubile, Bach-Yen Nguyen, Randi Leavitt, Peter Sklar, for the STARTMRK investigators*

Lancet 2009; 374: 796–806
Published Online August 3, 2009
DOI:10.1016/S0140-6736(09)60918-1

Summary

Background Use of raltegravir with optimum background therapy is effective and well tolerated in treatment-experienced patients with multidrug-resistant HIV-1 infection. We compared the safety and efficacy of raltegravir with efavirenz as part of combination antiretroviral therapy for treatment-naive patients.

- 2009
- STARTMRK trial
- RCT of treatment naïve patients, comparing RAL to EFV based ART
- Rapid antiviral activity
- Non-inferior to EFV
- Fewer clinical adverse events

2010s

2012

First ARV combination for prevention

Truvada

2014

First results from the PARTNER study

2015

Results from START study

2011

Kate and William's wedding

2013

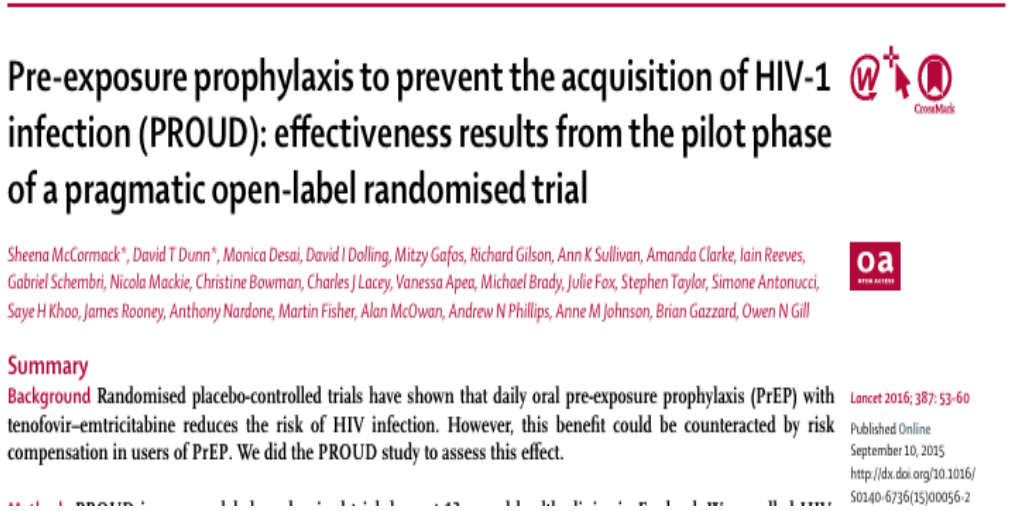
Death of Nelson Mandella

2017

Ed Sheeran

Shape of You

Pre-exposure Prophylaxis (PrEP)



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

Summary

Background Randomised placebo-controlled trials have shown that daily oral pre-exposure prophylaxis (PrEP) with tenofovir–emtricitabine reduces the risk of HIV infection. However, this benefit could be counteracted by risk compensation in users of PrEP. We did the PROUD study to assess this effect.

Lancet 2016; 387: 53-60
Published Online September 10, 2015
http://dx.doi.org/10.1016/S0140-6736(15)00056-2

- 2016
- PROUD study
- RCT of PrEP that represented routine clinical practice
- Truvada
- Reduced HIV incidence

Undetectable = Untransmittable

Research

Original Investigation

Sexual Activity Without Condoms and Risk of HIV Transmission in Serodifferent Couples When the HIV-Positive Partner Is Using Suppressive Antiretroviral Therapy

Alison J. Rodger, MD; Valentina Cambiano, PhD; Tina Bruun, RN; Pietro Vernazza, MD; Simon Collins; Jan van Lunzen, PhD; Giulio Maria Corbelli; Vicente Estrada, MD; Anna Maria Geretti, MD; Apostolos Beloukas, PhD; David Asboe, FRCP; Pompeyo Viciana, MD; Félix Gutiérrez, MD; Bonaventura Clotet, PhD; Christian Pradier, MD; Jan Gerstoft, MD; Rainer Weber, MD; Katarina Westling, MD; Gilles Wandeler, MD; Jan M. Prins, PhD; Armin Rieger, MD; Marcel Stoeckle, MD; Tim Kümmerle, PhD; Teresa Bini, MD; Adriana Ammassari, MD; Richard Gilson, MD; Ivanka Krznaric, PhD; Matti Ristola, PhD; Robert Zangerle, MD; Pia Handberg, RN; Antonio Antela, PhD; Sris Allan, FRCP; Andrew N. Phillips, PhD; Jens Lundgren, MD; for the PARTNER Study Group

IMPORTANCE A key factor in assessing the effectiveness and cost-effectiveness of antiretroviral therapy (ART) as a prevention strategy is the absolute risk of HIV transmission through condomless sex with suppressed HIV-1 RNA viral load for both anal and vaginal sex.

OBJECTIVE To evaluate the rate of within-couple HIV transmission (heterosexual and men who have sex with men [MSM]) during periods of sex without condoms and when the HIV-positive partner had HIV-1 RNA load less than 200 copies/mL.

Editorial page 149

Supplemental content at jama.com

CME Quiz at jamanetworkcme.com and CME Questions page 217

- 2016
- PARTNER study
- HIV serodifferent couples (heterosexual & MSM)
- PLWH on suppressive ART
- No documented cases of within-couple HIV transmission

2020s

2021
First LAI
Cabotegravir/rilpivirine

2023
REPRIEVE study

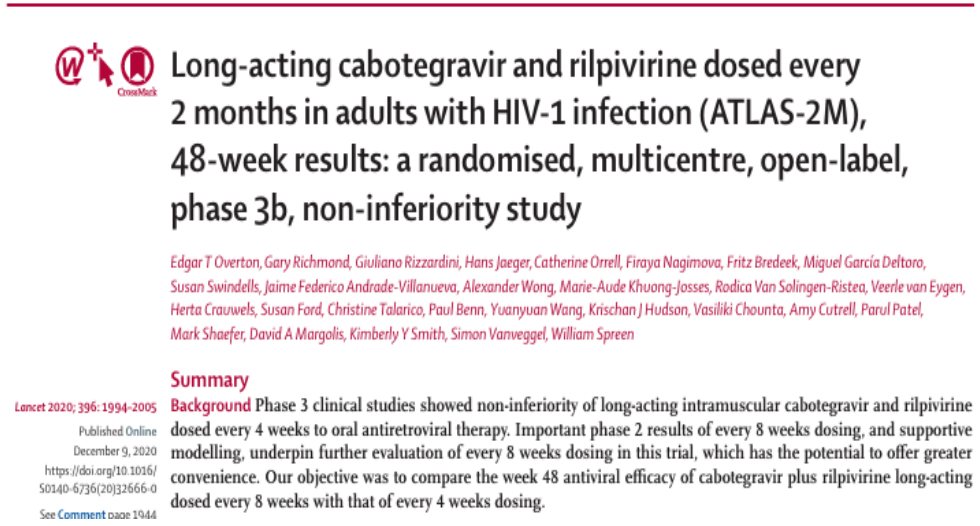
2025
Lenacapavir approved for PrEP

2020
COVID-19 pandemic

2021
The Weeknd & Ariana Grande
Save your Tears

2022
Death of Queen Elizabeth II

Long-acting Injectables



Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2M), 48-week results: a randomised, multicentre, open-label, phase 3b, non-inferiority study

Edgar T Overton, Gary Richmond, Giuliano Rizzardini, Hans Jaeger, Catherine Orrell, Firaya Nagimova, Fritz Bredeek, Miguel García Deltoro, Susan Swindells, Jaime Federico Andrade-Villanueva, Alexander Wong, Marie-Aude Khuong-Josses, Rodica Van Solingen-Ristea, Veerle van Eygen, Herta Crauwels, Susan Ford, Christine Talarico, Paul Benn, Yuanyuan Wang, Krischan J Hudson, Vasiliki Chounta, Amy Cutrell, Parul Patel, Mark Shaefer, David A Margolis, Kimberly Y Smith, Simon Vanveggel, William Spreen

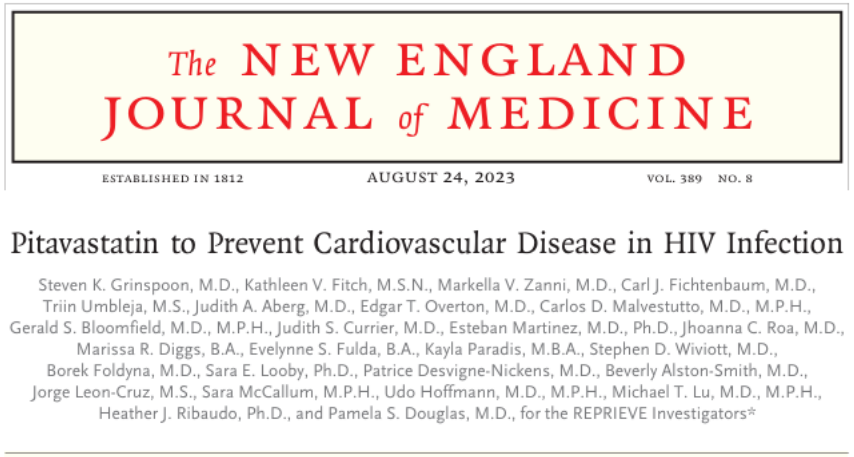
Lancet 2020; 396: 1994-2005
Published Online December 9, 2020
https://doi.org/10.1016/S0140-6736(20)32666-0
See Comment page 1944

Summary

Background Phase 3 clinical studies showed non-inferiority of long-acting intramuscular cabotegravir and rilpivirine dosed every 4 weeks to oral antiretroviral therapy. Important phase 2 results of every 8 weeks dosing, and supportive modelling, underpin further evaluation of every 8 weeks dosing in this trial, which has the potential to offer greater convenience. Our objective was to compare the week 48 antiviral efficacy of cabotegravir plus rilpivirine long-acting dosed every 8 weeks with that of every 4 weeks dosing.

- 2020
- ATLAS-2M study
- Phase 3 study of LAI cabotegravir and rilpivirine
- Showed dosing every 8 weeks is non-inferior to 4 weeks

Pitavastatin to prevent CVD



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ESTABLISHED IN 1812 AUGUST 24, 2023 VOL. 389 NO. 8

Pitavastatin to Prevent Cardiovascular Disease in HIV Infection

Steven K. Grinspoon, M.D., Kathleen V. Fitch, M.S.N., Markella V. Zanni, M.D., Carl J. Fichtenbaum, M.D., Triin Umbleja, M.S., Judith A. Aberg, M.D., Edgar T. Overton, M.D., Carlos D. Malvestutto, M.D., M.P.H., Gerald S. Bloomfield, M.D., M.P.H., Judith S. Currier, M.D., Esteban Martinez, M.D., Ph.D., Jhoanna C. Roa, M.D., Marissa R. Diggs, B.A., Evelynne S. Fulda, B.A., Kayla Paradis, M.B.A., Stephen D. Wiviott, M.D., Borek Foldyna, M.D., Sara E. Looby, Ph.D., Patrice Desvigne-Nickens, M.D., Beverly Alston-Smith, M.D., Jorge Leon-Cruz, M.S., Sara McCallum, M.P.H., Udo Hoffmann, M.D., M.P.H., Michael T. Lu, M.D., M.P.H., Heather J. Ribaudo, Ph.D., and Pamela S. Douglas, M.D., for the REPRIEVE Investigators*

- 2023
- REPRIEVE study
- Phase 3 RCT of PLWH with low to moderate CVD risk
- Pitavastatin vs placebo
- Lower risk of CVD with pitavastatin

Thank you for listening