CONTROLLING THE HIV EPIDEMIC WITH ANTIRETROVIRALS

Avoiding the Cost of Inaction

18-19 September 2014 • Royal Garden Hotel, London

Innovations in Health Care Delivery

Smart investments in HIV care and treatment

Benjamin Young
International Association of Providers of AIDS Care
Washington, DC, USA

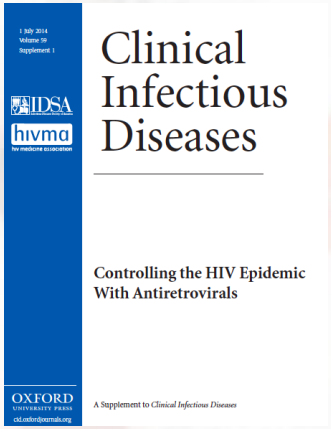
Innovations in Health Care Delivery

Better medicines

Easier adherence

Diagnostics

Task shifting



Global Response to HIV: Treatment as Prevention, or Treatment for Treatment?

Kim C. E. Sigaloff,[1,2,3] Joep M. A. Lange,[1] and Julio Montaner[4]

Departments of [1]Global Health and [2]Internal Medicine, Academic Medical Center, University of Amsterdam, and [3]Amsterdam Institute for Global Health and Development, Amsterdam, The Netherlands; and [4]British Columbia Center for Excellence in HIV/AIDS, Vancouver, Canada

The concept of "treatment as prevention" has emerged as a means to curb the global HIV epidemic. There is, however, still ongoing debate about the evidence on when to start antiretroviral therapy in resource-poor settings. Critics have brought forward multiple arguments against a "test and treat" approach, including the potential burden of such a strategy on weak health systems and a presumed lack of scientific support for individual patient benefit of early treatment initiation. In this article, we highlight the societal and individual advantages of treatment as prevention in resource-poor settings. We argue that the available evidence renders the discussion on when to start antiretroviral therapy unnecessary and that, instead, efforts should be aimed at offering treatment as soon as possible.

"…the available evidence renders the discussion on when to start ART unnecessary and that, instead, efforts should be aimed at offering treatment as soon as possible."

Sigaloff, Lange, Montaner, Clin Infect Dis 2014

New combinations, superior tolerability

INNOVATIONS IN ART

New Recommended Combinations

- The Panel recommends one of the following regimens for ART-naive patients regardless of baseline viral load or CD4 count:

  NNRTI-Based Regimen:
  - EFV/TDF/FTC[a] **(AI)**

  PI-Based Regimens:
  - ATV/r plus TDF/FTC[a] **(AI)**
  - DRV/r plus TDF/FTC[a] **(AI)**

  INSTI-Based Regimens:
  - DTG plus ABC/3TC[a] **(AI)**—**only** for patients who are HLA-B*5701 negative
  - DTG plus TDF/FTC[a] **(AI)**
  - EVG/cobi/TDF/FTC—**only** for patients with pre-ART CrCl >70 mL/min **(AI)**
  - RAL plus TDF/FTC[a] **(AI)**

- In addition to the regimens listed above, the following regimens are also recommended, **but only for patients with pre-ART plasma HIV RNA <100,000 copies/mL**:

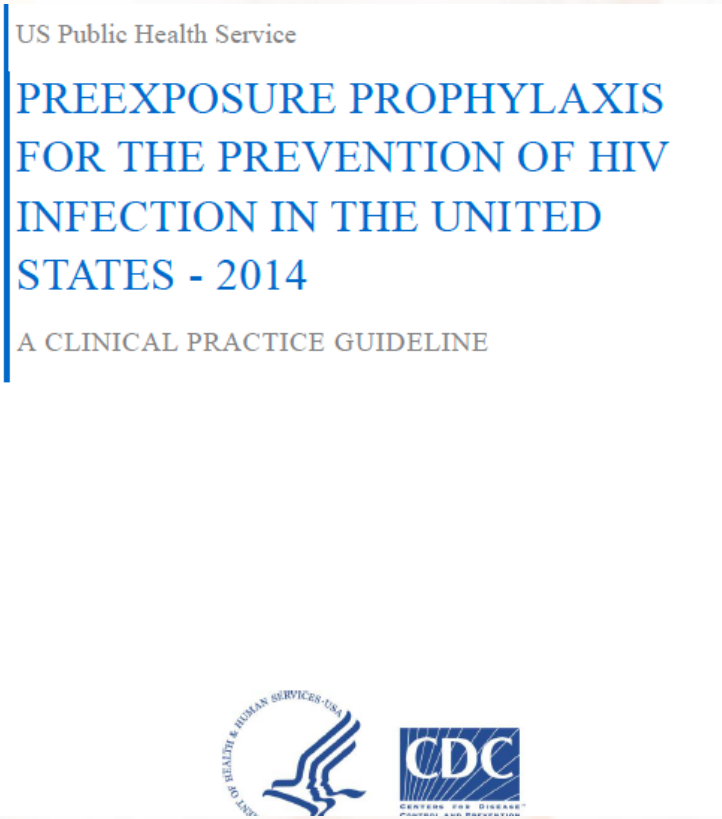
  NNRTI-Based Regimens:
  - EFV plus ABC/3TC[a] **(AI)**—**only** for patients who are HLA-B*5701 negative
  - RPV/TDF/FTC[a] **(AI)**—**only** for patients with CD4 count >200 cells/mm^3

  PI-Based Regimen:
  - ATV/r plus ABC/3TC[a] **(AI)**–**only** for patients who are HLA-B*5701 negative

DHHS Panel, 2014

PrEP Guidelines: USA

- PrEP is recommended as one prevention option for:
  - Sexually–active adult MSM (**IA**)
  - Adult heterosexually-active men and women (**IA**)
  - Adult injection drug users (**IA**)



US Public Health Service, 2014

Better Tolerated ART

	Dolutegravir (n=411)	Raltegravir (n=411)
Virological success	361 (88%)	351 (85%)
Virologic non-response*	20 (5%)	31 (8%)
Data in window not <50 copies per mL	8 (2%)	5 (1%)
Discontinued for lack of efficacy	5 (1%)	13 (3%)
Discontinued for other reasons while HIV-1 RNA not <50 copies per mL	2 (<1%)	11 (3%)
Change in ART	5 (1%)	2 (<1%)
No virological data at week 48	30 (7%)	29 (7%)
Discontinued because of adverse event or death	9 (2%)	6 (1%)
Discontinued for other reasons†	21 (5%)	23 (6%)

Data are n (%), by US Food and Drug Administration snapshot analysis. ART=antiretroviral therapy. *Virological failure. †Protocol deviation, lost to follow-up, or withdrawal of consent.

Table 2: **Patients with plasma HIV-1 RNA less than 50 copies per mL at week 48**

Raffi, et al., Lancet, 2013

Long-term exposure to combination antiretroviral therapy and risk of death from specific causes: no evidence for any previously unidentified increased risk due to antiretroviral therapy

the EuroSIDA study group

AIDS 2012, **26**:315–323

103 centers; 16,597 patients,
12,069 on HAART. Median FU time. 5.43 years;
Median time on HAART: 4.42 years

All-cause mortality **decreased** with longer exposure to cART.
Rates of non-AIDS deaths remained constant

Table 3. The adjusted IRR of cause-specific death by year longer on cART.

Cause of death	IRR	95% CI	*P*
All-cause	0.95	0.92–0.97	<0.001
AIDS	0.86	0.81–0.91	<0.001
Non-AIDS	0.97	0.95–1.00	0.061
NARI-death	0.97	0.90–1.05	0.417
LR-death	0.94	0.89–1.00	0.053
NADM-death	1.07	1.00–1.14	0.056
CVD-death	0.99	0.93–1.06	0.885
Violent death	0.90	0.81–0.99	0.027
Other death	1.01	0.94–1.09	0.725
Unknown death	0.94	0.86–1.01	0.096

Conclusion: In conclusion, we found no evidence of an increased risk of both all-cause and non-AIDS-related deaths with long-term cumulative cART exposure.

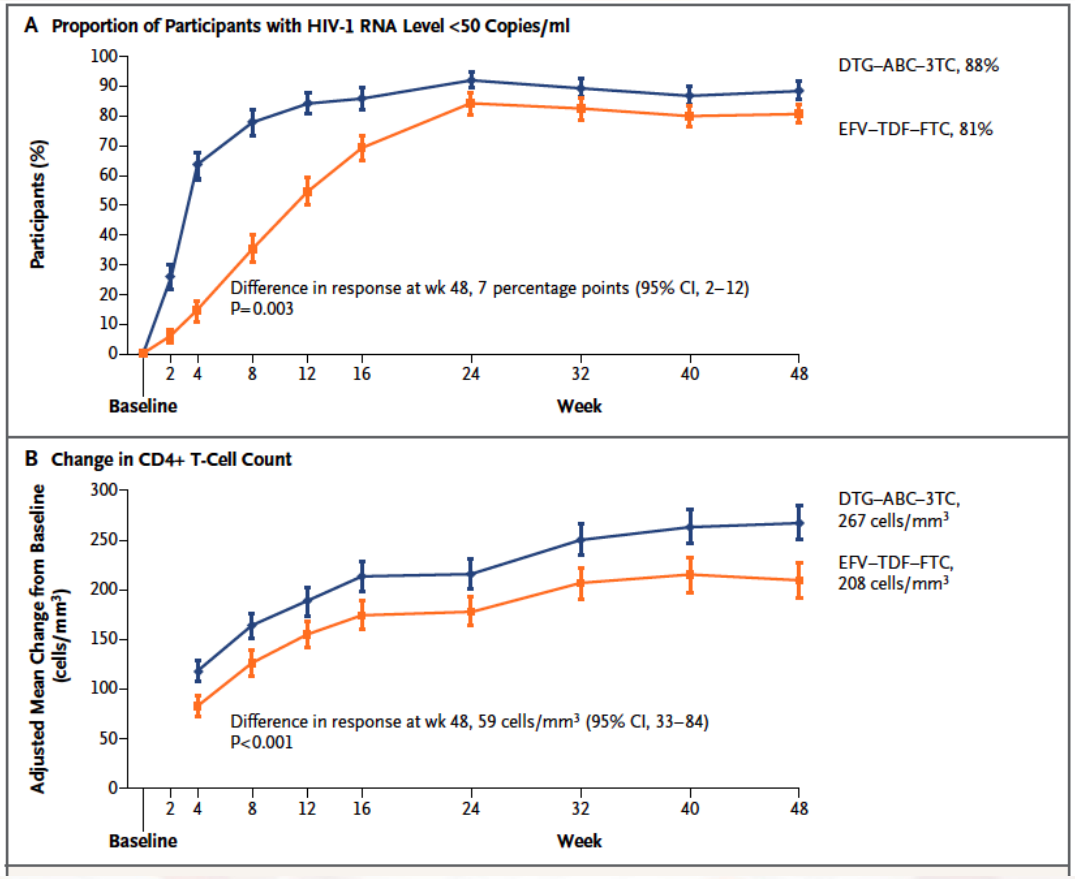
Innovations in first-line ART

- **DTG superior to EFV**
  - SINGLE (Walmsley, New Engl J Med, 2013)
- **DTG superior to DRV/r**
  - FLAMINGO (Clotet, Lancet 2014)
- **RAL superior to EFV**
  - STARTMRK 5 year analysis (Rockstroh, JAIDS 2013)
- **RAL superior to DRV/r and ATV/r**
  - ACTG 5257 (Landovitz, CROI 2014)

The NEW ENGLAND JOURNAL of MEDICINE

Dolutegravir plus Abacavir–Lamivudine for the Treatment of HIV-1 Infection

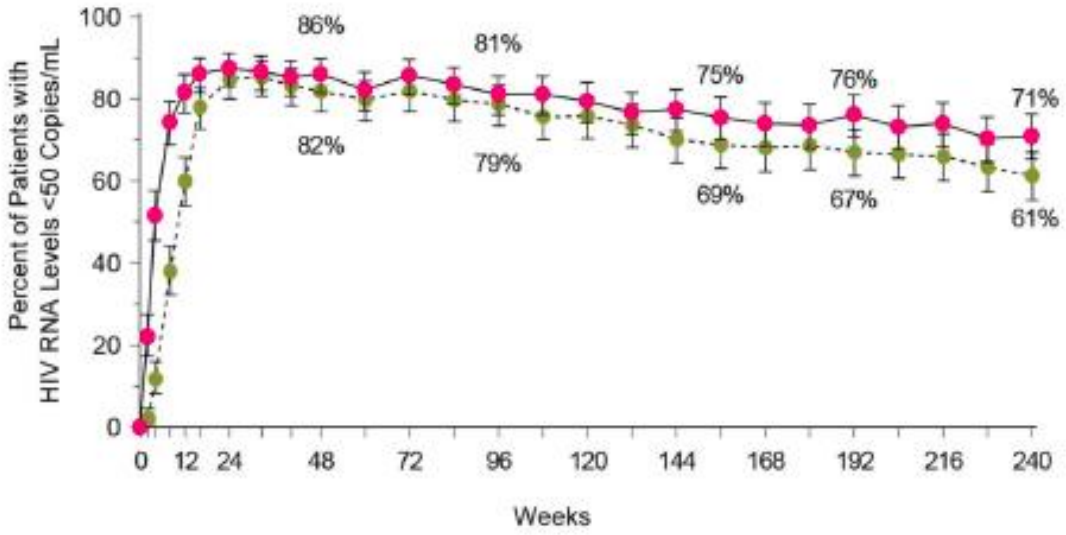
Sharon L. Walmsley, M.D., Antonio Antela, M.D., Ph.D., Nathan Clumeck, M.D., Dan Duiculescu, M.D., Andrea Eberhard, M.D., Felix Gutiérrez, M.D., Laurent Hocqueloux, M.D., Franco Maggiolo, M.D., Uriel Sandkovsky, M.D., Catherine Granier, D.E.S.S., Keith Pappa, Pharm.D., Brian Wynne, M.D., Sherene Min, M.D., and Garrett Nichols, M.D., for the SINGLE Investigators*



Durable Efficacy and Safety of Raltegravir Versus Efavirenz When Combined With Tenofovir/Emtricitabine in Treatment-Naive HIV-1–Infected Patients: Final 5-Year Results From STARTMRK

Jürgen K. Rockstroh, MD, Edwin DeJesus, MD,† Jeffrey L. Lennox, MD,‡ Yazdan Yazdanpanah, MD, PhD,§ Michael S. Saag, MD,|| Hong Wan, MS,¶ Anthony J. Rodgers, MS,¶ Monica L. Walker, BS,¶ Michael Miller, PhD,¶ Mark J. DiNubile, MD,¶ Bach-Yen Nguyen, MD,¶ Hedy Teppler, MD,¶ Randi Leavitt, MD, PhD,¶ and Peter Sklar, MD, MPH,¶ for the STARTMRK Investigators*

A



Number of Contributing Patients

Raltegravir 400 mg b.i.d.	281	278	279	280	281	281	277	280	281	281	277	279
Efavirenz 600 mg q.h.s.	282	282	282	281	282	282	281	281	282	282	282	279

Possible Impact of Newer ART

- Rapid suppression of viremia (INSTIs)
  - role in PMTCT, TasP?
- Superior tolerability=superior ITT
  - Improved retention on ART and care?
- Fewer side effects and toxicity
  - Less resources needed to deliver ART?

Perfection not required

INNOVATIONS IN ADHERENCE

"I am on ART for the past 2 years, I always take it at the same time, everyday, but one day, I missed my pill by 15 minutes. Does it mean that I will become drug resistant? I am very worried."

-Question on TheBody.com

Innovations in Adherence

- Newer medications are better
- Perfection not required
  - 90% (maybe lower?) adherence is adequate
  - Stopwatch not required
- Substance dependency doesn't prevent adherence or ART success

Better Medications and Adherence

Better medications: fewer barriers to engagement in care, retention on ART and human resources needed to deliver care

- Fewer pills (4 single tablet regimens)
- Fewer doses (most regimens once-daily)
- Fewer dietary restrictions (some)
- Fewer side effects (INSTI < NNRTI $\leq$ PI/r)
- Fewer drug-drug interactions (some)

Similar Adherence Rates Favor Different Virologic Outcomes for Patients Treated with Nonnucleoside Analogues or Protease Inhibitors

Franco Maggiolo,[1,2] Laura Ravasio,[1] Diego Ripamonti,[1,2] Giampietro Gregis,[1,2] Giampaolo Quinzan,[1,2] Claudio Arici,[1] Monica Airoldi,[1] and Fredy Suter[1]

[1]Division of Infectious Diseases and [2]Unit of Antiviral Therapy, Ospedali Riuniti, Bergamo, Italy

- "95% adherence" derived from unboosted PI data
- ~80% adherence may be adequate with newer regimens

Less Than 95% Adherence to Nonnucleoside Reverse-Transcriptase Inhibitor Therapy Can Lead to Viral Suppression

David R. Bangsberg

Epidemiology and Prevention Interventions Center, Division of Infectious Diseases, and the Positive Health Program, San Francisco General Hospital, University of California, San Francisco, California

(See the editorial commentary by Gulick on pages XXX–XX.)

For antiretroviral therapy, the 95% adherence "threshold" is based on nucloside-exposed patients who are receiving partially suppressive, unboosted protease inhibitor regimens. Using unannounced pill counts and electronic medication monitoring, viral suppression is common with a 54%–100% mean adherence level to nonnucleoside reverse-transcriptase-inhibitor regimens. Although perfect adherence is an important goal, viral suppression is possible with moderate adherence to potent regimens.

Patterson, *Ann Int Med,* 1998
Bangsberg, *Clin Infect Dis, 2006*
Maggiolo, Clin Infect Dis, 2005

Lower Pill Burden and Once-Daily Antiretroviral Treatment Regimens for HIV Infection: A Meta-Analysis of Randomized Controlled Trials

Jean B. Nachega,[1,2,3,4,a] Jean-Jacques Parienti,[5,6,a] Olalekan A. Uthman,[7,8,9] Robert Gross,[10] David W. Dowdy,[2] Paul E. Sax,[11] Joel E. Gallant,[12] Michael J. Mugavero,[13] Edward J. Mills,[14] and Thomas P. Giordano[15]

- Lower pill burden associated with both better adherence and virological suppression
- Adherence but not virological suppression was slightly better with once- vs twice-daily regimens.

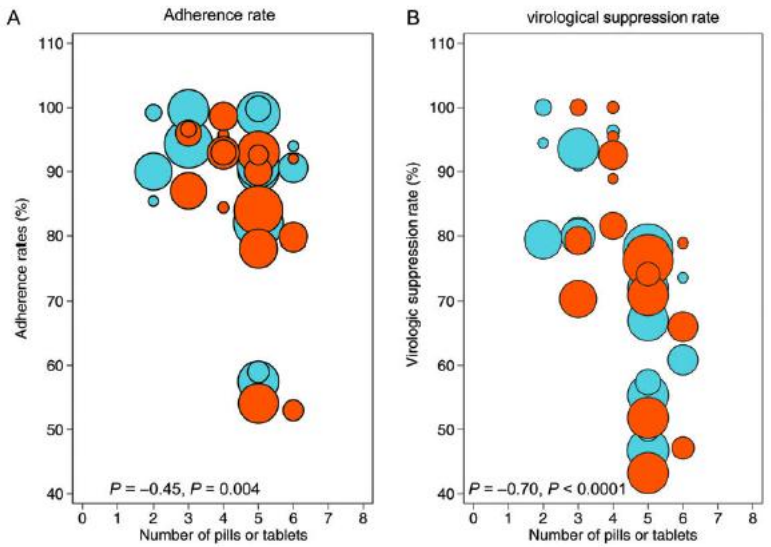
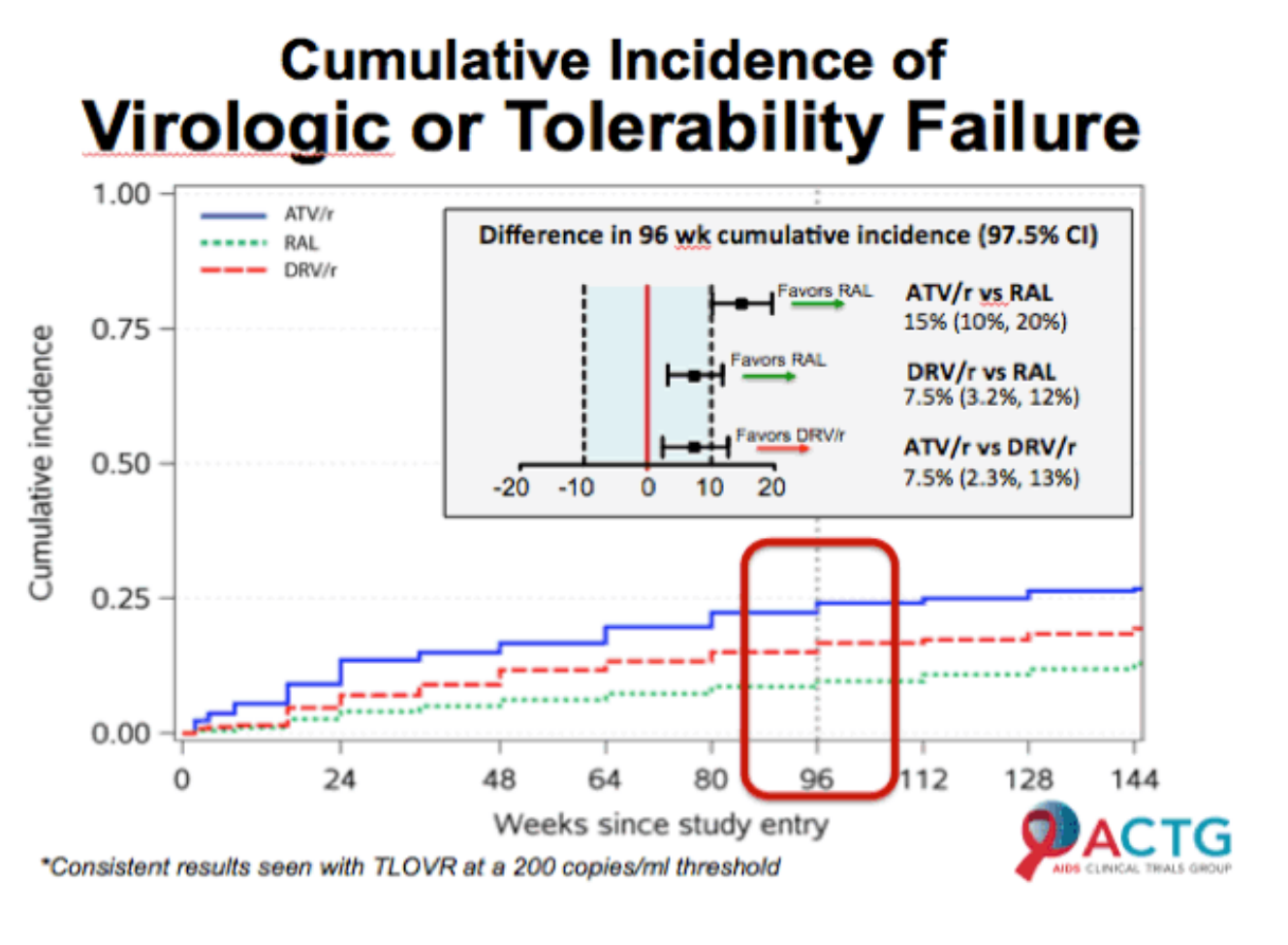


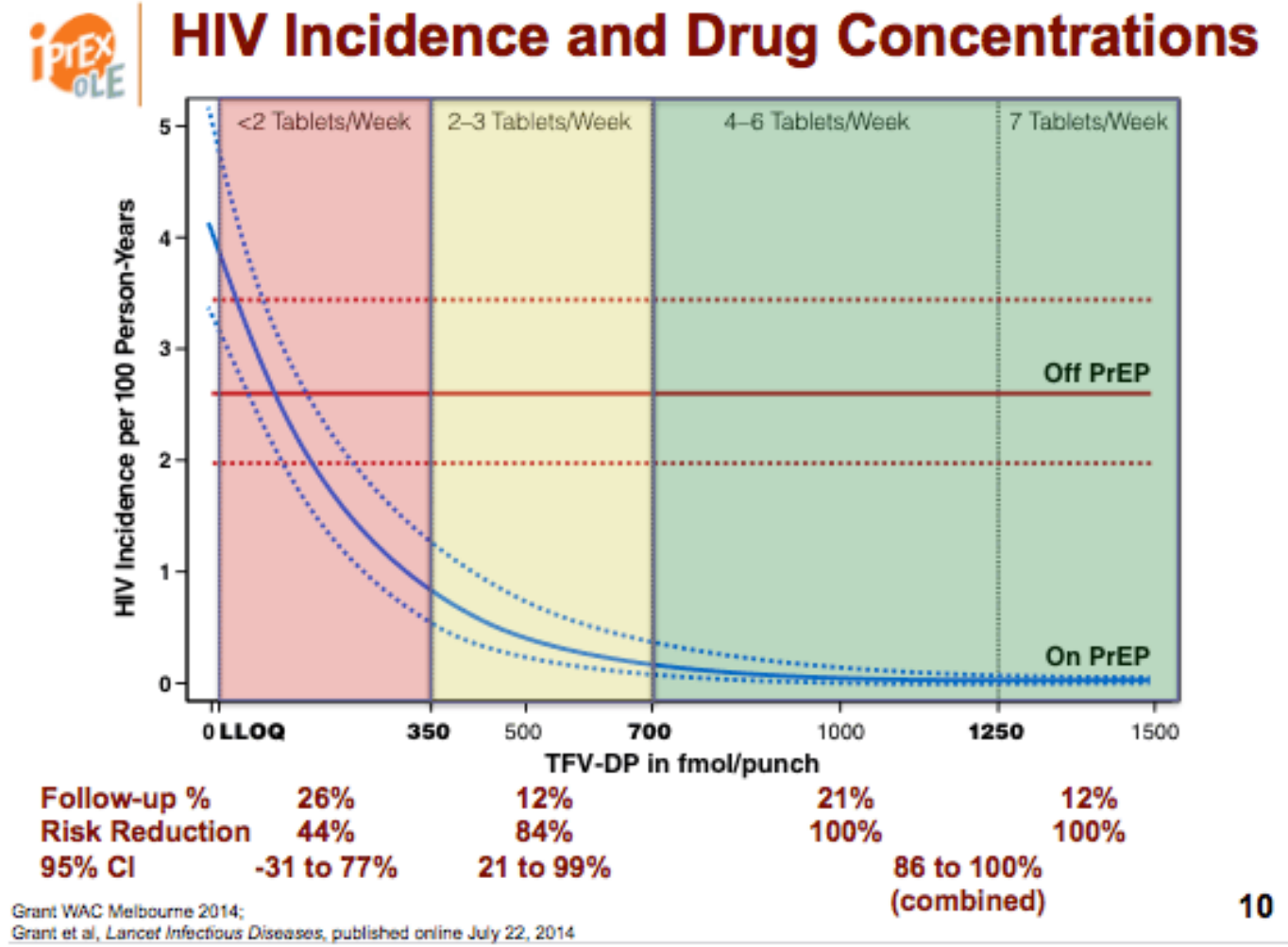
Figure 2. Antiretroviral therapy adherence rate, virological response, and pill burden. Area of circle is proportional to the sample size. Blue, once-daily regimens; orange, twice-daily regimens.

Clin Infect Dis, 2014

Once vs Twice Daily: ACTG 5257



PrEP Adherence: Good but not perfect is ok



Impact of adherence innovations

- Current meds don't require perfect adherence to work.
- Tolerability drives superiority of regimens
  - Even twice-daily can be superior to once-daily

What to test and when to test

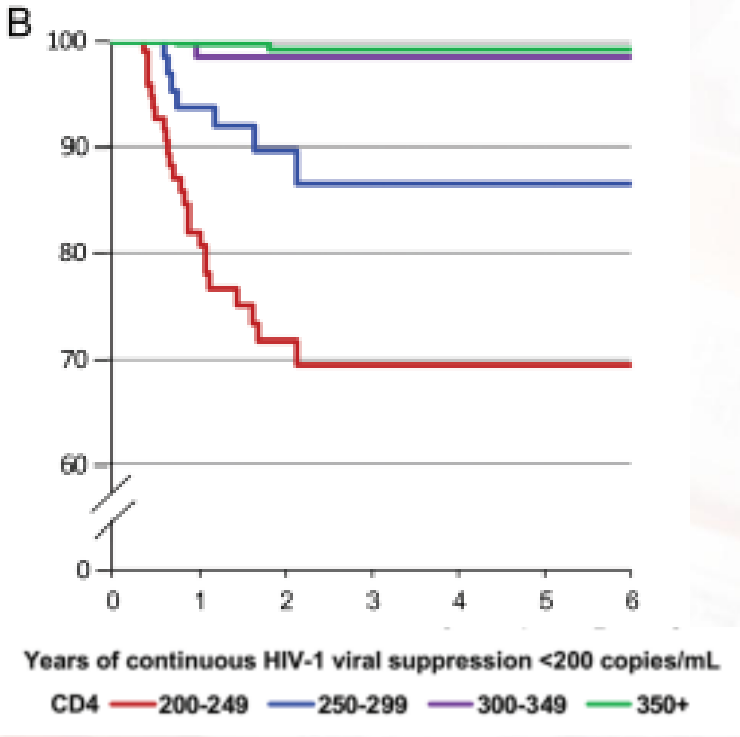
INNOVATIONS IN DIAGNOSTICS

Innovations in Diagnostics

- HIV self-testing
- Point of care testing
  - CD4
  - VL

Is Frequent CD4$^+$ T-Lymphocyte Count Monitoring Necessary for Persons With Counts ≥300 Cells/μL and HIV-1 Suppression?

Howard B. Gale,[1] Steven R. Gitterman,[1] Heather J. Hoffman,[2] Fred M. Gordin,[1,3] Debra A. Benator,[1,3] Ann M. Labriola,[1,3] and Virginia L. Kan[1,3]



Gale, Clin Inf Dis 2013

Viral load testing: WHO 2013

7.3.2 Monitoring the response to ART and the diagnosis of treatment failure

New recommendations

NEW

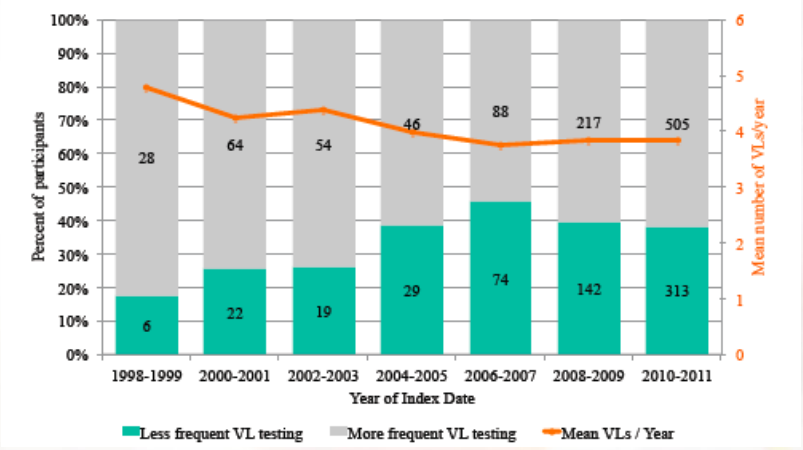
- Viral load is recommended as the preferred monitoring approach to diagnose and confirm ARV treatment failure *(strong recommendation, low-quality evidence)*.
- If viral load is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure *(strong recommendation, moderate-quality evidence)*.

HIV viral load monitoring frequency and risk of treatment failure among immunologically stable HIV-infected patients prescribed combination antiretroviral therapy

Benjamin Young[1,2], Rachel Debes[3], Kate Buchacz[4], Mia Scott[1], Frank Palella[5], John T. Brooks[4] and the HOPS Investigators
[1]APEX Family Medicine, Denver, CO; [2]International Association of Providers of AIDS Care, Washington DC; [3]Cerner Corporation, Vienna, VA; [4]Centers for Disease Control and Prevention (CDC), Atlanta, GA; [5]Northwestern University, Chicago, IL

- Large immunologically stable and virologically suppressed US cohort (n=1,607, less frequent (≤2/yr) VL testing not associated with increased risk of viral failure (OR 1.1; 95% CI: 0.8-1.6)
- Supports DHHS guidelines for VL monitoring.
- May result in substantial cost savings.

Figure 1. Frequency of VL testing and mean number of VL tests performed in the year prior to index date (i.e., period 2), the HIV Outpatient Study, 1998-2011 (N=1,607)



CONTROLLING THE HIV EPIDEMIC WITH ANTIRETROVIRALS
Avoiding the Cost of Inaction

Lab Monitoring: DHHS Guidelines

CD4 monitoring:

After 2 years on ART with consistently suppressed viral load:

- CD4 count 300-500 cells/mm^3: ***Every 12 months*** **(BII)**
- CD4 count >500 cells/mm^3: ***CD4 monitoring is optional*** **(CIII)**

HIV RNA monitoring:

Clinicians may extend the interval of viral load testing to 6 months for adherent patients whose viral load has been suppressed for more than 2 years and whose clinical and immunologic status is stable (**AIII**).

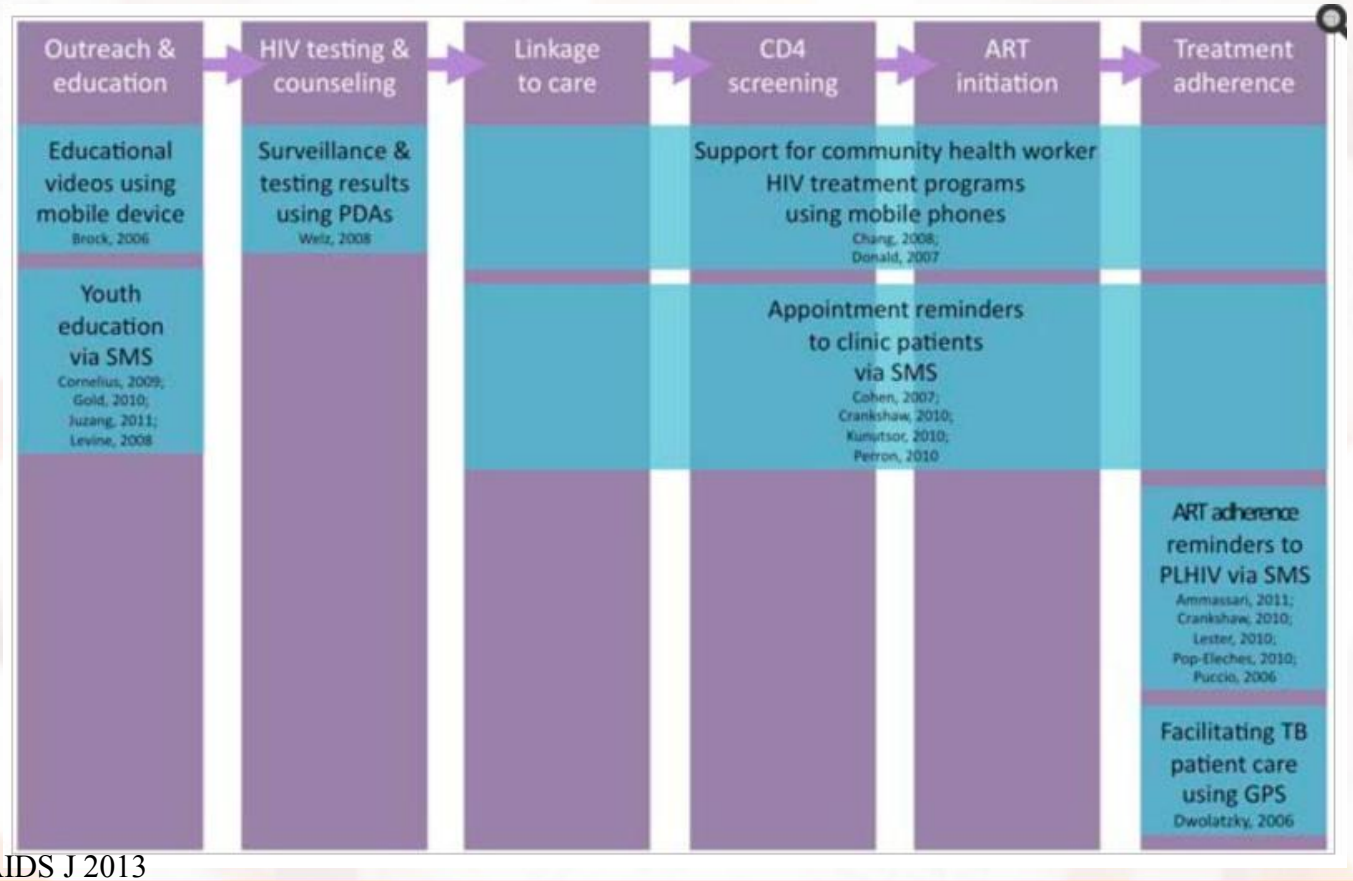
Impact of diagnostic innovation?

- Improving case finding (step 1 of cascade)
- Improving access to lab testing
- Among stable patients:
  - less frequent monitoring=resource savings

Building human capacity

TASK SHIFTING

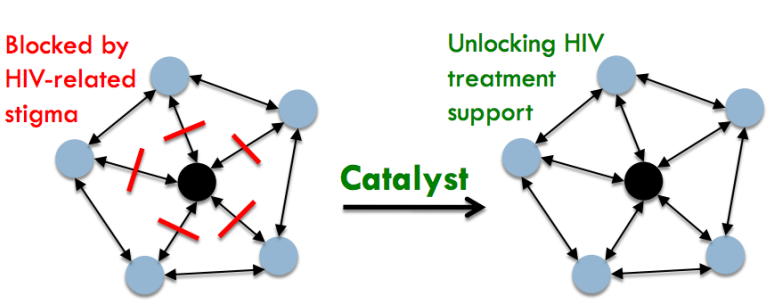
mHealth

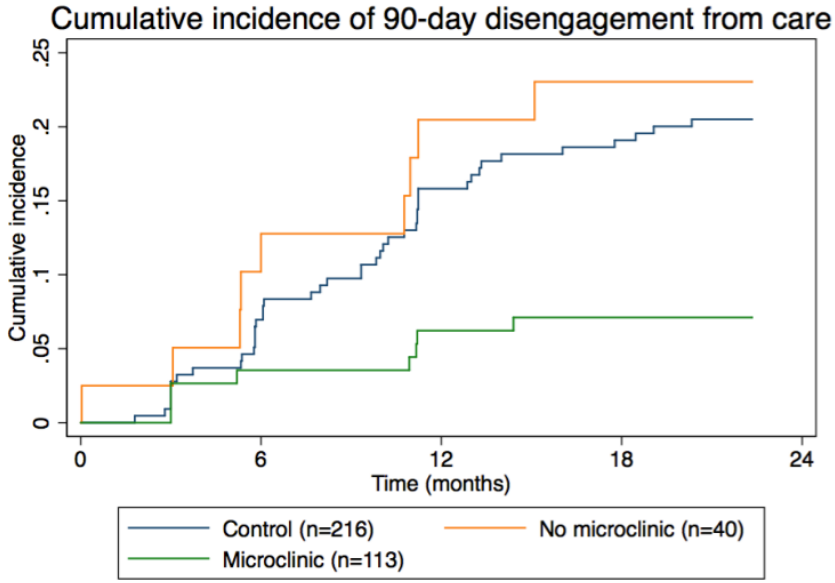


Catalani, Open AIDS J 2013

Pulling the network together:
The 'microclinic' social network intervention for promoting engagement in HIV care on Mfangano Island, Kenya

Exploiting social capital to address stigma and engagement in care



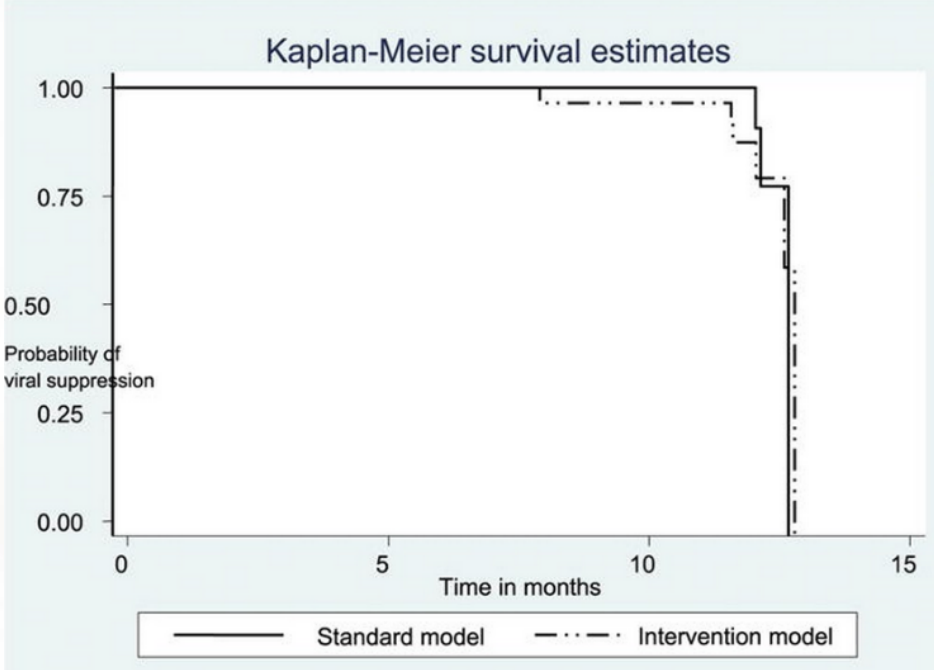


Hickey, Adherence2014

Noninferiority of a Task-Shifting HIV Care and Treatment Model Using Peer Counselors and Nurses Among Ugandan Women Initiated on ART: Evidence From a Randomized Trial

Kiweewa, Flavia M. MBChB, Msc (Epidemiology)[*,†]; Wabwire, Deo MBChB, MMED[*]; Nakibuuka, Jessica MBChB[*]; Mubiru, Mike BStat, DMS[*]; Bagenda, Danstan Msc, PhD[*,†]; Musoke, Phillippa MBChB, MMED, PhD[*,‡]; Fowler, Mary G. MD, MPH[*,§]; Antelman, Gretchen MPH, ScD[‖]

Nurses and peer counselors were not inferior to physicians in providing ART follow-up care to postpartum women, an approach that may help deliver treatment to many more HIV-infected people.

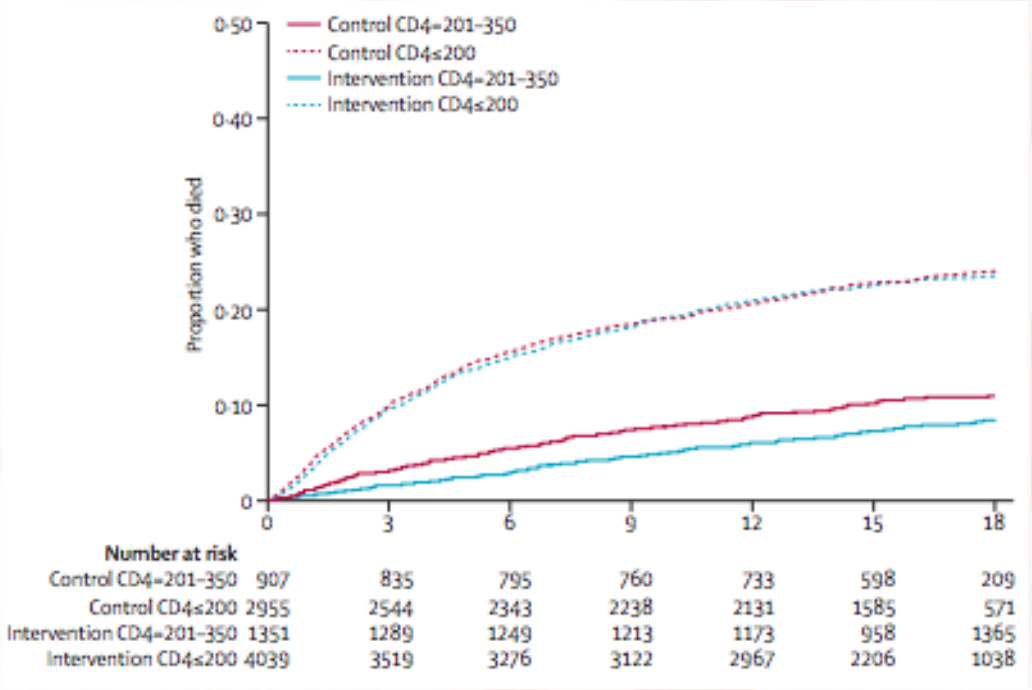


Kiweewa, et al., JAIDS. 2013.

Task shifting of antiretroviral treatment from doctors to primary-care nurses in South Africa (STRETCH): a pragmatic, parallel, cluster-randomised trial

Lara Fairall, Max O Bachmann, Carl Lombard, Venessa Timmerman, Kerry Uebel, Merrick Zwarenstein, Andrew Boulle, Daniella Georgeu, Christopher J Colvin, Simon Lewin, Gill Faris, Ruth Cornick, Beverly Draper, Mvula Tshabalala, Eduan Kotze, Cloete van Vuuren, Dewald Steyn, Ronald Chapman, Eric Bateman

"Expansion of primary-care nurses' roles to include ART initiation and represcription can be done safely, and improve health outcomes and quality of care, but might not reduce time to ART or mortality."



Fairall, Lancet 2012

Innovations: Summary

- HIV medications are safer and better tolerated
- Medication adherence doesn't require perfection
- Among stable patients, lab monitoring may be less frequent
- Task shifting works
- Innovations in HIV care will facilitate expanded access to ARTs for treatment and prevention

Innovations in Health Care Delivery

Influence on HIV care and treatment

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