Evolving HIV Treatment Paradigms

What we need to know

Benjamin Young

International Association of Providers of AIDS Care

Washington, DC, USA

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Evolving HIV Treatment Paradigms

When/who to treat

Better medicines

Easier adherence

Diagnostics

Task shifting

Clinical Infectious Diseases

Controlling the HIV Epidemic With Antiretrovirals

A Supplement to *Clinical Infectious Diseases*

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."

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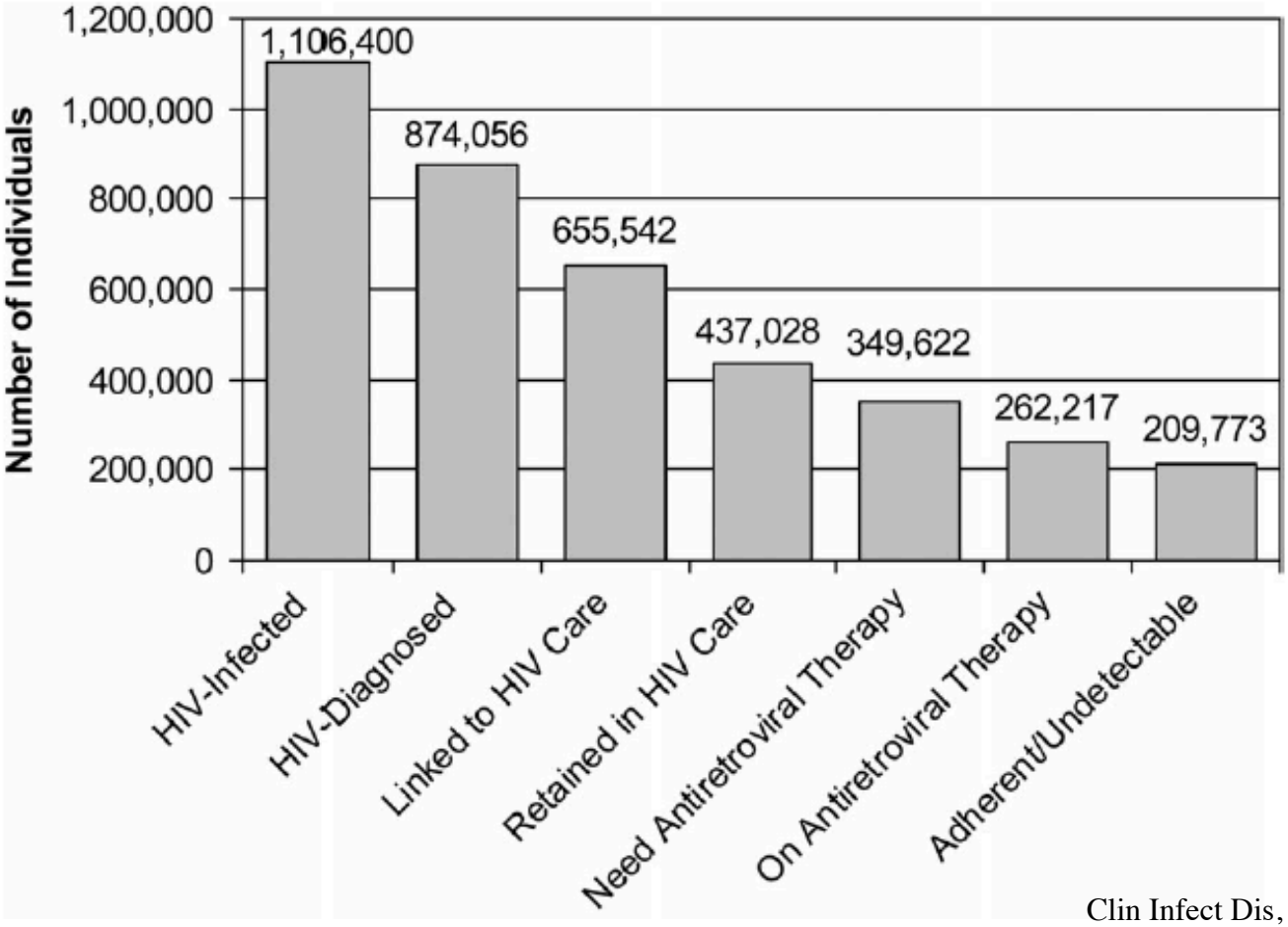
Sigaloff, Lange, Montaner, Clin Infect Dis 2014

The Spectrum of Engagement in HIV Care and its Relevance to Test-and-Treat Strategies for Prevention of HIV Infection

Edward M. Gardner,[1,3] Margaret P. McLees,[1,3] John F. Steiner,[2] Carlos del Rio,[4,5] and William J. Burman[1,3]

[1]Denver Public Health and [2]Kaiser Permanente Colorado, Denver, [3]University of Colorado Denver, Aurora, Colorado, and [4]Rollins School of Public Health of Emory University, and [5]Emory Center for AIDS Research, Atlanta, Georgia



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Clin Infect Dis, 2011

New combinations, superior tolerability

EVOLVING ART

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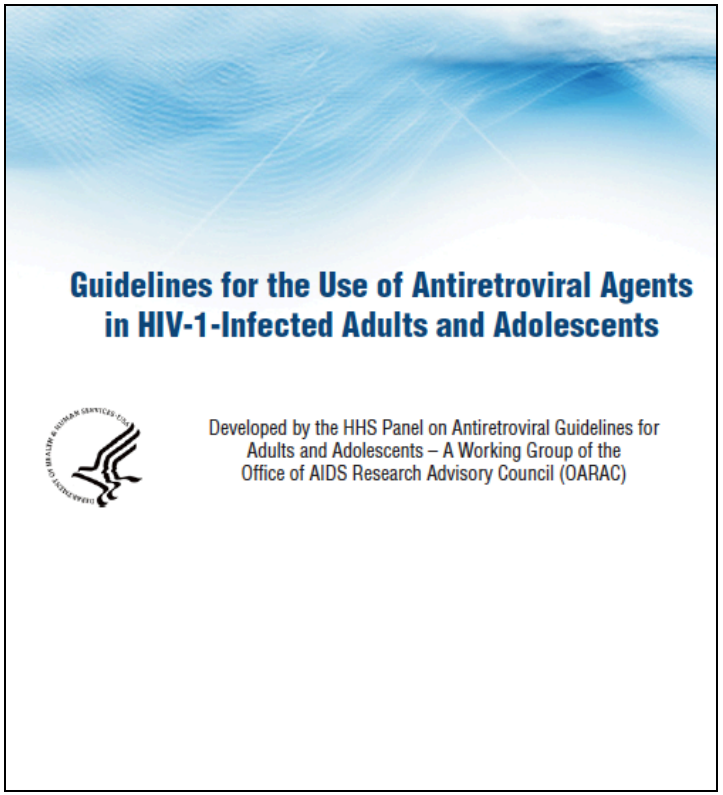
Evolving ART Combinations



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)**

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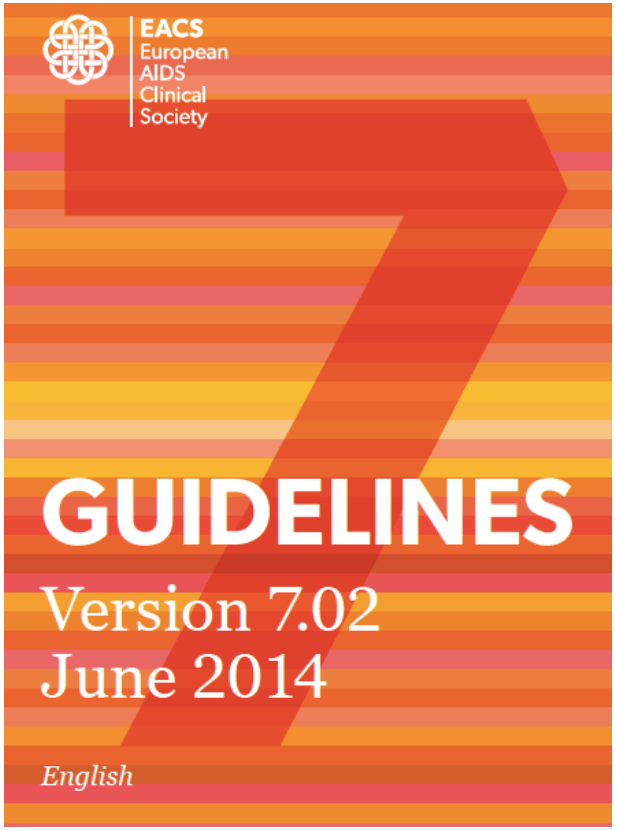
DHHS Panel, 2014

Evolving ART Combinations



A	B
NNRTI	**NRTI**
EFV[(i)] RPV[(ii)]	ABC/3TC[(vii)] or TDF/FTC
PI/r	
ATV/r[(iv)] DRV/r[(iv)]	ABC/3TC[(vii)] or TDF/FTC
INSTI	
EVG + COBI	FTC/TDF
RAL	TDF/FTC or ABC/3TC

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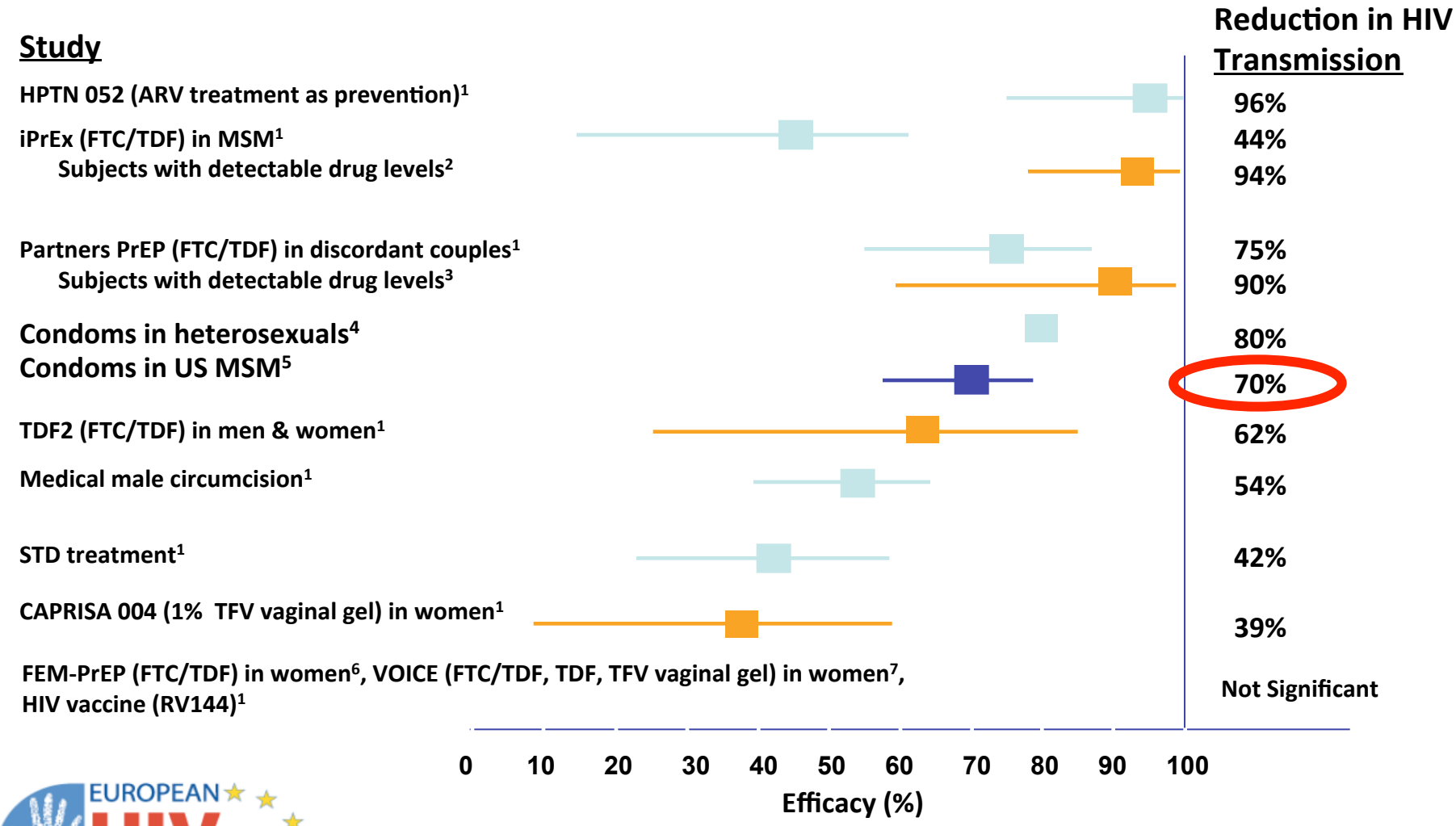
EACS, 2014

Relative Efficacy of HIV Prevention Strategies



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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

PREEXPOSURE PROPHYLAXIS FOR THE PREVENTION OF HIV INFECTION IN THE UNITED STATES - 2014

A CLINICAL PRACTICE GUIDELINE

US Public Health Service, 2014

Evolving ART Tolerability

	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**

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Raffi, et al., Lancet, 2013

Evolving first-line ART:
Integrase Inhibitor-based Treatments

- **Dolutegravir**
  - **DTG superior to EFV** (SINGLE;Walmsley, New Engl J Med, 2013)
  - **DTG superior to DRV/r** (FLAMINGO,Clotet, Lancet 2014)
- **Elvitegravir**
  - **EVG/c/TDF/FTC switch superior to continued PI/r ART** (STRATEGY studies, Pozniak, Lancet ID 2014)
- **Raltegravir**
  - **RAL superior to EFV** (STARTMRK 5 year analysis; Rockstroh, JAIDS 2013)
  - **RAL superior to DRV/r and ATV/r** (ACTG 5257 (Landovitz, CROI2014)

Perfection not required

EVOLVING ADHERENCE

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"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

Evolving 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)

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.

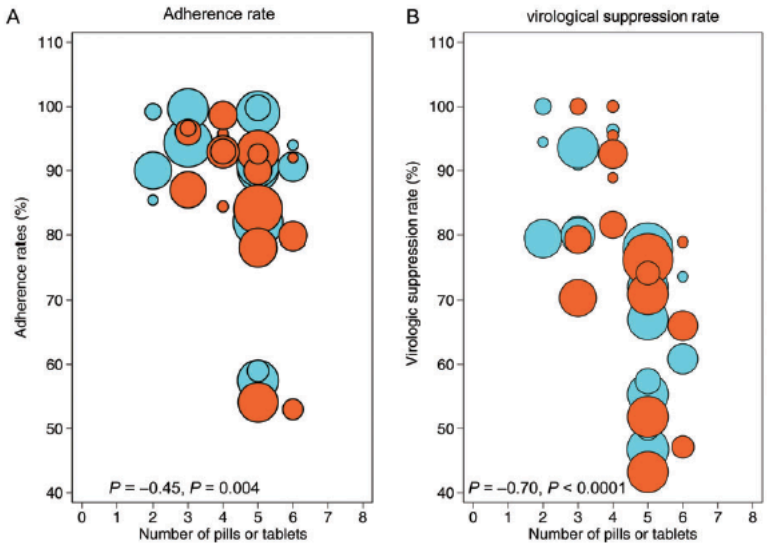

Figure 2. Antiretroviral therapy adherence rate, virological response, and pill burden. Area of circle is proportional to the sample size. Blue, once-daily regimens; orange, twice-daily regimens.

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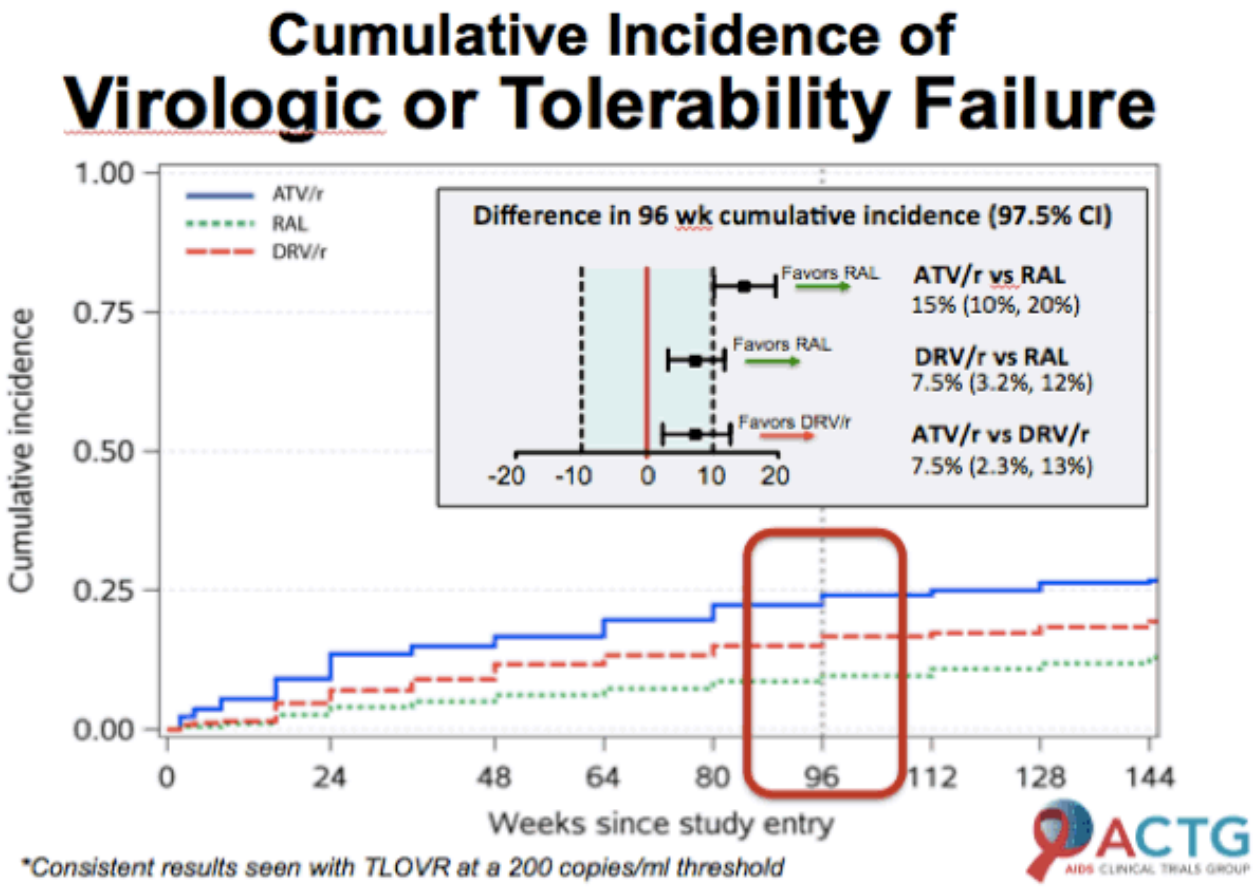
Clin Infect Dis, 2014

Once vs Twice Daily: ACTG 5257



*Consistent results seen with TLOVR at a 200 copies/ml threshold

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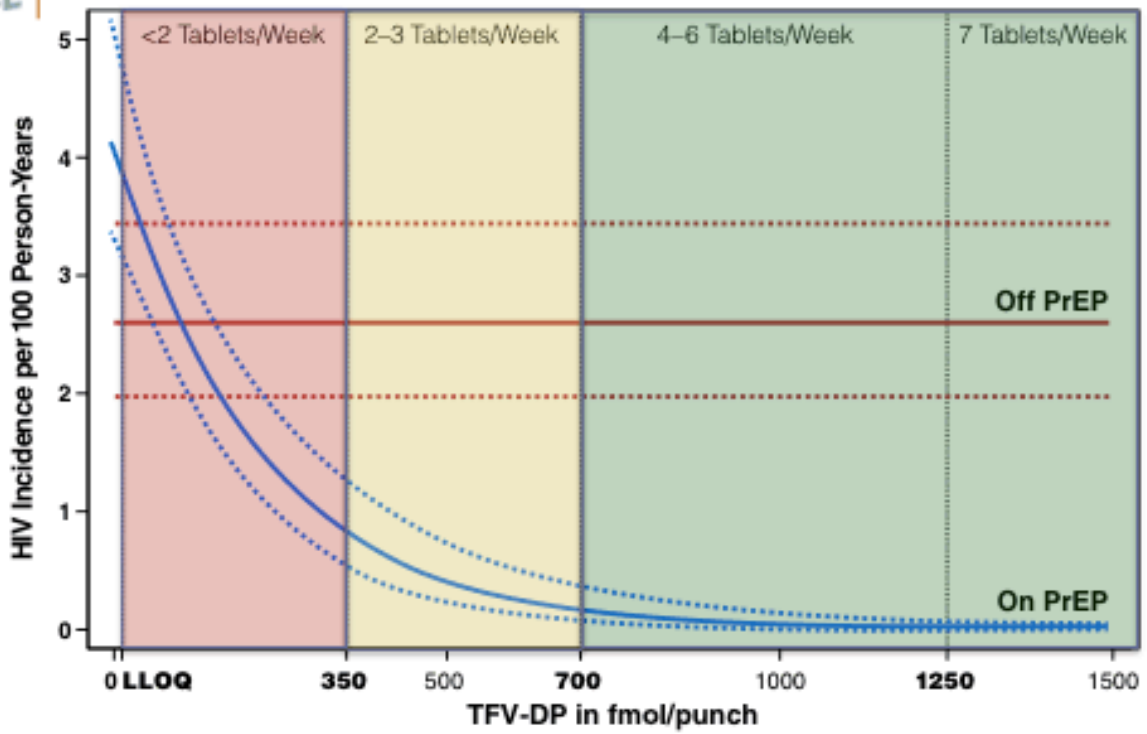
PrEP Adherence: Good but not perfect is ok

HIV Incidence and Drug Concentrations



Follow-up %	26%	12%	21%	12%
Risk Reduction	44%	84%	100%	100%
95% CI	-31 to 77%	21 to 99%	86 to 100% (combined)	

Grant WAC Melbourne 2014;
Grant et al, *Lancet Infectious Diseases*, published online July 22, 2014

What to test and when to test

EVOLVING DIAGNOSTICS

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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)*.

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**).

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DHHS Treatment Guidelines March 2014

Building human capacity

EVOLVING TASK SHIFTING

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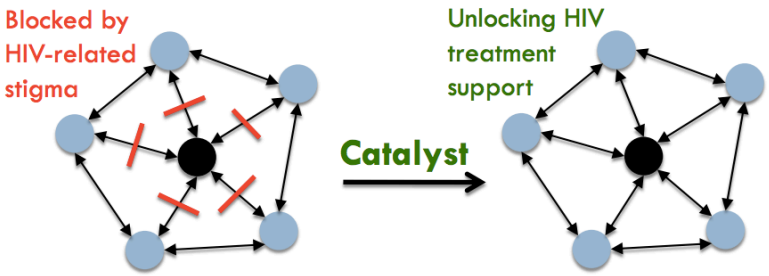
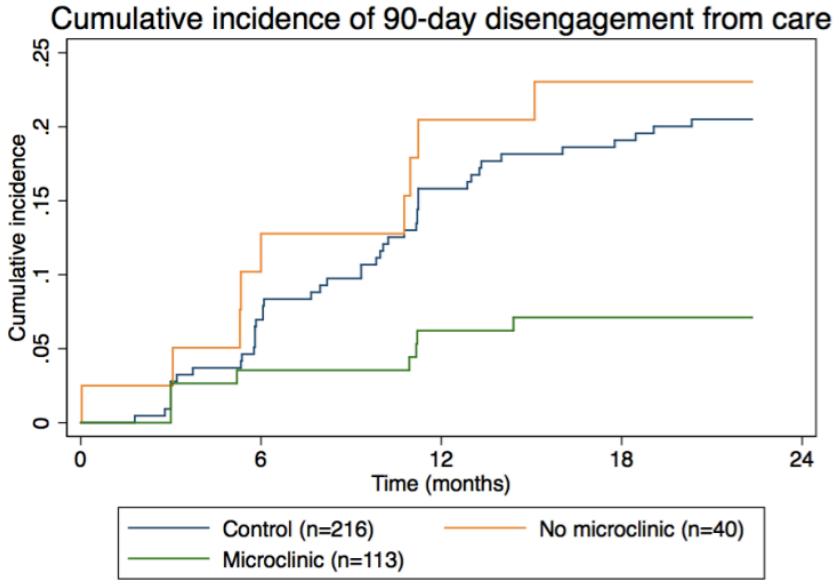
Pulling the network together:
The 'microclinic' social network intervention for promoting engagement in HIV care on Mfangano Island, Kenya

Exploiting social capital to address stigma and engagement in care





Hickey, Adherence2014

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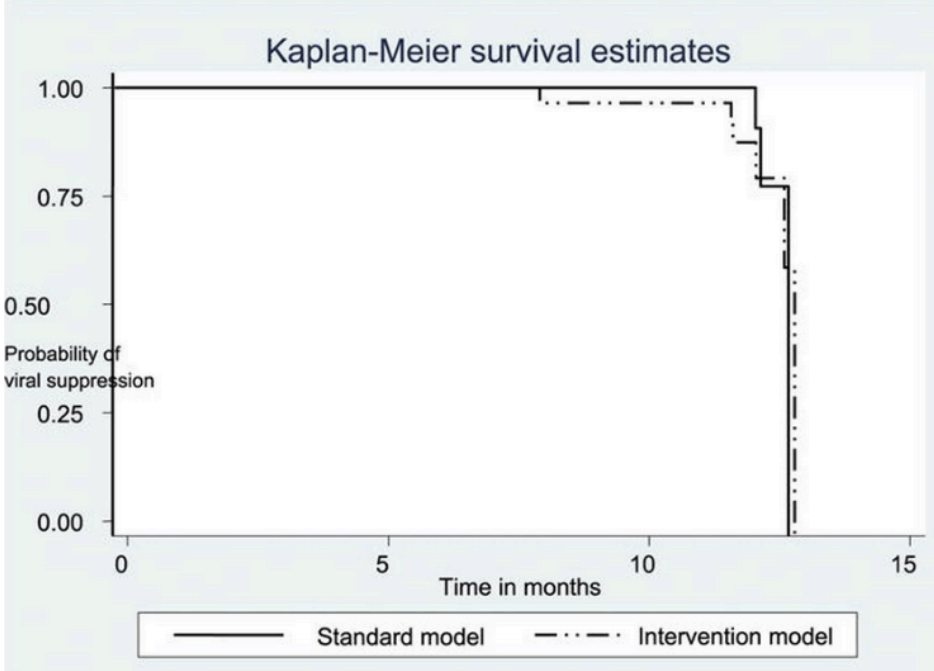
Noninferiority of a Task-Shifting HIV Care and Treatment Model Using Peer Counselors and Nurses Among Ugandan Women Initiated on ART: Evidence From a Randomized Trial

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.



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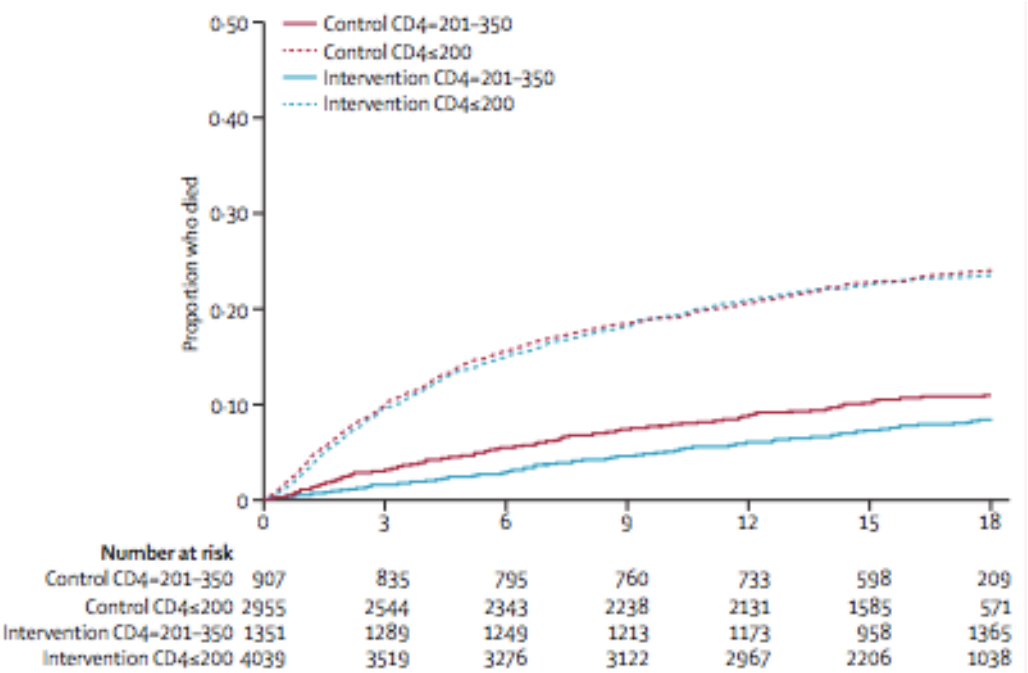
Kiweewa, et al., JAIDS. 2013.

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

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Ending epidemic AIDS

EVOLVING TARGETS

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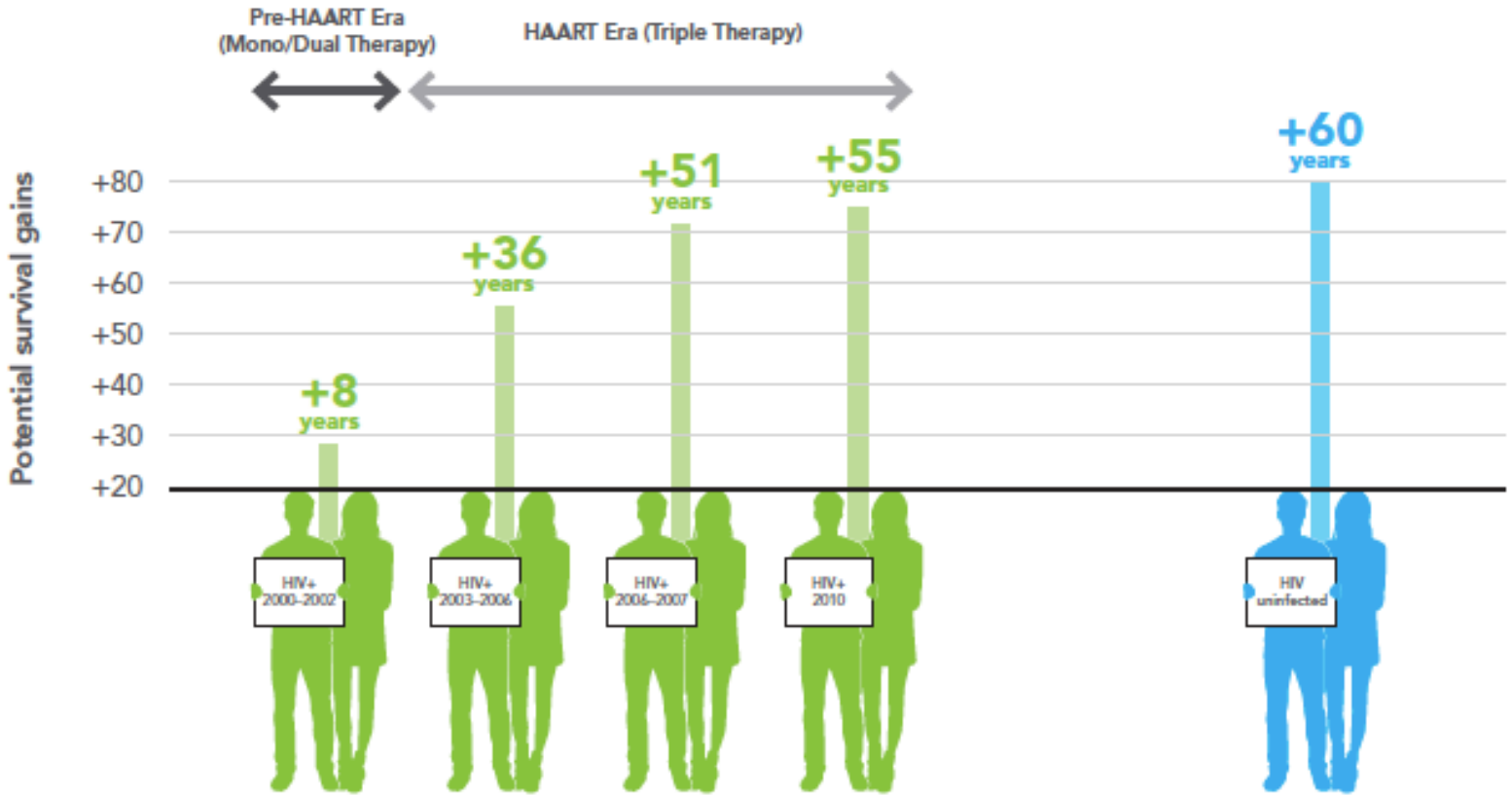
Normal Life Expectancy?



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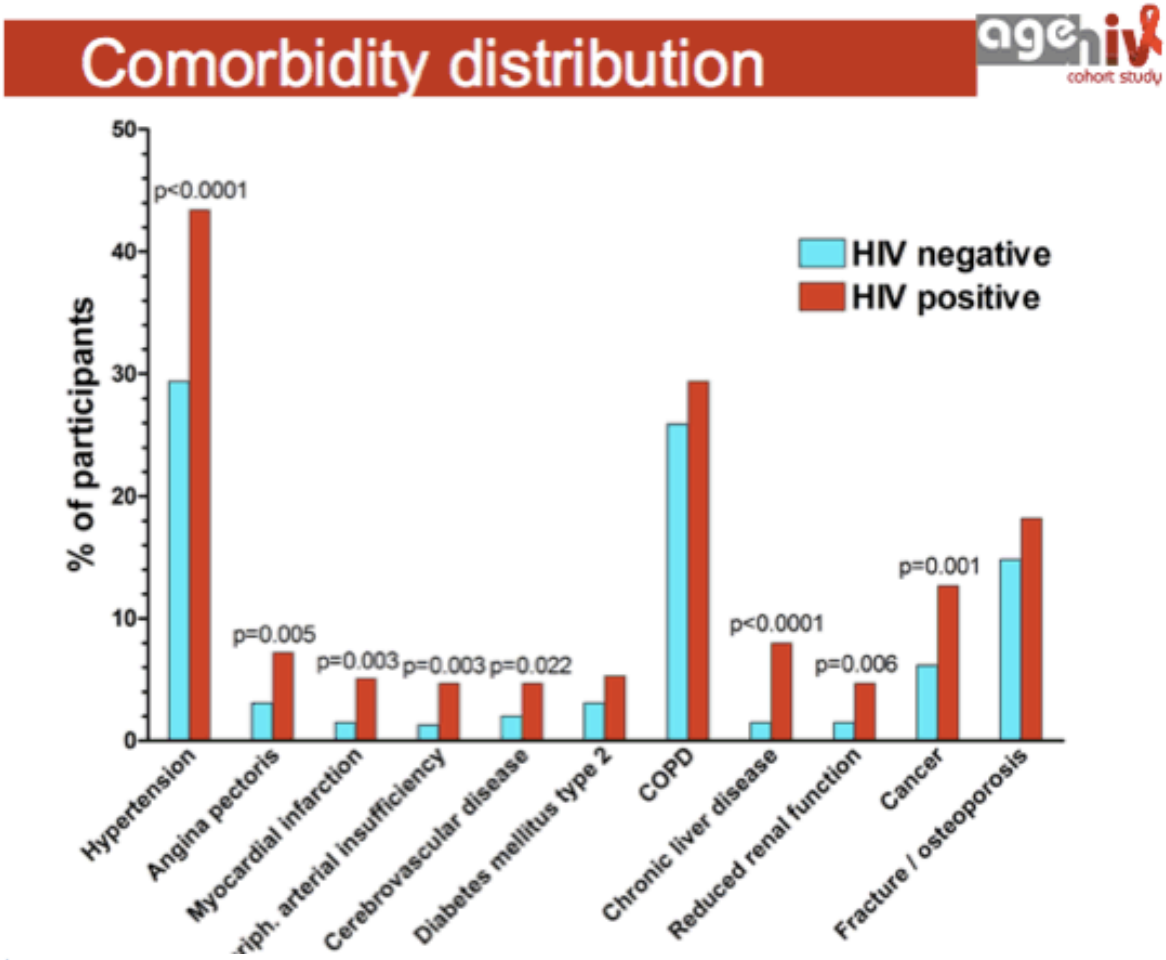
Healthy Aging and HIV



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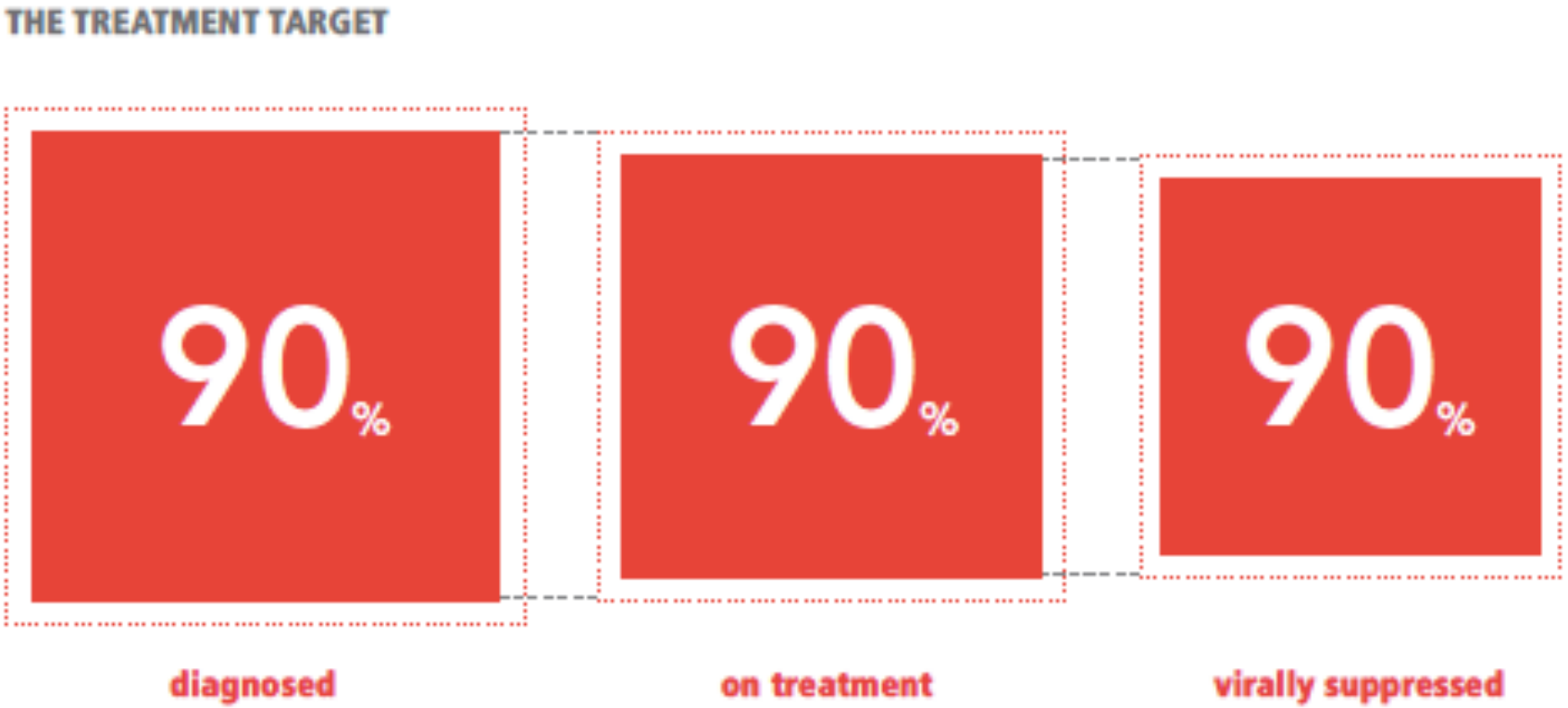
Schouten, XIX IAC, 2012

Evolving Targets



UNAIDS, 2014

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Evolving HIV Treatment Paradigms:
Summary

- Treat all
- 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 = larger role for nurses
- Evolving targets

Educational Matters

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