Early Treatment for HIV

The Case for Starting Antiretroviral Medications As Early As Possible

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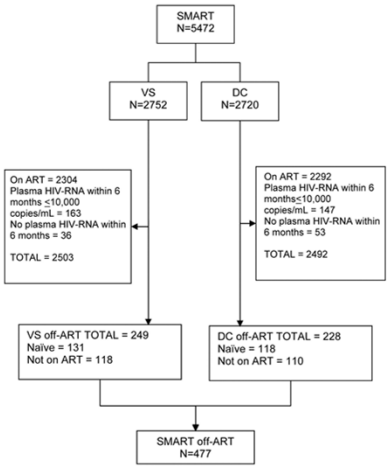
Why Start Early:

- It's good for the individual's health
- It's good for the public health
- It's in the guidelines

Starting HIV Medications Early is Good for the Health of the Individual

The SMART Study

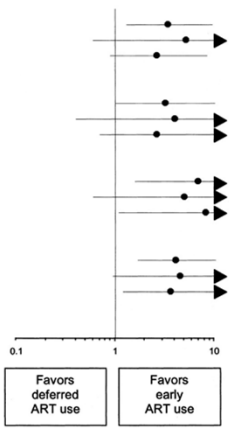
- Randomized study that looked at whether intermittent or continuous HIV treatment was better
- Sub-study looked at outcomes between individuals with later start of ARV (drug conservation group, started T cells <250) vs early treatment (viral suppression group) among naïve individuals and those not on ARV 6 months prior to entry
- Outcomes were death, opportunistic disease, non-AIDS related major events, and composite of all events



SMART Study

Hazard ratios (HRs) for clinical outcomes among the overall cohort and among those who were either antiretroviral therapy (ART) naïve or not receiving ART at baseline.

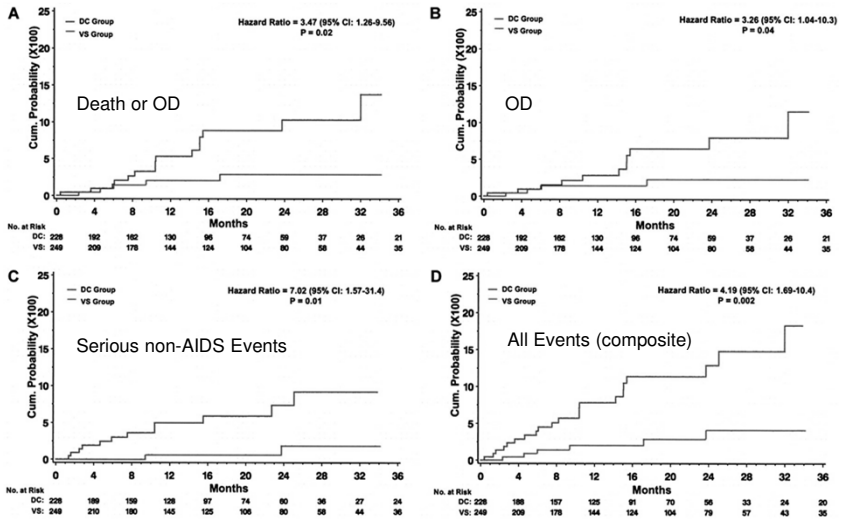
	No. Events (rate per 100 person years) DC	VS	HR (DC/VS)	Hazard Ratio (DC/VS) and 95% Confidence Interval	P-value	P-value for Interaction
OD/Death						
Overall	15 (4.8)	5 (1.3)	3.5		0.02	
ART naïve	4 (2.7)	1 (0.5)	5.3		0.13	0.63
Off ART	11 (6.8)	4 (2.2)	2.7		0.09	
OD						
Overall	11 (3.5)	4 (1.1)	3.3		0.04	
ART naïve	3 (2.0)	1 (0.5)	4.1		0.22	0.81
Off ART	8 (4.9)	3 (1.6)	2.7		0.14	
Serious Non-AIDS						
Overall	12 (3.9)	2 (0.5)	7.0		0.01	
ART naïve	4 (2.8)	1 (0.5)	5.1		0.15	0.76
Off ART	8 (4.8)	1 (0.5)	8.4		0.04	
Composite						
Overall	21 (7.0)	6 (1.6)	4.2		0.002	
ART naïve	7 (4.9)	2 (1.0)	4.6		0.06	0.84
Off ART	14 (9.0)	4 (2.2)	3.7		0.02	



The Strategies for Management of Antiretroviral Therapy (SMART) Study Group J Infect Dis. 2008;197:1133-1144

The SMART Study

Kaplan-Meier time curves for cumulative probability of opportunistic disease (OD) and death (A) OD alone (B) serious non-AIDS events (C) non-OD death (D) and the composite of OD and serious non-AIDS events, which includes all-cause death (D).



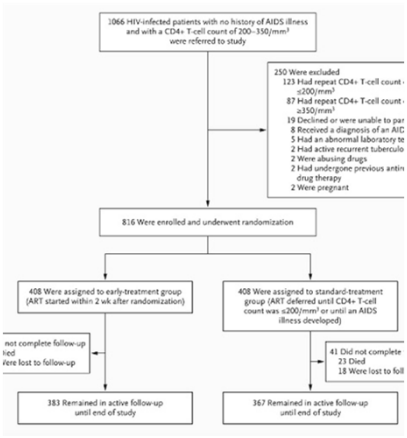
The Strategies for Management of Antiretroviral Therapy (SMART) Study Group J Infect Dis. 2008;197:1133-1144

SMART Study Conclusion

Initiation of ART at CD4+ cell counts >350 cells/μL compared with <250 cells/μL may reduce both OD and serious non-AIDS events.

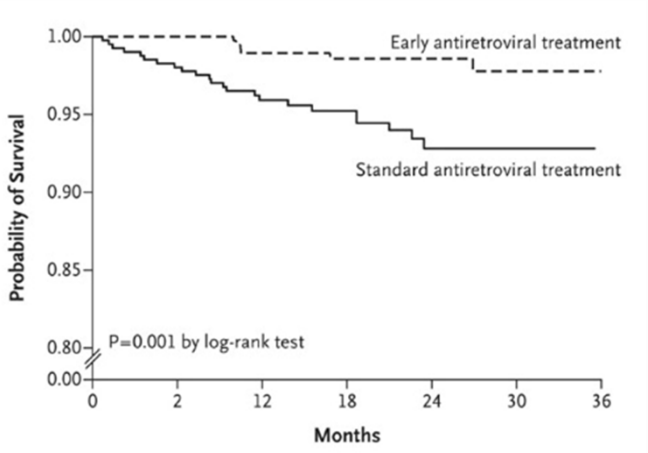
CIPRA HT-001 Study (Haiti)

- Randomized, open-label trial of early initiation of antiretroviral therapy, as compared with the standard timing for initiation of therapy
- Participants had T cells 200-350 without symptomatic HIV disease
- "Early" started within 2 weeks of enrollment
- "Standard" started when T cells <200 or symptoms



Severe et al. NEJM 2010

Severe Study in Haiti



CIPRA HT-001 Conclusion

- Early initiation of antiretroviral therapy decreased the rates of death and incident tuberculosis.
- Access to antiretroviral therapy should be expanded to include all HIV-infected adults who have CD4+ T-cell counts of less than 350 per cubic millimeter, including those who live in areas with limited resources.

NA-ACCORD

- North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD)
- Large Cohort study that includes data from nearly 90,000 individuals
- Racially diverse
- 30% women
- Diverse baseline HIV risk factors

United States

Atlanta, GA	Denver, CO	Minneapolis, MN	San Diego, CA	
Baltimore, MD	Detroit, MI	Nashville, TN	San Juan, PR	
Birmingham, AL	Durham, NC	New Orleans, LA	San Francisco, CA	
Boston, MA	Galveston, TX	New York, NY	San Leandro, CA	
Bronx, NY	Greensboro, NC	Oakland, CA	San Rafael, CA	
Brooklyn, NY	Honolulu, HI	Omaha, NE	Seattle, WA	
Buffalo, NY	Houston, TX	Philadelphia, PA	St. Louis, MO	
Chapel Hill, NC	Indianapolis, IN	Pittsburgh, PA	Stanford, CA	
Chicago, IL	Iowa City, IA	Portland, OR	Stony Brook, NY	
Cincinnati, OH	Kansas City, MO	Providence, RI	Tampa, FL	
Cleveland, OH	Los Angeles, CA	Rochester, NY	Torrance, CA	
Columbus, OH	Miami, FL	Sacramento, CA	Washington, DC	
Dallas, TX				

Canadian Region

British Columbia, Vancouver
Ontario: Hamilton, Kingston, London, Ottawa, Sudbury, Thunder Bay, Toronto, Windsor
Quebec: Montreal
Southern Alberta

Risk of Death- NA-ACCORD

Table 3. **Risk of Death Associated with Deferral of Antiretroviral Therapy, According to CD4+ Count at Baseline, with Adjustment for HIV RNA Level, Age, and Sex.***

Variable	351-to-500 CD4+ Count		More-Than-500 CD4+ Count	
	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
Without inclusion of HIV RNA data				
Deferral of antiretroviral therapy	1.69 (1.26–2.26)	<0.001	1.94 (1.37–2.79)	<0.001
Female sex	1.21 (0.89–1.64)	0.24	1.85 (1.33–2.59)	<0.001
Older age (per 10-yr increment)	1.68 (1.48–1.91)	<0.001	1.83 (1.62–2.06)	<0.001
Baseline CD4+ count (per 100 cells/mm^3)	1.13 (0.72–1.78)	0.59	0.93 (0.87–0.99)	0.03
With inclusion of HIV RNA data				
Deferral of antiretroviral therapy	1.63 (1.21–2.19)	0.002	1.85 (1.20–2.86)	0.006
Female sex	1.47 (1.02–2.12)	0.04	1.35 (0.85–2.15)	0.20
Older age (per 10-year increment)	1.89 (1.69–2.11)	<0.001	1.81 (1.58–2.07)	<0.001
Baseline CD4+ count (per 100 cells/mm^3)	0.74 (0.55–1.00)	0.06	0.97 (0.89–1.05)	0.45
Baseline HIV RNA level (per $\log_{10}$ copies/ml)	1.11 (0.96–1.28)	0.15	1.13 (0.96–1.33)	0.14

* The CD4+ count was measured in cells per cubic millimeter. Results were calculated with the use of Cox regression analyses with inverse probability-of-censoring weights. HIV denotes human immunodeficiency virus.

Kitahata et. al NEJM 2009

NA-ACCORD Conclusion

- Deferred therapy on 350-500 T cell range associated with 69% increased risk of death
- Deferred therapy in the >500 T cell range associated with 94% increased risk of death

Guidelines at a Glance

Slide #15

When to Start ART: IAS–USA Recommendations 2012

- Patient readiness should be considered when deciding to initiate antiretroviral therapy (ART)
- ART should be offered regardless of CD4 cell count (increasing strength of the recommendation as CD4 decreases)
  - CD4 < 500 cells/μL (AIa)
  - CD4 > 500 cells/μL (BIII)
  - Pregnancy (AIa)
  - Chronic HBV (AIIa)
  - HCV (may delay until after HCV treatment if CD4 > 500) (CIII)
  - Age older than 60 (BIIa)
  - HIV-associated nephropathy (AIIa)
  - Acute phase of primary HIV infection, regardless of symptoms (BIII)

Initiating Antiretroviral Therapy in Treatment-Naive Patients
(Last updated March 29, 2012; last reviewed March 27, 2012)

Panel's Recommendations

- Antiretroviral therapy (ART) is recommended for all HIV-infected individuals. The strength of this recommendation varies on the basis of pretreatment CD4 cell count:
  - CD4 count <350 cells/mm³ **(AI)**
  - CD4 count 350 to 500 cells/mm³ **(AII)**
  - CD4 count >500 cells/mm³ **(BIII)**
- Regardless of CD4 count, initiation of ART is strongly recommended for individuals with the following conditions:
  - Pregnancy **(AI)** (see perinatal guidelines for more detailed discussion)
  - History of an AIDS-defining illness **(AI)**
  - HIV-associated nephropathy (HIVAN) **(AII)**
  - HIV/hepatitis B virus (HBV) coinfection **(AII)**
- Effective ART also has been shown to prevent transmission of HIV from an infected individual to a sexual partner; therefore, ART should be offered to patients who are at risk of transmitting HIV to sexual partners **(AI** [heterosexuals] or **AII** [other transmission risk groups]; see text for discussion).
- Patients starting ART should be willing and able to commit to treatment and should understand the benefits and risks of therapy and the importance of adherence **(AII)**. Patients may choose to postpone therapy, and providers, on a case-by-case basis, may elect to defer therapy on the basis of clinical and/or psychosocial factors.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

ART should be offered regardless of CD4 cell count (increasing strength of the recommendation as CD4 decreases)

Antiretroviral therapy (ART) is recommended for all HIV-infected individuals. The strength of this recommendation varies on the basis of pretreatment CD4 cell count:

- CD4 count <350 cells/mm³ **(AI)**
- CD4 count 350 to 500 cells/mm³ **(AII)**
- CD4 count >500 cells/mm³ **(BIII)**

Currently Underway

START
TIMING IS EVERYTHING

When is the best time to start HIV medications?

This is one of the most important unanswered questions in HIV treatment, and the START Study is a large international trial designed to answer it.

The Strategic Timing of AntiRetroviral Treatment–the START Study–is enrolling 4,000 HIV-positive people with CD4+ T-cells above 500 who have never taken HIV medications.

Half of the volunteers will be randomized to start HIV medications immediately, and half to wait to start treatment until their CD4+ T-cell counts fall to 350 or until HIV symptoms develop.

The START Study is being conducted at over 235 clinical sites in 35 countries in North and South America, Europe, Africa, the Middle East, Asia, and Australia. Enrollment is expected to continue through December 2012 and study follow-up of all those enrolled through December 2015.

Follow up to continue through Dec 2015

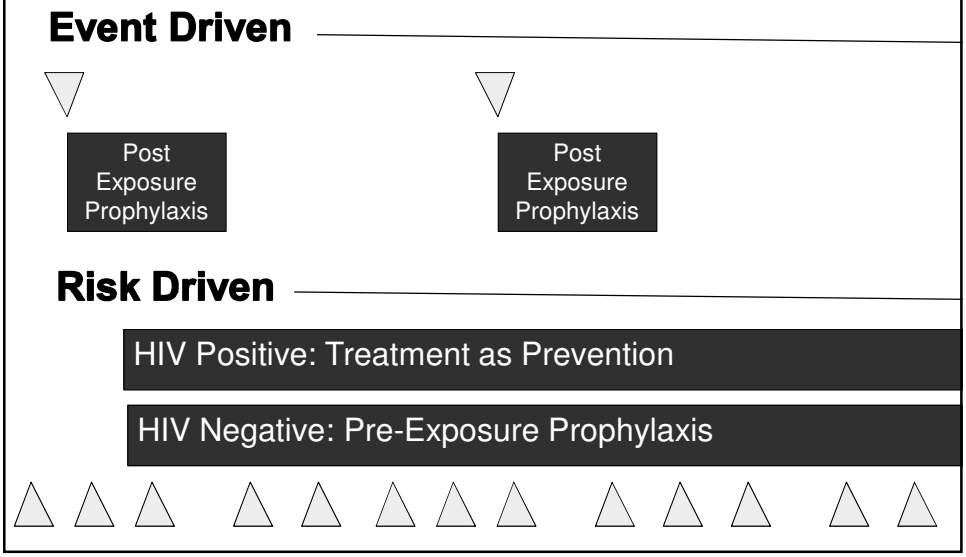
And There's More…

- Early Treatment
  - Prevents virologic failure
  - Prevents resistance
  - Improves T cell recovery
  - Decreases non-AIDS related events
  - Is associated with less drug toxicity
  - Decreases damage caused by inflammation
  - Increases life expectancy

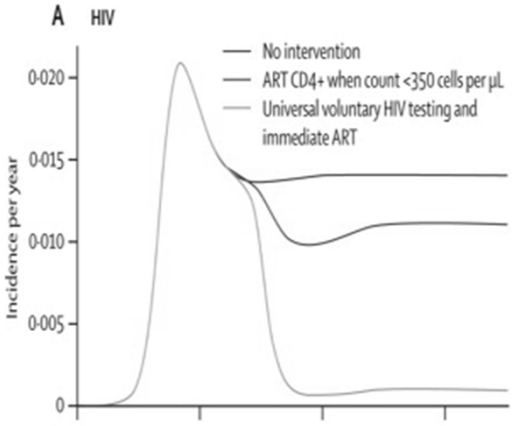
Kitahata Topics in HIV Medicine 2010

Starting HIV Medications Early is Good for the Public Health

ARV and Prevention



Test and Treat…A Model



Granich et al. Lancet 2009

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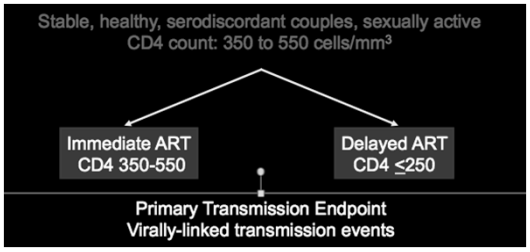
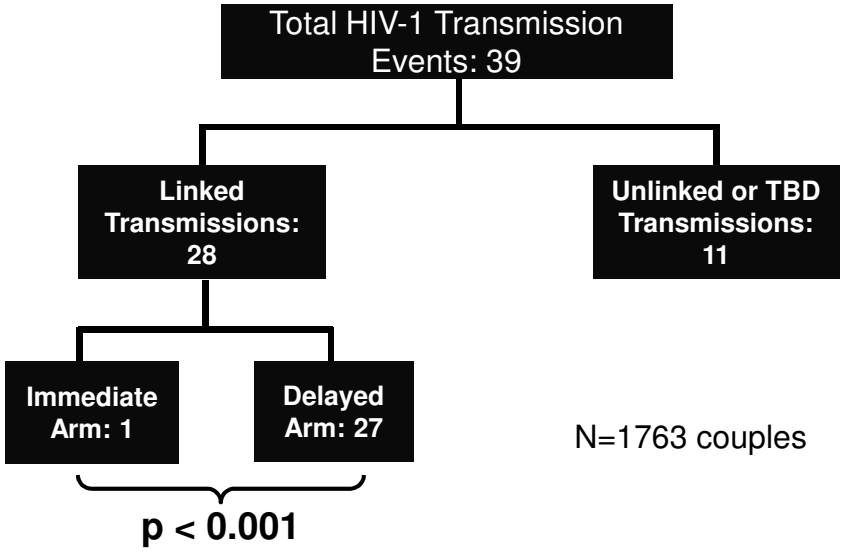
Prevention of HIV-1 Infection with Early Antiretroviral Therapy

Myron S. Cohen, M.D., Ying Q. Chen, Ph.D., Marybeth McCauley, M.P.H., Theresa Gamble, Ph.D., Mina C. Hosseinipour, M.D., Nagalingeswaran Kumarasamy, M.B., B.S., James G. Hakim, M.D., Johnstone Kumwenda, F.R.C.P., Beatriz Grinsztejn, M.D., Jose H.S. Pilotto, M.D., Sheela V. Godbole, M.D., Sanjay Mehendale, M.D., Suwat Chariyalertsak, M.D., Breno R. Santos, M.D., Kenneth H. Mayer, M.D., Irving F. Hoffman, P.A., Susan H. Eshleman, M.D., Estelle Piwowar-Manning, M.T., Lei Wang, Ph.D., Joseph Makhema, F.R.C.P., Lisa A. Mills, M.D., Guy de Bruyn, M.B., B.Ch., Ian Sanne, M.B., B.Ch., Joseph Eron, M.D., Joel Gallant, M.D., Diane Havlir, M.D., Susan Swindells, M.B., B.S., Heather Ribaudo, Ph.D., Vanessa Elharrar, M.D., David Burns, M.D., Taha E. Taha, M.B., B.S., Karin Nielsen-Saines, M.D., David Celentano, Sc.D., Max Essex, D.V.M., and Thomas R. Fleming, Ph.D., for the HPTN 052 Study Team*



HPTN 052: HIV-1 Transmission



HPTN 052 Prevention Conclusion

Early ART that suppresses viral replication led to 96% reduction of sexual transmission of HIV-1 in serodiscordant couples****

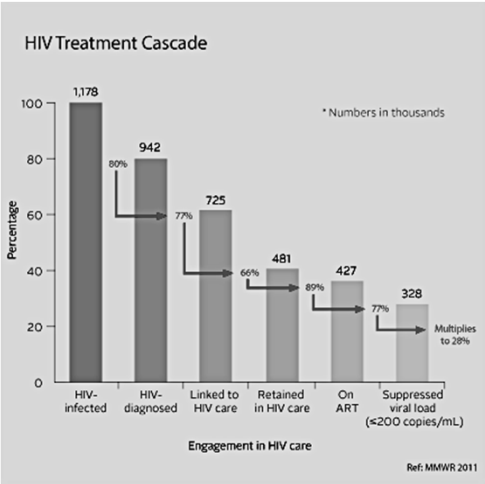
******3% of these couples were MSM**

HPTN HIV Prevention Trials Network

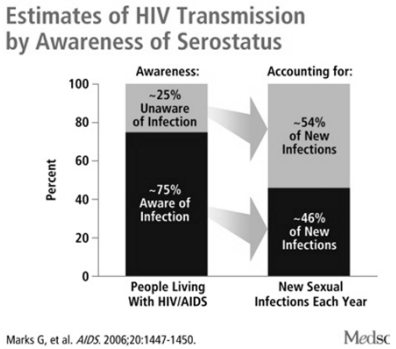
The Data Gap in MSM

- Rate of HIV transmission via anal 5-10 X greater than penile-vaginal sex 50 per 10,000 vs 10 per 10,000
  - Can extrapolations be made from vaginal sex?
- Conflicting data from community and cohort studies estimating impact of ARV coverage on transmission
  - San Francisco: Decreased Transmission (Das et al,2010)
  - Syndey: Unchanged (Jin et al,2010)
  - Netherlands: Increased (Holligsworth et al, 2008)
  - England: Decreased transmission on ART (Fisher 2010)

Barriers to Treatment as Prevention I



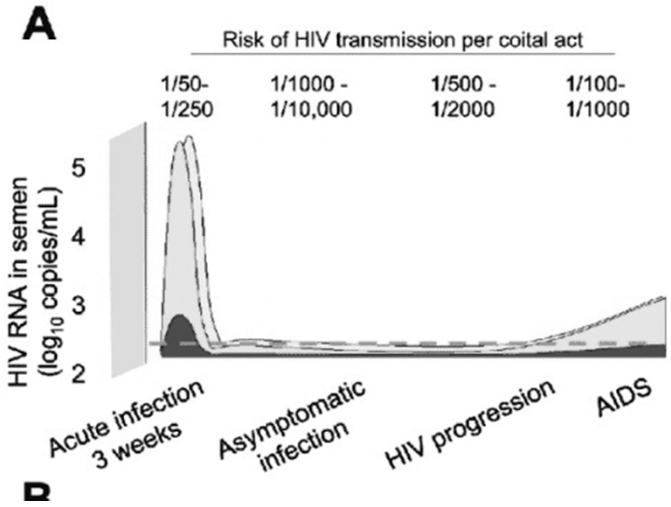
Barriers to Treatment as Prevention II



- Up to 34% of MSM with HIV are unaware of their status
- Less likely to know were:
  - young MSM aged 18–29 (51%)
  - racial/ethnic minority MSM (44%)

Wejnert et al., CROI #90.

Barriers to Treatment as Prevention III



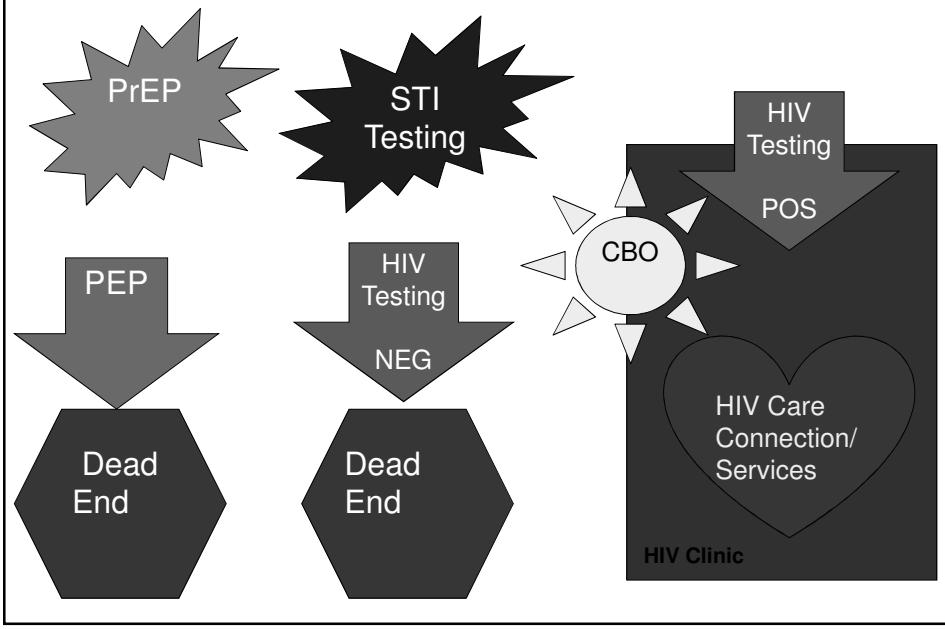
PEP/PrEP and Early Treatment all work…But There Are Barriers

You are preaching to the choir…

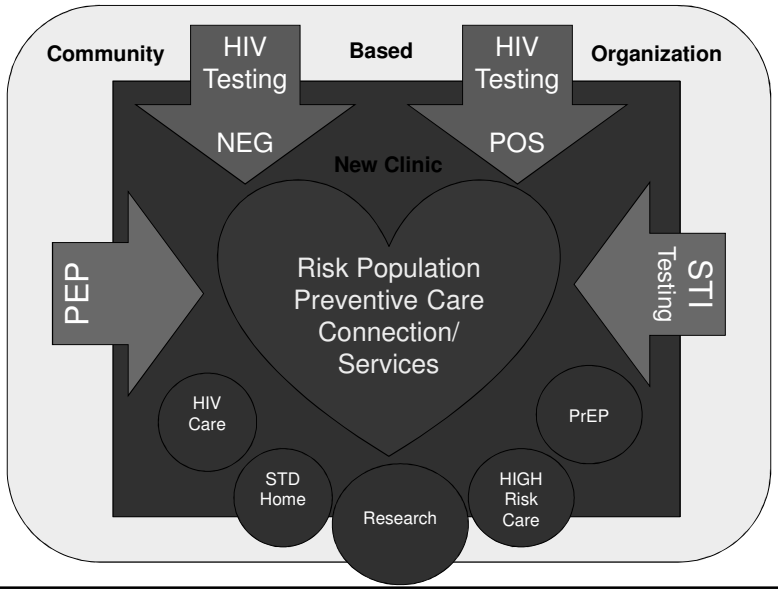
We haven't invited the right people to church…

The Pews Are Only Half Full…

Current Model



Future Model?



HIV Primary Care= Combination Prevention