Terapia come prevenzione e ruolo del community viral load (CVR)

Andrea Antinori

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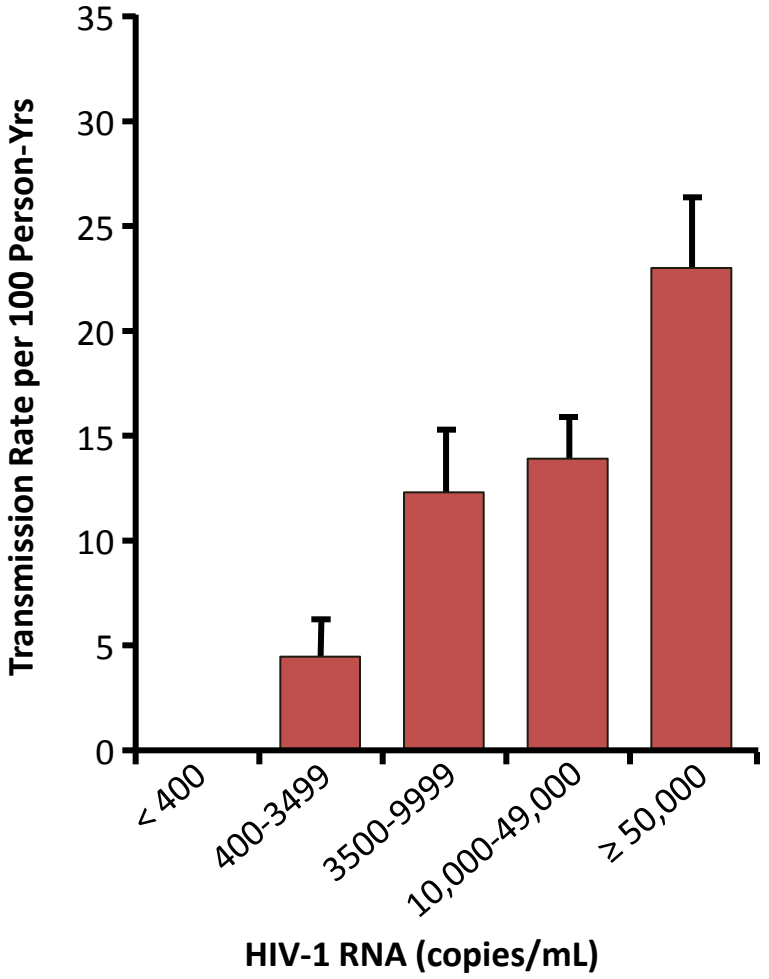
ART for HIV Prevention: The Hypothesis

- The quantity of HIV in plasma (and genital secretions) is the prime determinant of whether someone with HIV will transmit the virus to a sexual partner[1]
- Initiation of ART results in early and sustained reductions in plasma and genital HIV levels
- Led to the hypothesis that ART use would result in decreased infectiousness



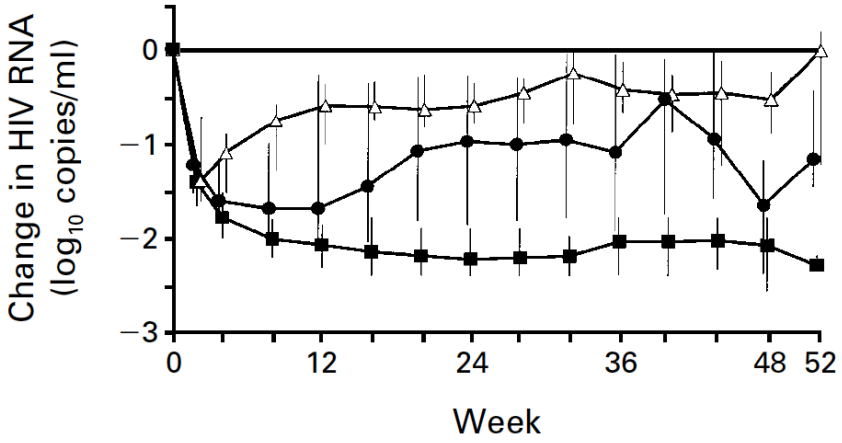
1. Quinn TC, et al. N Engl J Med. 2000;342:921-929.

Treatment as prevention.
A definition

"As a concept and a strategy, treating HIV infected persons to improve their health and to reduce the risk of onward transmission sometimes called *treatment as prevention*— refers to the personal and public health benefits of using ART to continuously suppress HIV viral load in the blood and genital fluids, which decreases the risk of transmitting the virus to others."

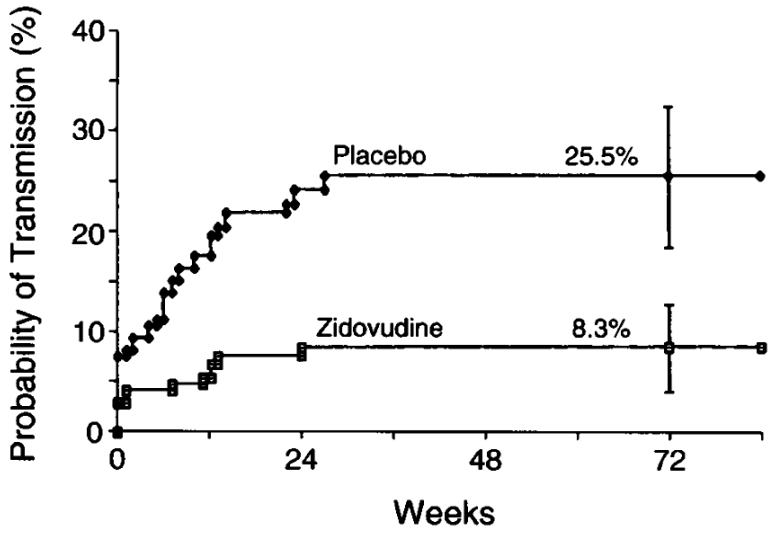
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Division of HIV Prevention, January 2013

Treatment HIV as prevention: a new practice?



No. of Patients Studied					
■ Three drugs	30	30	25	10	5
● Indinavir	31	28	25	8	5
△ Zidovudine–lamivudine	33	30	25	9	5

Gulick RM, et al. N Engl J Med, 1997



Placebo	183	84	42	37
Zidovudine	180	105	51	43

Connor EM, et al. N Engl J Med, 1994

TasP update

- Evidence from randomized trials and observational studies
- Guidelines recommendations
- Individual benefit (per-act risk reduction)
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- Cost-effectiveness
- Caveats and limitations

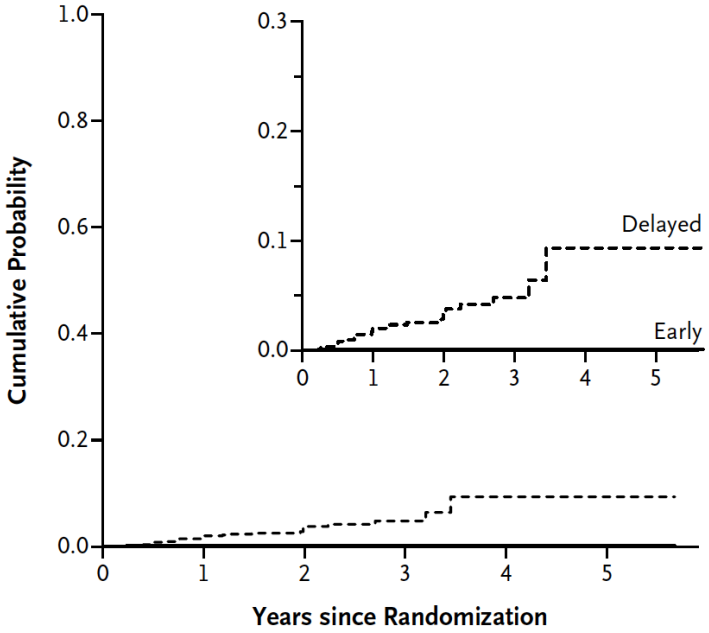
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 11, 2011 VOL. 365 NO. 6

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*

A Linked HIV Transmission



No. at Risk

Early	893	658	298	79	31	24
Delayed	882	655	297	80	26	22

HPTN 052. Prognostic factors for partner-linked and any HIV-1 transmission

Variable	Linked Transmission	Any Transmission	Clinical Events	Composite Events
		hazard ratio (95% CI)		
Univariate analysis				
Early therapy vs. delayed therapy	0.04 (0.01–0.26)	0.11 (0.04–0.32)	0.60 (0.41–0.90)	0.28 (0.18–0.45)
Baseline CD4 count (per 100 CD4 increment)	1.27 (1.02–1.59)	1.25 (1.02–1.52)	0.84 (0.70–1.00)	1.06 (0.91–1.24)
Baseline viral load (per unit $\log_{10}$ increment)	1.96 (1.17–3.27)	1.66 (1.08–2.55)	1.74 (1.32–2.30)	1.51 (1.15–1.97)
Male sex vs. female sex	0.69 (0.31–1. 52)	0.88 (0.45–1.71)	1.61 (1.05–2.48)	1.18 (0.78–1.78)
Baseline condom use (100% vs. <100%)	0.35 (0.14–0.88)	0.47 (0.19–1.14)	NA	0.68 (0.29–1.60)
Multivariate analysis				
Early therapy vs. delayed therapy	0.04 (0.01–0.28)	0.11 (0.04–0.33)	0.59 (0.40–0.89)	0.28 (0.18–0.45)
Baseline CD4 count (per 100 CD4 increment)	1.24 (1.00–1.54)	1.22 (1.02–1.47)	0.90 (0.75–1.08)	1.11 (0.96–1.28)
Baseline viral load (per unit $\log_{10}$ increment)	2.85 (1.51–5.41)	2.13 (1.30–3.50)	1.65 (1.24–2.20)	1.60 (1.21–2.11)
Male sex vs. female sex	0.73 (0.33–1.65)	1.00 (0.51–1.97)	1.46 (0.95–2.26)	1.18 (0.78–1.80)
Baseline condom use (100% vs. <100%)	0.33 (0.12–0.91)	0.41 (0.16–1.08)	NA	0.64 (0.27–1.52)

Cohen MS, et al. N Engl J Med, 2011

Observational Studies: ART Decreases Risk of Transmitting HIV

Study	Population	Rate Ratio (95% CI)
Musicco 1994	436 monogamous HIV-uninfected female sexual partners of HIV-infected men in Italy	0.88 (0.36-2.16)
Melo 2008	93 heterosexual serodiscordant couples in Brazil	0.10 (0.01-1.67)
Sullivan 2009	2993 HIV-discordant couples in Rwanda and Zambia	0.21 (0.08-0.56)
Del Romero 2010	648 heterosexual couples in Madrid	0.21 (0.01-3.75)
Donnell 2010	3408 heterosexual African couples; index partner HIV positive and HSV positive	0.08 (0.01-0.57)
Lu 2010	1927 heterosexual couples for testing and treatment at county hospitals in China	1.44 (0.85-2.44)
Reynolds 2011	250 HIV-discordant couples in Rakai, Uganda	0.10 (0.01-1.64)
Birungi 2012	550 heterosexual couples attending a clinic in Uganda	0.91 (0.38-2.20)
Jia 2012	Large population-based cohort (> 38,000 couples) of HIV-positive persons and their HIV-negative partners in China	0.74 (0.65-0.84)
SUMMARY		0.58 (0.35-0.96)

Anglemyer A, et al. Cochrane Database Syst Rev. 2013;4:CD009153.

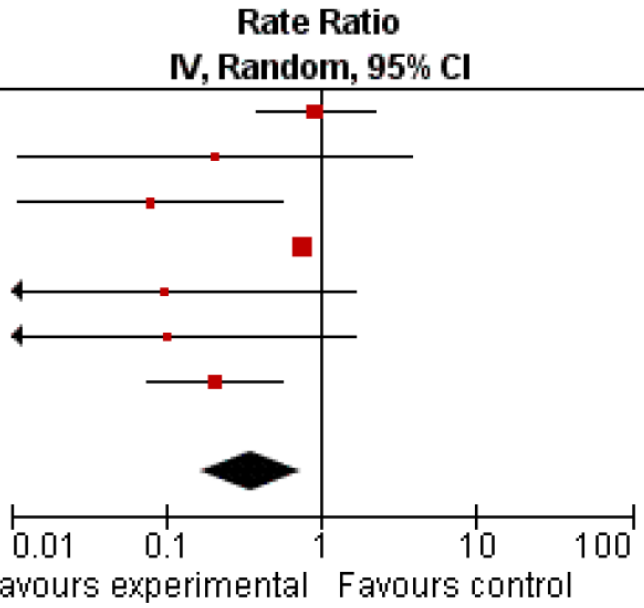
COCHRANE Systematic Review

ART is a potent intervention for prevention of HIV in discordant couples in which the index partner has ≤550 CD4 cells/µL

One RCT and nine observational studies. Ten studies identified 2,112 episodes of HIV transmission, 1,016 among treated couples and 1,096 among untreated couples. The rate ratio for the single randomised controlled trial was 0.04 [95% CI 0.00, 0.27]. All index partners in this study had CD4 cell counts at baseline of 350-550 cells/µL. Similarly, the summary rate ratio for the nine observational studies was 0.58 [95% CI 0.35, 0.96], with substantial heterogeneity (I^2=64%). After excluding two studies with inadequate person-time data, we estimated a summary rate ratio of 0.36 [95%CI 0.17, 0.75] with substantial heterogeneity (I^2=62%).

Study or Subgroup	log[Rate Ratio]	SE	Weight	Rate Ratio IV, Random, 95% CI
Birungi 2012	-0.0943	0.45	21.9%	0.91 [0.38, 2.20]
Del Romero 2010	-1.58	1.48	5.4%	0.21 [0.01, 3.75]
Donnell 2010	-2.53	1	9.9%	0.08 [0.01, 0.57]
Jia 2012 (1)	-0.3011051	0.065	31.4%	0.74 [0.65, 0.84]
Melo 2008	-2.33	1.45	5.6%	0.10 [0.01, 1.67]
Reynolds 2011	-2.29	1.42	5.8%	0.10 [0.01, 1.64]
Sullivan 2009	-1.58	0.51	20.1%	0.21 [0.08, 0.56]
Total (95% CI)			**100.0%**	**0.36 [0.17, 0.75]**

Heterogeneity: Tau² = 0.45; Chi² = 15.83, df = 6 (P = 0.01); I² = 62%
Test for overall effect: Z = 2.72 (P = 0.006)



Anglemyer A, et al. The Cochrane Collaboration, 2013

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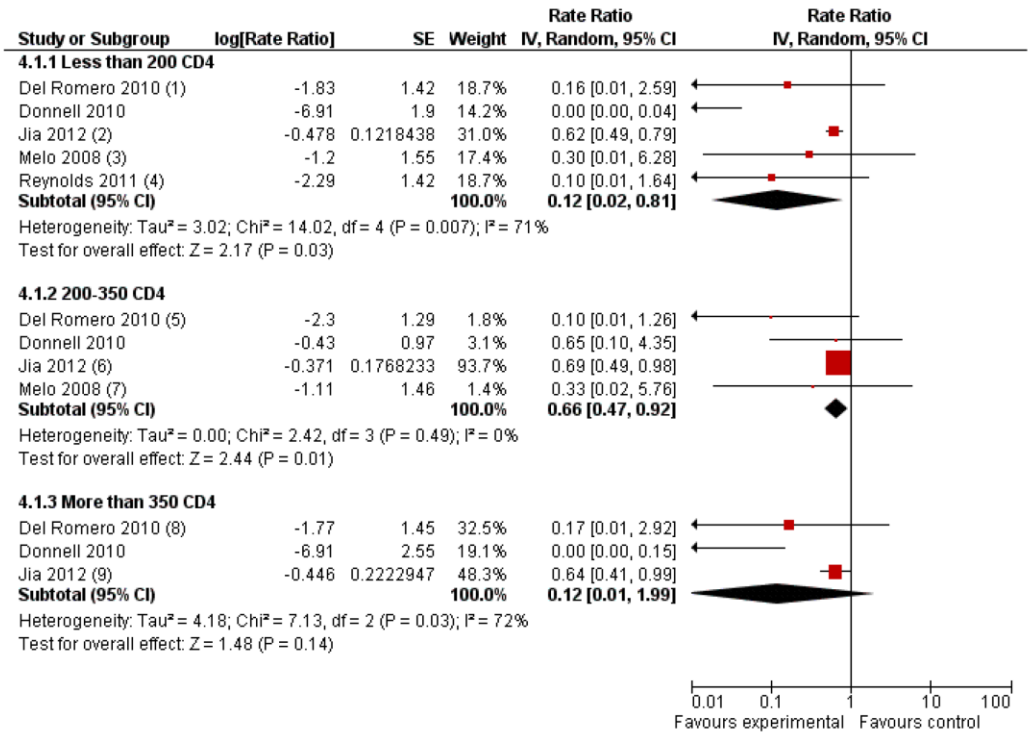
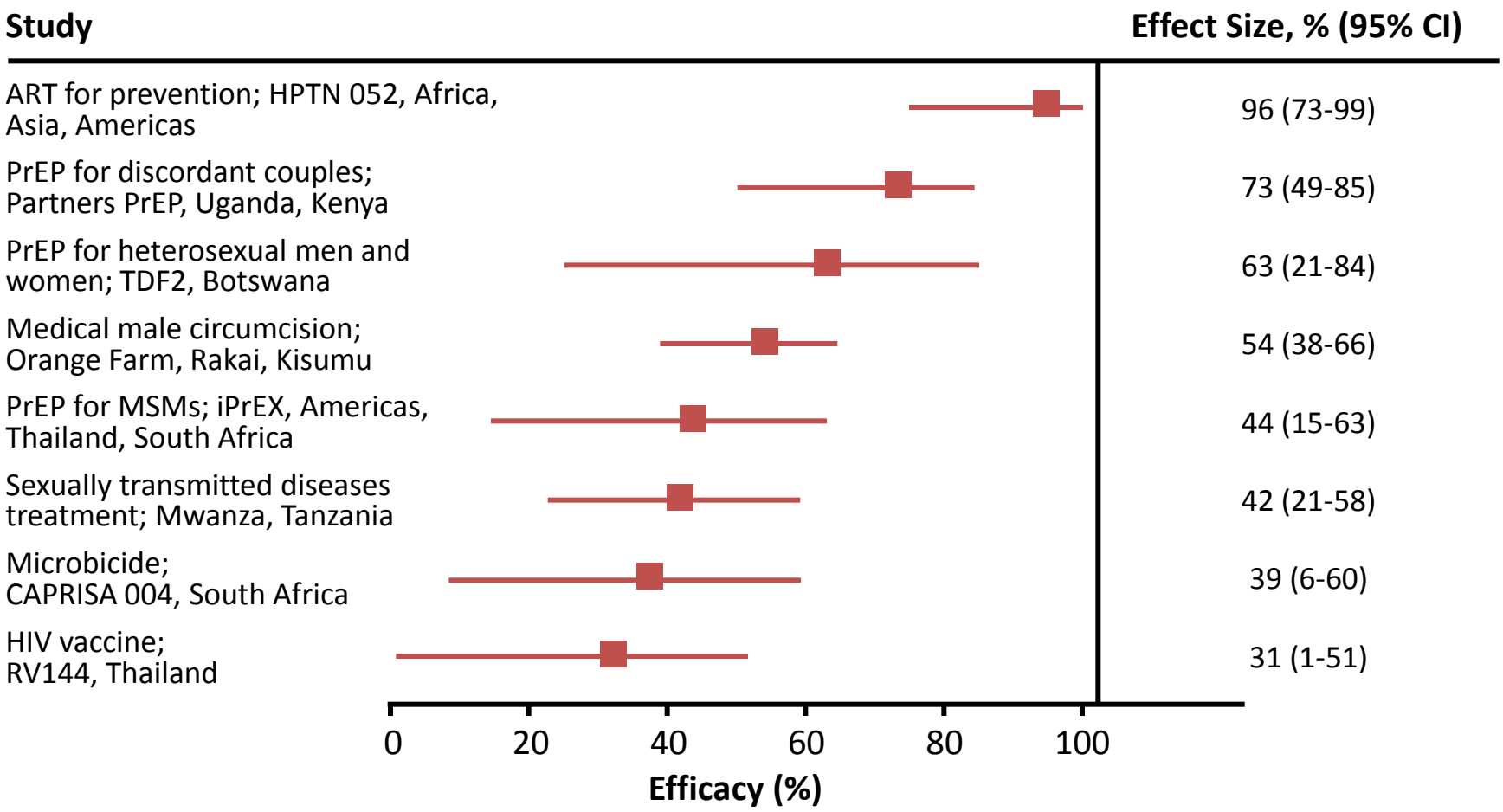


Subgroup analyses among the observational studies to see if the effect of ART on prevention of HIV differed by the index partner's CD4 cell count. Among couples in which the infected partner had ≥350 CD4 cells/µL, we estimated a rate ratio of 0.12 [95% CI 0.01, 1.99]. In this subgroup, there were 247 transmissions in untreated couples and 30 in treated couples.

Anglemyer A, et al. The Cochrane Collaboration, 2013

Efficacy of HIV Prevention Strategies From Randomized Clinical Trials



Abdool Karim SS, et al. Lancet. 2011;[Epub ahead of print].

TasP update

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DHHS 2014

Initiating Antiretroviral Therapy in Treatment-Naive Patients

(Last updated May 1, 2014; last reviewed May 1, 2014)

Panel's Recommendations

- Antiretroviral therapy (ART) is recommended for all HIV-infected individuals to reduce the risk of disease progression.
  - The strength of and evidence for this recommendation vary by pretreatment CD4 T lymphocyte (CD4) cell count: CD4 count <350 cells/mm^3 **(AI)**; CD4 count 350 to 500 cells/mm^3 **(AII)**; CD4 count >500 cells/mm^3 **(BIII)**.
- ART is also recommended for HIV-infected individuals to prevent of transmission of HIV.
  - The strength of and evidence for this recommendation vary by transmission risks: perinatal transmission **(AI)**; heterosexual transmission **(AI)**; other transmission risk groups **(AIII)**.
- Patients starting ART should be willing and able to commit to treatment and understand the benefits and risks of therapy and the importance of adherence **(AIII)**. 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*

When to start cART? 2012-2014 Guidelines Update

Clinical category	CD4 cells/mm^3	WHO 13[1]	DHHS 14[2]	IAS-USA 12[3]	EACS 13[4]	CNA-SIMIT 13[5]	BHIVA 13[6]	GESIDA 14[7]	CNS-ANRS 13[8]
AIDS-defining or symptoms	Any value	Treat (AI)	Treat (AI)	Treat (AI)	Treat	Treat (AI)	Treat (AI)	Treat (AI)	Treat (AI)
Pregnancy	Any value	Treat (AI)	Treat (AI)	Treat (AI)	Treat	Treat (AI)	Treat (AI)	Treat (AI)	Treat (AI)
HBV, HCV	Any value	Treat HBV (AIII)	Treat (AI-II)	Treat (AII/CIII)	Treat or consider only if CD4 <500/mm^3	Treat (AI-II)	Treat or consider only if CD4 <500/mm^3	Treat (AII)	Treat (AIII)
Other clinical conditions	Any value	TB	HIVAN	HIVAN	HIVAN, Malignancies, HAND	HIVAN, Malignancies, HAND, CVD	HIVAN, Malignancies, HAND	HIVAN, Malignancies, HAND, CVD	Malignancies
Asymptomatic	<350	Treat (AI)	Treat (AI)	Treat (AI)	Treat	Treat (AI)	Treat (AI)	Treat (AI)	Treat (AI)
Asymptomatic	350–500	Treat (AII)	Treat (AII)	Treat (AI)	Consider treatment	Treat (AII)	Generally defer	Treat (AII)	Treat (AII)
Asymptomatic	>500	Defer	Treat as moderate (BIII)	Treat as moderate (BIII)	Consider treatment	Treat only on individual basis (AII/BIII)	Generally defer	Treat as moderate (BIII)	Treat as moderate (BIII)
Prevent sexual transmission	Any value	Treat (AI)	Treat (AI-III)	Consider treatment Treat PHI (BIII)	Consider treatment	Treat (AI-II)	Consider (GPP)	Treat (AI-II)	Treat (AI/BIII)

1. WHO consolidated guidelines onthe use of antiretroviral drugs for treating and preventing HIV infection. June 2013
2. DHHS Guidelines 2014 Available at http://aidsinfo.nih.gov/guidelines
3. ARV Treatment of Adult HIV Infection. 2012 Recommendation of the IAS-USA panel. JAMA 2012;308:387-402.
4. EACS Guidelines 2013. Available at http://www.europeanaidsclinicalsociety.org/guidelinespdf/1_Treatment_of_HIV_Infected_Adults.pdf.
5. Linee Guida Italiane sull'utilizzo dei farmaci antiretrovirali e sulla gestione diagnostico-clinica delle persone con infezione da HIV-1, 2013. Available at: http://www.salute.gov.it/imgs/C_17_pubblicazioni_1301_allegato.pdf;
6. BHIVA Guidelines 2012-Updated 2013. HIV Medicine (2014), 15 (Suppl. 1), 1–85
7. GESIDA. Documento de consenso de Gesida/Plan Nacional sobre el SIDA respecto al tratamiento antirretroviral en adultos infectados por el virus de la inmunodeficiencia humana. Actualización enero 2014
8. CNS-ANRS. Prise en charge médicale des personnes vivant avec le HIV. Rapport 2013

TasP update

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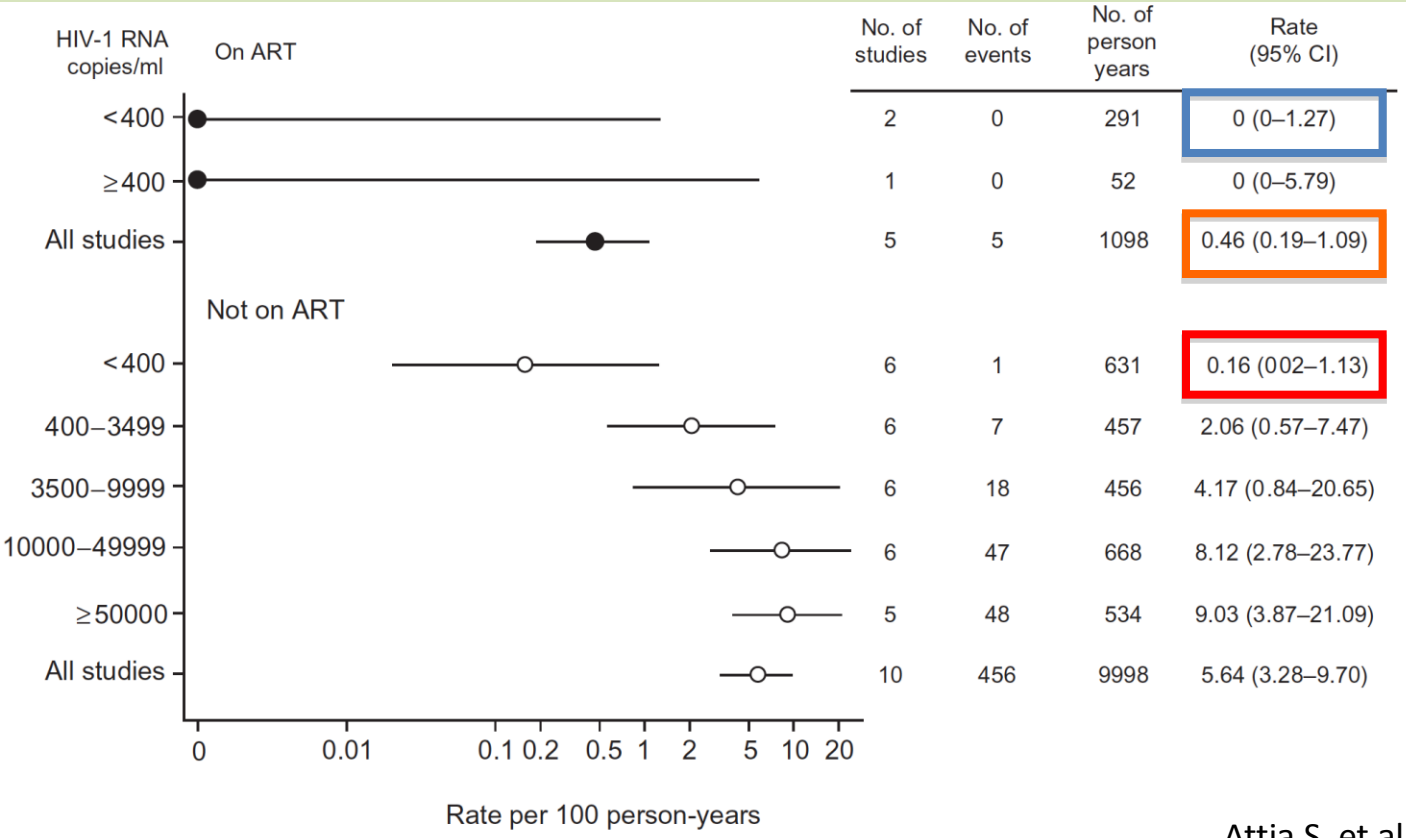
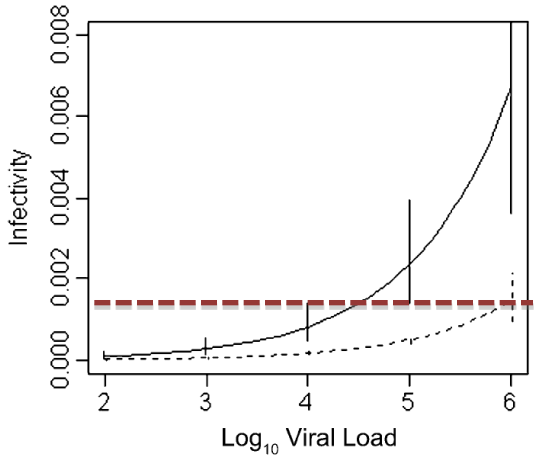
Sexual transmission of HIV according to viral load and ARV therapy

11 cohorts reporting on 5021 heterosexual couples and 461 HIV-transmission events. The rate of transmission overall from ART-treated patients was **0.46 (95% CI 0.19–1.09)** per 100 person-years, based on five events. The transmission rate from a seropositive partner with viral load below 400 copies/ml on ART, based on two studies, was **zero with an upper 97.5% confidence limit of 1.27** per 100 personyears, and **0.16 (95% CI 0.02–1.13)** per 100 person-years if not on ART, based on five studies and one event.



Attia S, et al. AIDS, 2009

Relative Risks in Per-Act Probability of HIV-1 Transmission



3297 serodiscordant African couples experiencing 86 linked HIV-1 transmissions

The unadjusted per-act risks of unprotected male-to-female (MTF) and female-to-male (FTM) transmission were 0.0019 (95% confidence interval [CI], .0010–.0037) and 0.0010 (95% CI, .00060–.0017).

Per-act probability of transmission (infectivity) vs log10 plasma HIV-1 RNA (copies/mL) from a model that includes plasma human immunodeficiency virus type 1 RNA and condom use only. Solid line is without reported condom use and dashed line is with reported condom use. Vertical lines represent 95% confidence intervals

	Final Multivariate Model		
	RR	95% CI	*P* value
Characteristics of the HIV-1–infected partner[a]			
Plasma HIV-1 RNA during follow-up, per $\log_{10}$ copies/mL	2.89	2.19–3.82	<.001
Reported condom use during follow-up	0.22	.11–.42	<.001
Characteristics of the HIV-1–uninfected partner			
Age, per 5 y	0.82	.71–.94	.006
HSV-2 seropositive at enrollment	2.14	1.18–3.88	.012
GUD, by exam or self-report, during follow-up	2.65	1.35–5.19	.004
Trichomonas vaginalis at enrollment, female	2.57	1.42–4.65	.002
Cervicitis or vaginitis during follow-up, female	3.63	1.47–8.92	.005
Circumcision, male	0.53	.29–.96	.037

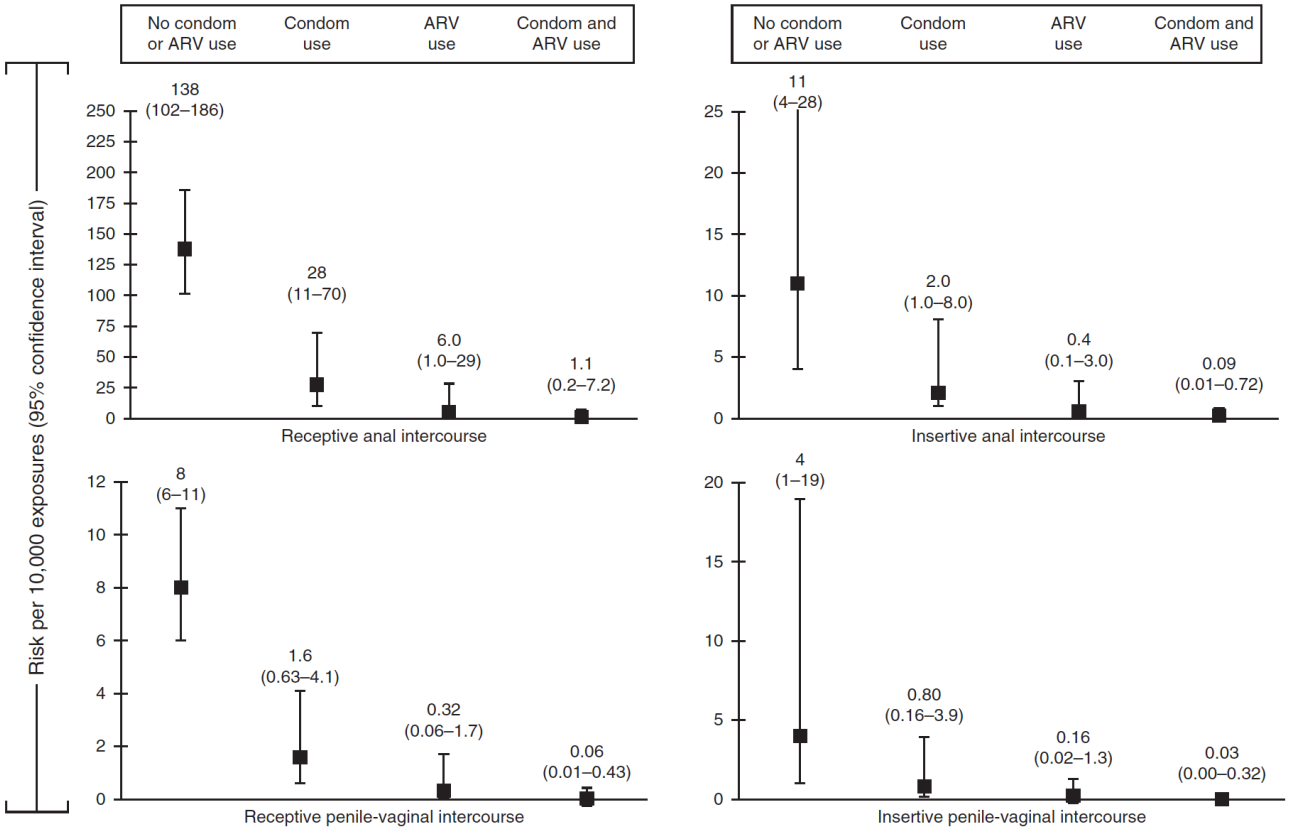
Abbreviations: CI, confidence interval; GUD, genital ulcer disease; HIV-1, human immunodeficiency virus type 1; HSV-2, herpes simplex virus type 2; RR, relative risk; y, years.

[a] Gender is included in the model to ensure interpretability of the sex-specific covariates.

Hughes JP, et al. J Infect Dis, 2012

Modifying effects of ARV treatment and condom use on the per-act HIV transmission risk estimates

The risk associated with sexual intercourse was reduced most substantially by the combined use of condoms and antiretroviral treatment of HIV-infected partners.

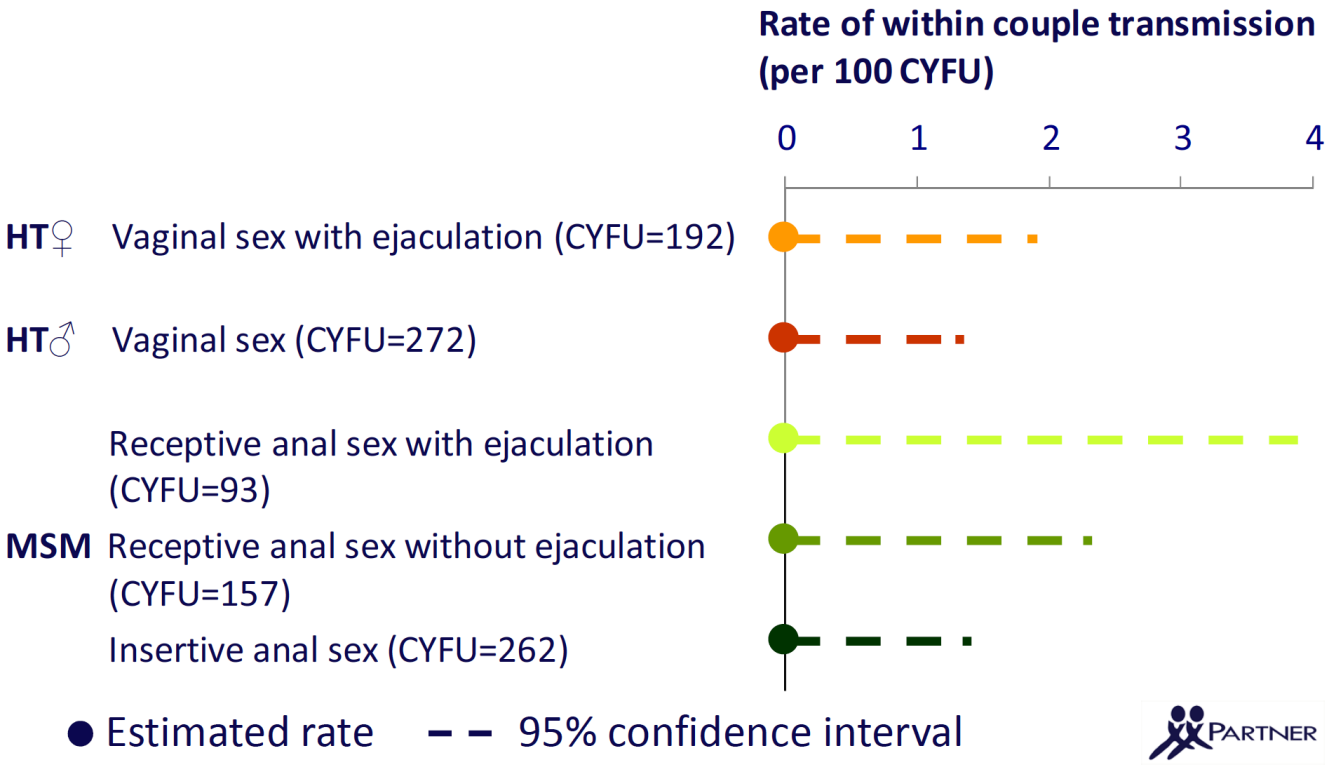


Patel P, et al. AIDS, 2014

PARTNER Study

Rate of HIV transmission according to sexual behaviour

Condomless penetrative sex on suppressive ART
Overall 1,110 couples were recruited by 1st Nov 2013, of which 767 couples contributed 894 eligible couple-years of follow-up (CYFU)



Rodger A, et al. CROI 2014; Boston (MA). Abst.#153LB

TasP update

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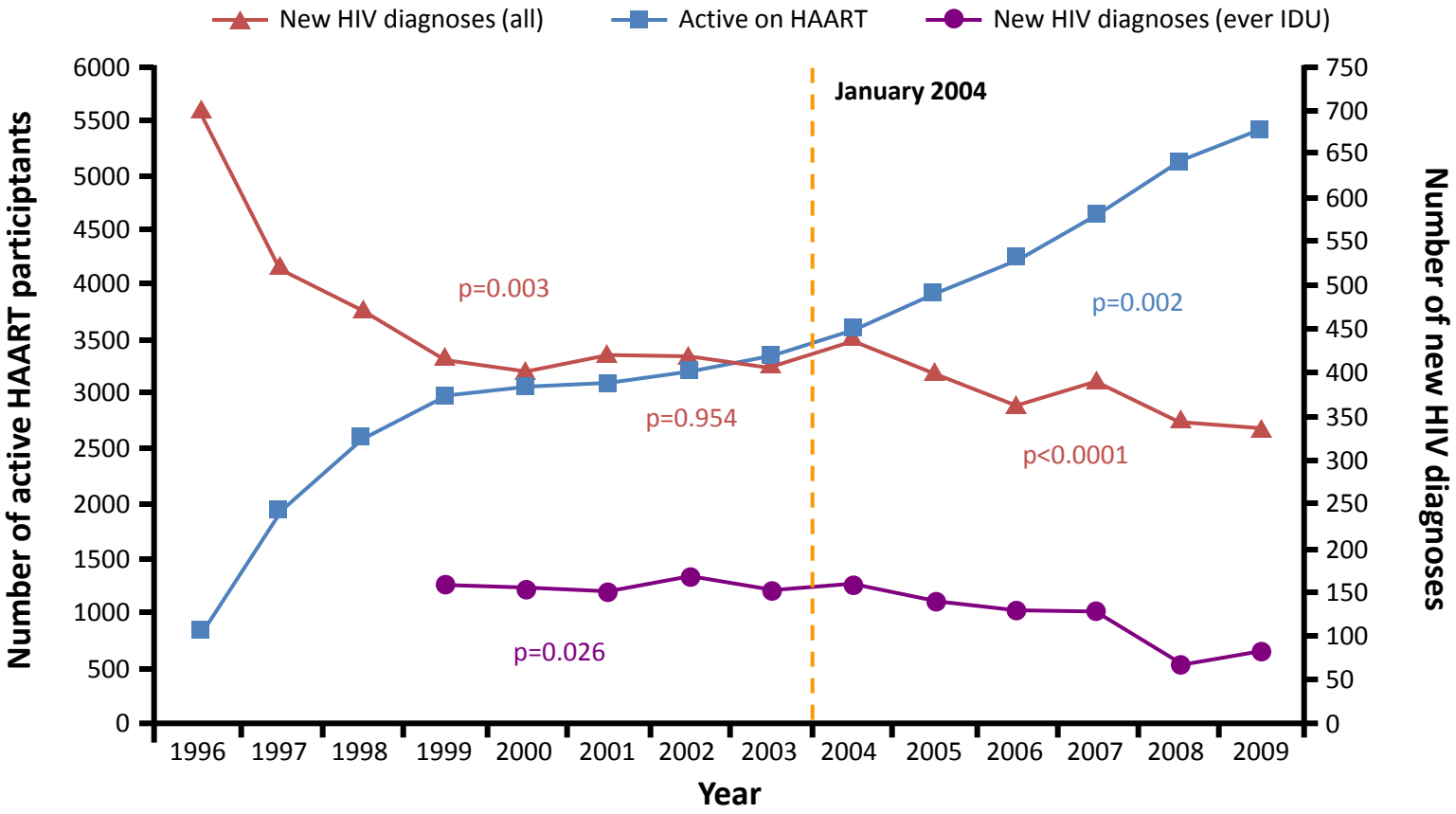
Expanded HAART coverage decreases new HIV diagnoses



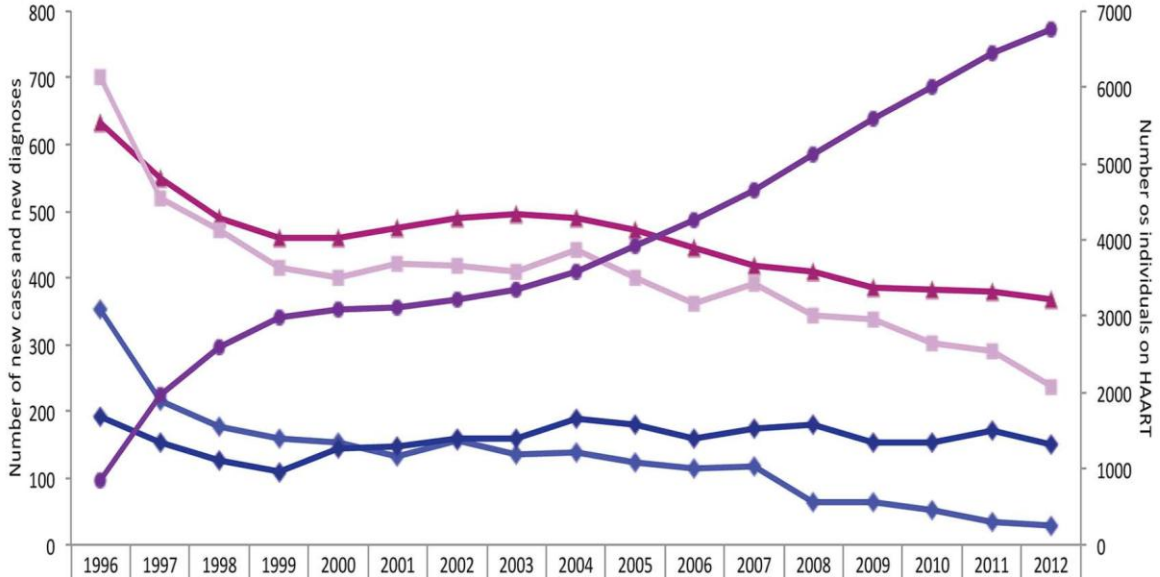
- HAART significantly decreased new HIV diagnoses in 1996–1999 (*P*=0.027) and in 2004–2009 (*P*=0.001)
- New HIV diagnoses among IDU decreased ~50% after 2007

Adapted from Montaner JSG, et al. Lancet 2010;376:532–39.

ART expansion was associated with a sustained and profound population-level decrease in morbidity, mortality and HIV transmission

New HIV diagnoses declined from 702 to 238 cases (66% decrease; p = 0.0004) with a consequent estimated decline in HIV incident cases from 632 to 368 cases per year (42% decrease; p = 0.0003). Finally, our models suggested that for each increase of 100 individuals on HAART, the estimated HIV incidence decreased 1.2% and for every 1% increase in the number of individuals suppressed on HAART, the estimated HIV incidence also decreased by 1%.

From January 1st 1996 to December 31˚ 2012, the estimated HIV prevalence in BC increased from 7,900 to 11,972 cases (52%; p-value <0.0001), and the number of individuals actively on HAART increased from 837 to 6772 (709%; p-value <0.0001).
Based on these figures, we estimated that HAART coverage increased from 11% to 57% (p-value 0.0004) during this period.

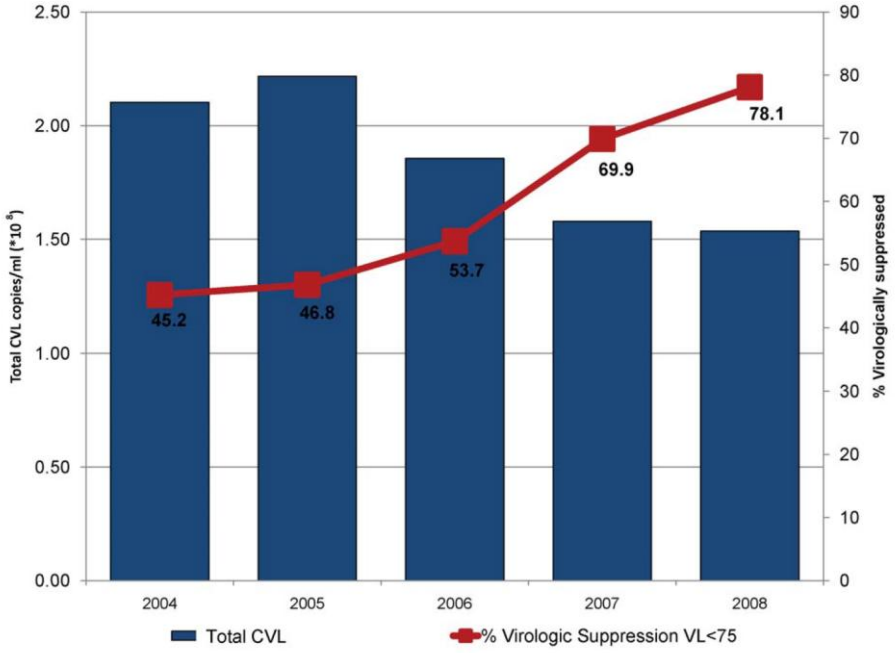


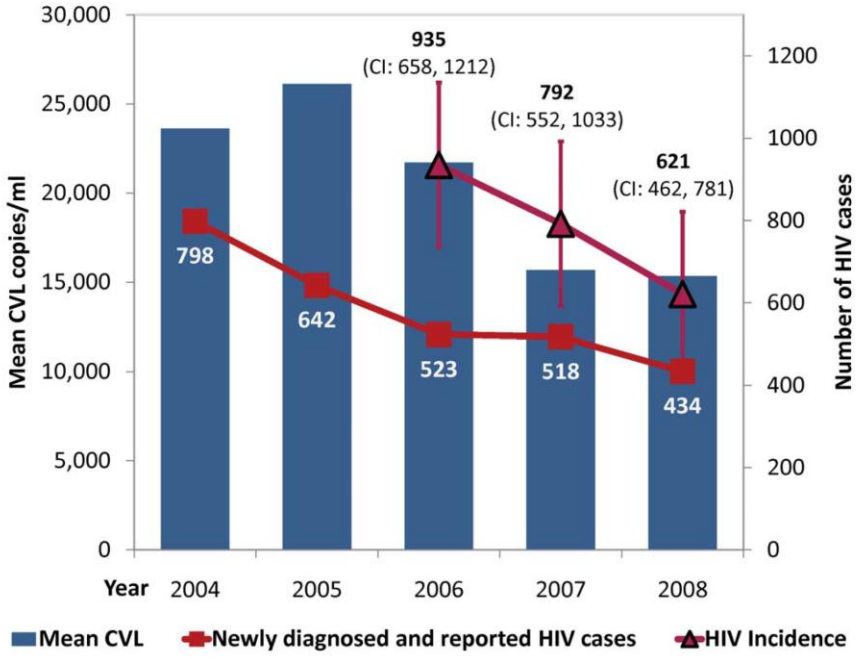
	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
HIV Incidence	632	551	490	461	461	476	489	495	490	472	446	418	408	387	382	380	368
New HIV Diagnoses	702	519	471	416	400	420	418	408	442	400	361	391	345	337	301	289	238
New HIV Diagnoses (ever IDU)	352	215	177	159	152	132	156	136	137	125	115	118	65	64	52	34	29
New HIV Diagnoses (MSM)	192	154	126	110	144	147	158	158	188	181	160	173	181	153	153	170	149
Active on HAART	837	1960	2596	2994	3079	3120	3211	3356	3585	3913	4256	4654	5123	5594	5999	6459	6772
HIV Prevalence	7900	8228	8593	8933	9150	9408	9690	9936	10216	10398	10566	10790	11040	11280	11500	11700	11972

Montaner JSG, et al. PLoS One, 2014

Decreases in CVL are accompanied by reductions in new HIV infections in San Francisco

Both mean and total CVL decreased from 2004–2008 and were accompanied by decreases in new HIV diagnoses from 798 (2004) to 434 (2008). The mean ($p = 0.003$) and total CVL ($p = 0.002$) were significantly associated with new HIV cases from 2004–2008.





Das M, et al. PLoS One, 2010

The effect of expanded ART strategies on the HIV epidemic among MSMs in San Francisco

- Despite advancements in treatment and expanded outreach efforts, 600 incident HIV infections occurred in San Francisco in 2008.
- The San Francisco Department of Public Health estimates that 78% of all known HIV-infected persons were receiving care in 2008.

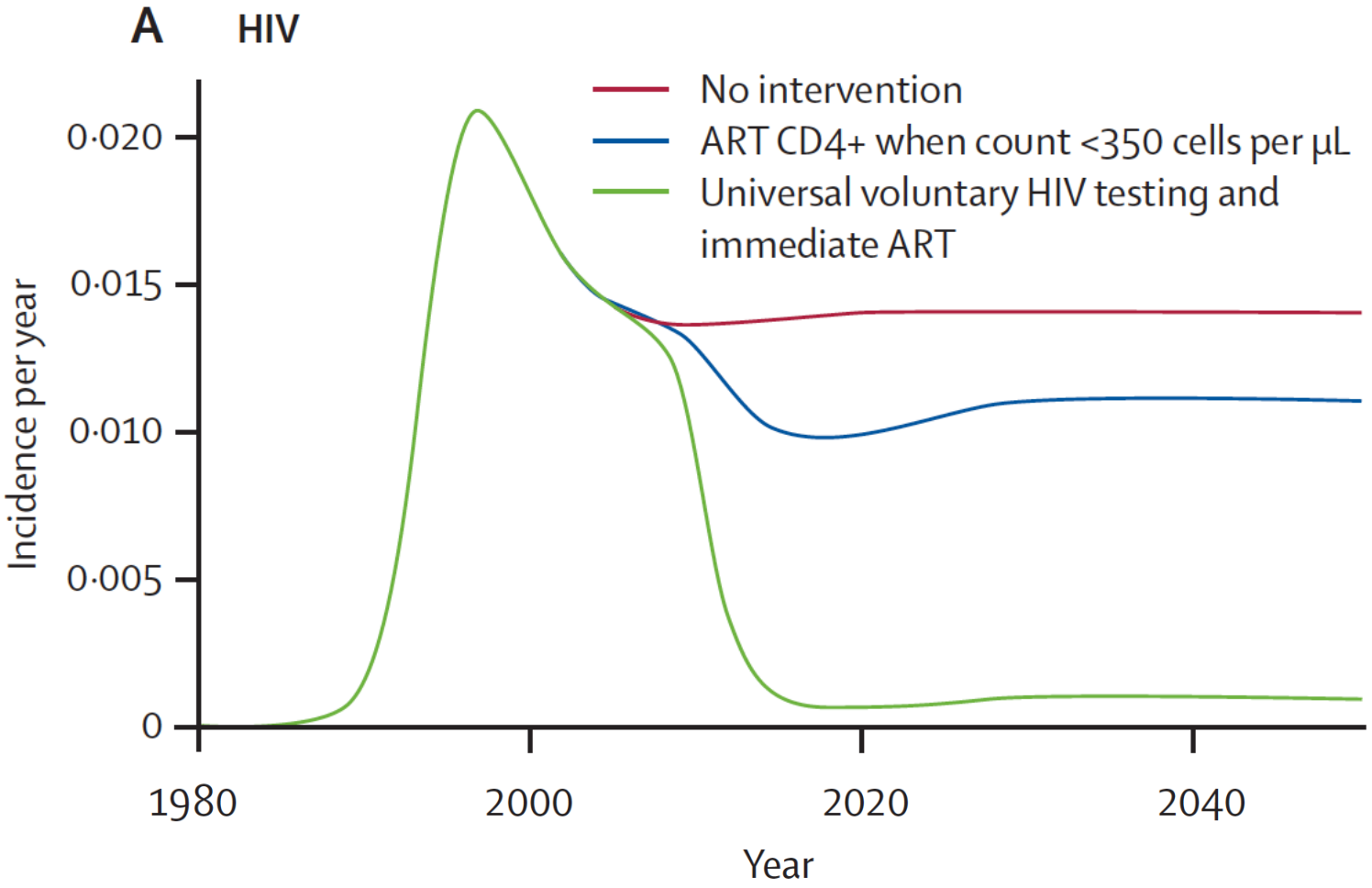
	Prevalence of HIV infection, %			
Year	Baseline CD4 cell count <350 cells/mm^3	ART initiation, CD4 cell count <500 cells/mm^3	Treat all in care	Test-and-treat all
2009	24.7	24.7	24.7	24.7
2014	25.1	22.9	21.9	20.9
2019	25.5	21.7	19.4	17.5
2029	26.2	21.8	17.1	12.8
New HIV infections since 2009	Baseline (CD4<350)	ART start CD4<500	Treat all in care	Test-and-treat all
2014	3703	2149	1534	893
2019	7446	4344	2896	1406
2029	14,960	10,020	6739	2771
HIV Infections Averted*		ART start CD4<500	Treat all in care	Test-and-treat all
2014	Reference	1554	2169	2810
2019	Reference	3102	4550	6040
2029	Reference	4940	8221	12,189
Percent reduction in new HIV infections[a]	Reference	ART start CD4<500	Treat all in care	Test-and-treat all
2014	Reference	42	59	76
2019	Reference	42	61	81
2029	Reference	33	55	81

[a] HIV infections averted and percent reduction in new infections are relative to 2009 model estimates. Expansion of ART treatment strategies are assumed to start in 2009.

Charlebois ED, et al. Clin Infect Dis, 2011

HIV incidence of people placed on ART

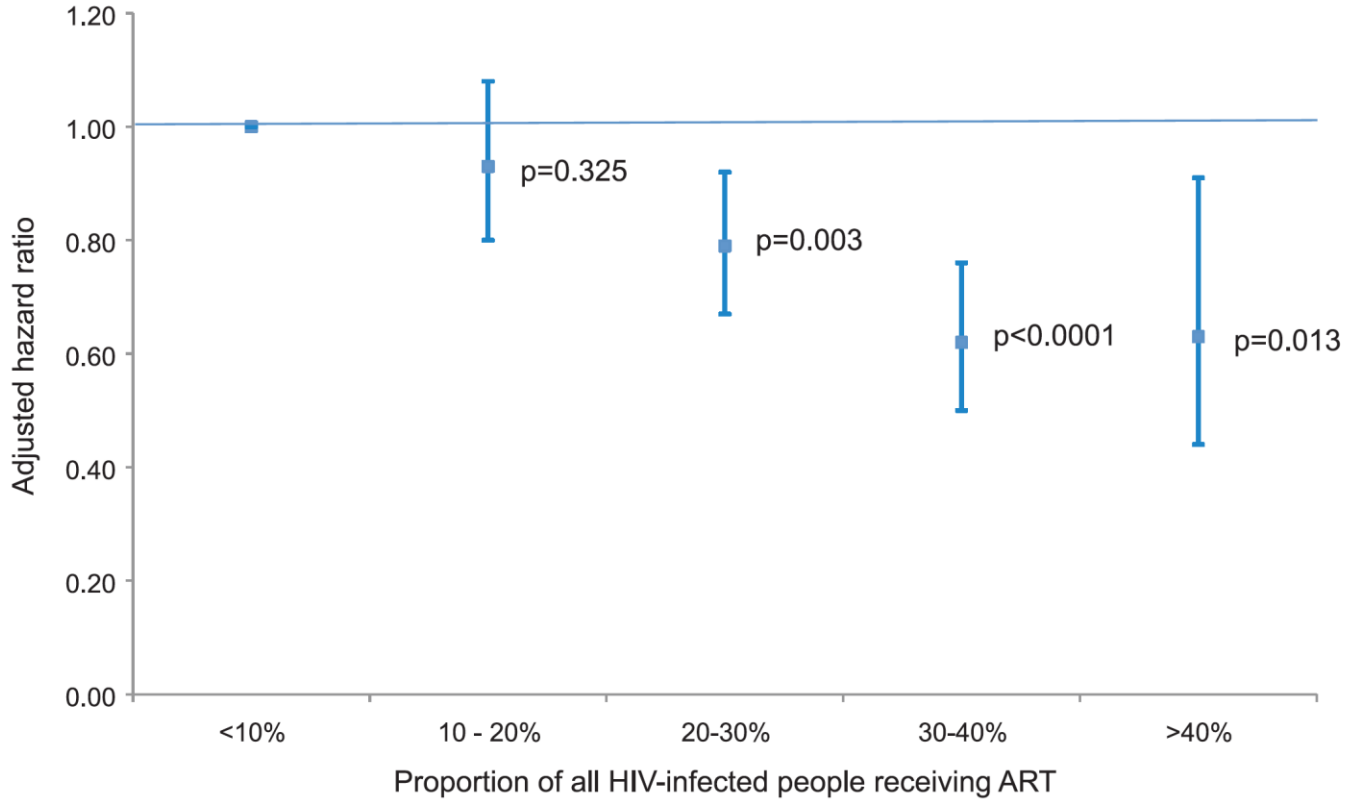
A mathematical model



Granich R, et al. Lancet, 2008

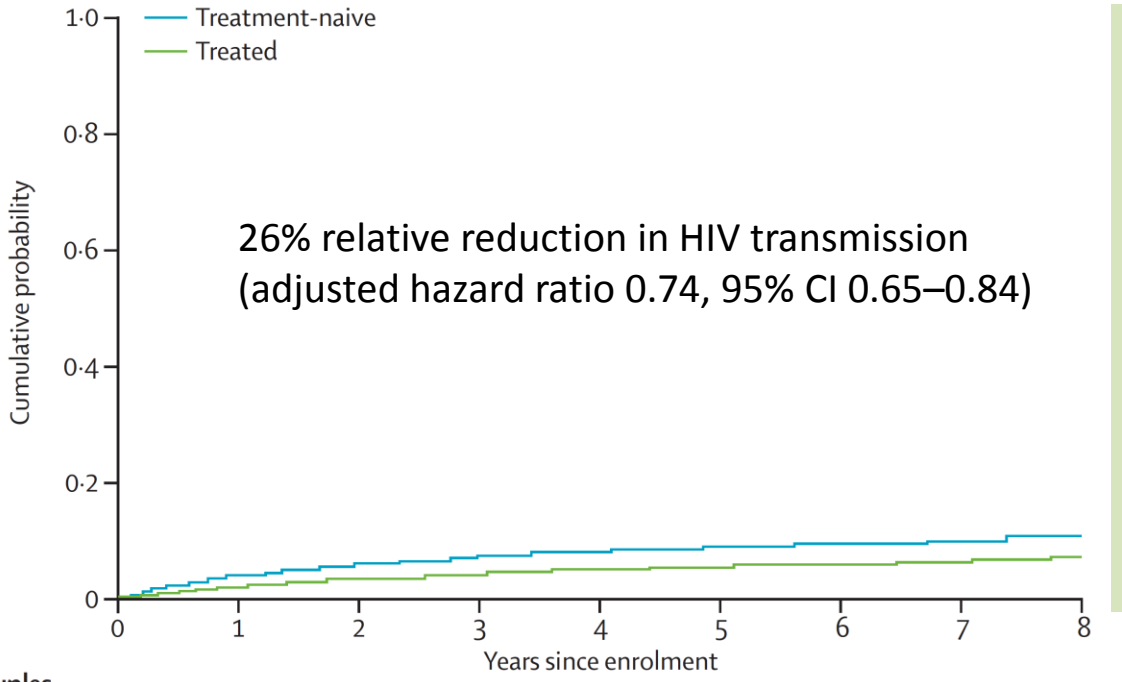
High coverage of ART associated with decline in risk of HIV acquisition

Cohort study (in rural KwaZulu-Natal, South Africa) to follow up a total of 16,667 individuals who were HIV-uninfected at baseline, observing individual HIV seroconversions over the period 2004 to 2011. An HIV-uninfected individual living in a community with high ART coverage (30 to 40% of all HIV-infected individuals on ART) was 38% less likely to acquire HIV than someone living in a community where ART coverage was low (<10% of all HIV-infected individuals on ART).



Tanser F, et al. Science, 2013

ART for HIV-positive individuals in serodiscordant couples reduced HIV transmission in China



Number of couples followed up								
Treated	24 057	16 739	13 187	10 318	8285	6563	4987	2917
Treatment-naive	14 805	8059	4928	2849	1804	1242	753	341

38,862 serodiscordant couples, with 101,295 person-years of follow-up for the seronegative partners, rates of HIV infection were 2.6 per 100 person-years (95% CI 2.4–2.8) among the 14,805 couples in the treatment-naive cohort and 1.3 per 100 person-years (1.2–1.3) among the 24,057 couples in the treated cohort. We calculated a 26% relative reduction in HIV transmission (adjusted hazard ratio 0.74, 95% CI 0.65–0.84) in the treated cohort.

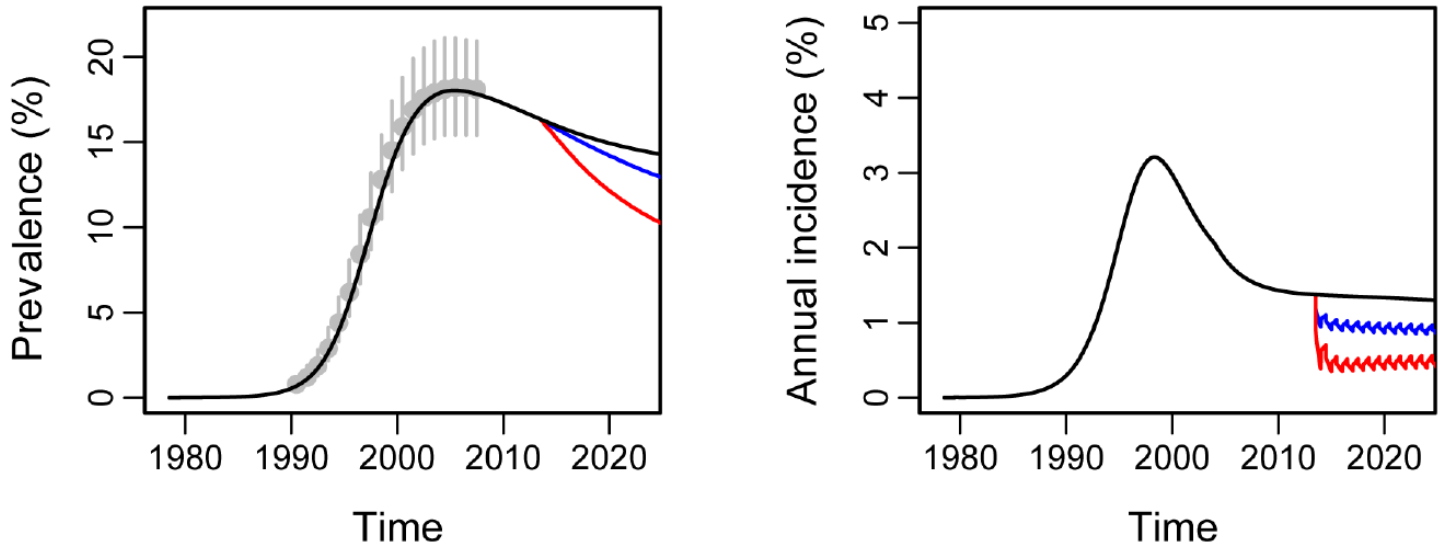
Treatment-as-prevention approach is a feasible public health prevention strategy on a national scale in a developing country context.

Jia Z, et al. Lancet, 2013

The HPTN 071 (PopART) trial intervention could reduce HIV population-level incidence by >60% over three years

Cluster-randomized trial of 21 communities in Zambia and South Africa, covering approximately 1.2 million people. Each community, will be randomized to one of three arms. Interventions in arms A and B will include home-based voluntary testing (HBT) and counseling, male circumcision, PMTCT services, treatment of STIs, condom distribution, and ART for HIV positive individuals. **ART will be offered universally (regardless of CD4 count) in arm A and according to national guidelines (currently CD4 <350 cell count/mL) in arm B. Arm C will serve as a control arm.**

The primary end-point will be **cumulative HIV incidence over 3 years**, measured in cohorts of 2,500 adults randomly selected in each of the 21 communities (total cohort size 52,500).



Model fit and projections under central target scenario for South Africa. The red, blue and black lines correspond to arms A, B and C respectively. The grey dots and error bars are the UNAIDS HIV prevalence estimates

Cori A, et al. PLoS One, 2014

TasP update

- Evidence from randomized trials and observational studies
- Guidelines recommendations
- Individual benefit (per-act risk reduction)
- Benefit at population level
- Cost-effectiveness
- Caveats and limitations

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Cost-Effectiveness of HIV Treatment as Prevention in Serodiscordant Couples

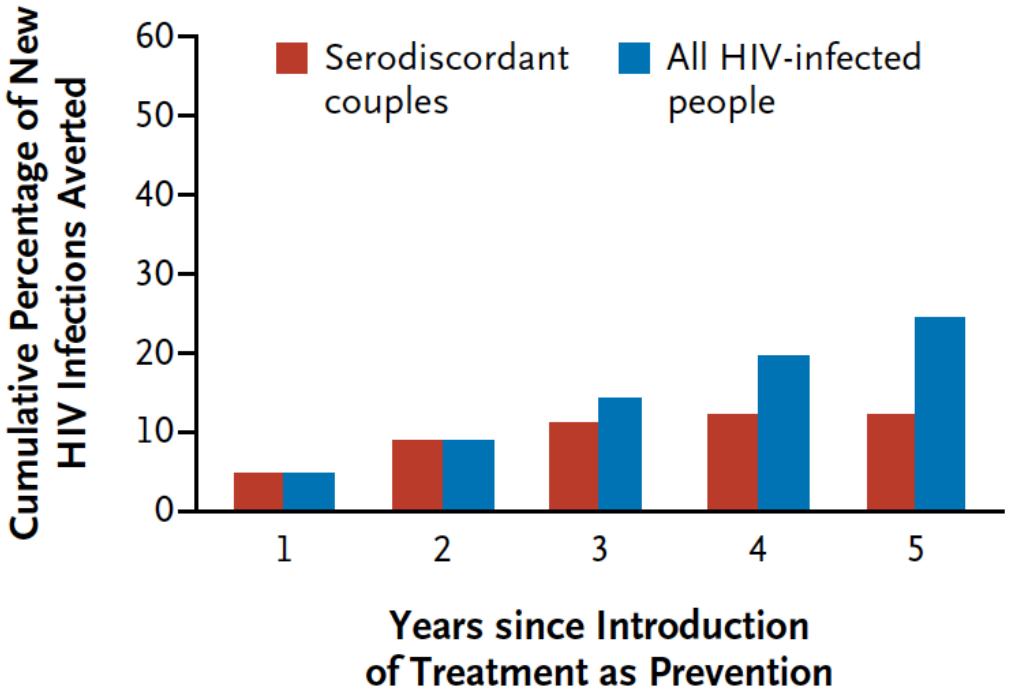
Rochelle P. Walensky, M.D., M.P.H., Eric L. Ross, B.A., Nagalingeswaran Kumarasamy, M.B., B.S., Ph.D., Robin Wood, D.Sc., Farzad Noubary, Ph.D., A. David Paltiel, Ph.D., M.B.A., Yoriko M. Nakamura, B.A., Sheela V. Godbole, M.D., Ravindre Panchia, M.B., B.Ch., Ian Sanne, M.B., B.Ch., D.T.M.&H., Milton 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.

CONCLUSIONS

In South Africa, early ART was cost-saving over a 5-year period. In both South Africa and India, early ART was projected to be very cost-effective over a lifetime. With individual, public health, and economic benefits, there is a compelling case for early ART for serodiscordant couples in resource-limited settings. (Funded by the National Institute of Allergy and Infectious Diseases and others.)

Variable	Index Patients				Patients with Newly Transmitted HIV		Overall Incremental Cost-Effectiveness Ratio†
	Survival	Life Expectancy	Costs	Transmissions per Index Patient‡	Life-Months Lost Due to Transmission	Cost Increase Due to Transmission	
	%	*mo*	*2011 U.S. $*	*no. (% change)*	*mo*	*2011 U.S. $*	
South Africa							
5-year period							
Delayed ART	83	51.7§	4,800¶	0.04	0.09	80	NA
Early ART	93	54.9§	4,800¶	0.01 (–69)	0.02	20	Cost-saving
Lifetime period							
Delayed ART	NA	165.2	15,100	0.08	5.26	760	NA
Early ART	NA	189.4	16,600	0.07 (–13)	2.64	560	590

Cumulative proportion of HIV infections averted by TasP in South Africa over a 5-year period



According to STDSIM model, treatment as prevention for serodiscordant couples would prevent 12% of new infections in South Africa after 5 years, whereas treatment as prevention for all HIV-infected people would prevent 25% of new infections. These values are much lower than the 69% reduction among serodiscordant couples that was predicted by Walensky et al. (N Engl J Med 2013;369:1815-1725)

Hontelez JAC, et al. N Engl J Med, 2014

TasP update

- Evidence from randomized trials and observational studies
- Guidelines recommendations
- Individual benefit (per-act risk reduction)
- Benefit at population level
- Cost-effectiveness
- Caveats and limitations

Antiretroviral therapy for prevention of HIV transmission: implications for Europe

V Cambiano (v.cambiano@ucl.ac.uk)[1], J O'Connor[1], A N Phillips[1], A Rodger[1], R Lodwick[2], A Pharris[3], F Lampe[1], F Nakagawa[1], C Smith[1], M J van de Laar[3]

1. Research Department of Infection and Population Health, Institute of Epidemiology and Health Care, University College London, London, United Kingdom
2. Research Department of Primary Care and Population Health, Institute of Epidemiology and Health Care, University College London, London, United Kingdom
3. European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden

The aim of this review is to summarise the evidence on the population-level effect of antiretroviral therapy (ART) in preventing HIV infections, and to discuss potential implications in the European context of recommending starting ART when the CD4 count is above 350 cells/mm³. The ability of ART to reduce the risk of HIV transmission has been reported in observational studies and in a randomised controlled trial (HPTN 052), in which ART initiation reduced HIV transmission by 96% within serodiscordant couples. As yet, there is no direct evidence for such an effect among men having sex with men or people who inject drugs. HPTN 052 led international organisations to develop recommendations with a higher CD4 threshold for ART initiation. However, there remains a lack of strong evidence of clinical benefit for HIV-positive individuals starting ART with CD4 count above 350 cells/mm³. The main goal of ART provision should be to increase ART coverage for all those in need, based on the current guidelines, and the offer of ART to those who wish to reduce infectivity; increased HIV testing is therefore a key requirement. Other proven prevention means such as condom use and harm reduction for people who inject drugs remain critical.

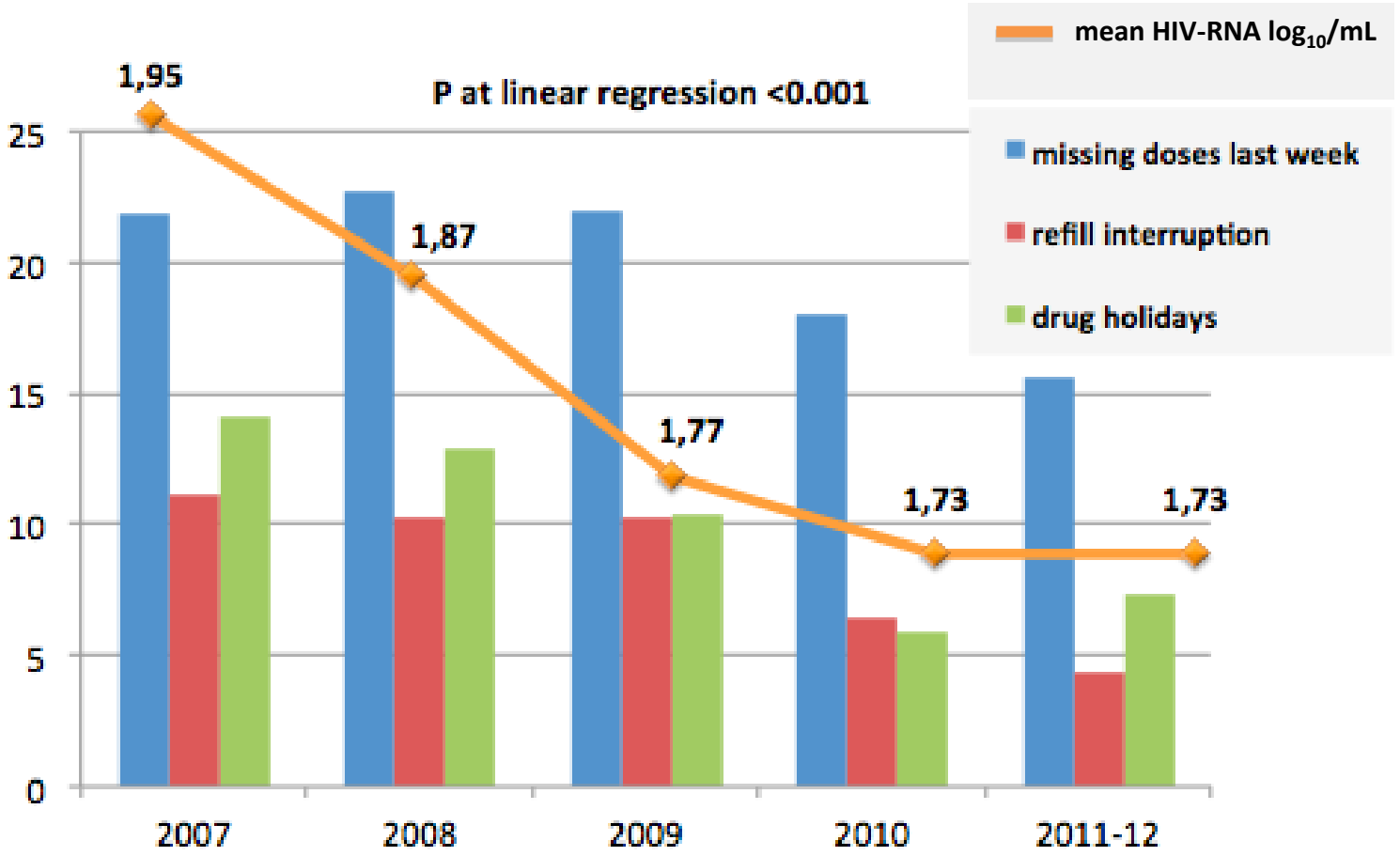
Eurosurveillance, 2014

Adherence and ART for HIV Prevention

- In HPTN 052, viral suppression was nearly universal in those receiving ART, reflecting intensive strategies to achieve nearly perfect adherence
  - **Adherence counselors with detailed checklists; patients received extensive education about ART[1]**
  - **Adherence assessed at Wk 2, monthly x 3, and then quarterly**
- Real-world adherence to ART is not as high as achieved in HPTN 052

1. Cohen MS, et al. N Engl J Med. 2011;365:493-505. Supplementary appendix.

CVL is decreased by higher cART adherence behaviors



Studied population: 1,176 ART-treated patients for at least 12 months
Self-reported adherence: 3,557 questionnaires

INMI, unpublished data, 2014

Limitations of Current Data on ART for HIV Prevention

- ART may mediate different degree of risk reduction when other modes of transmission (eg, needles, anal intercourse) taken into account
- Adherence to lifelong ART may be difficult when initiated in asymptomatic individuals
- Observational studies of the effect of ART on transmission among HIV serodiscordant couples have shown lower HIV risk reduction, likely as a result of lower adherence to ART[1]
- 28% of infections in HPTN 052 occurred from outside of study partnerships, for which ART use by the HIV-infected partner offered no protection[2]

1. Anglemyer A, et al. Cochrane Database Syst Rev. 2013;4:CD009153.
2. Cohen MS, et al. N Engl J Med. 2011;365:493-505.

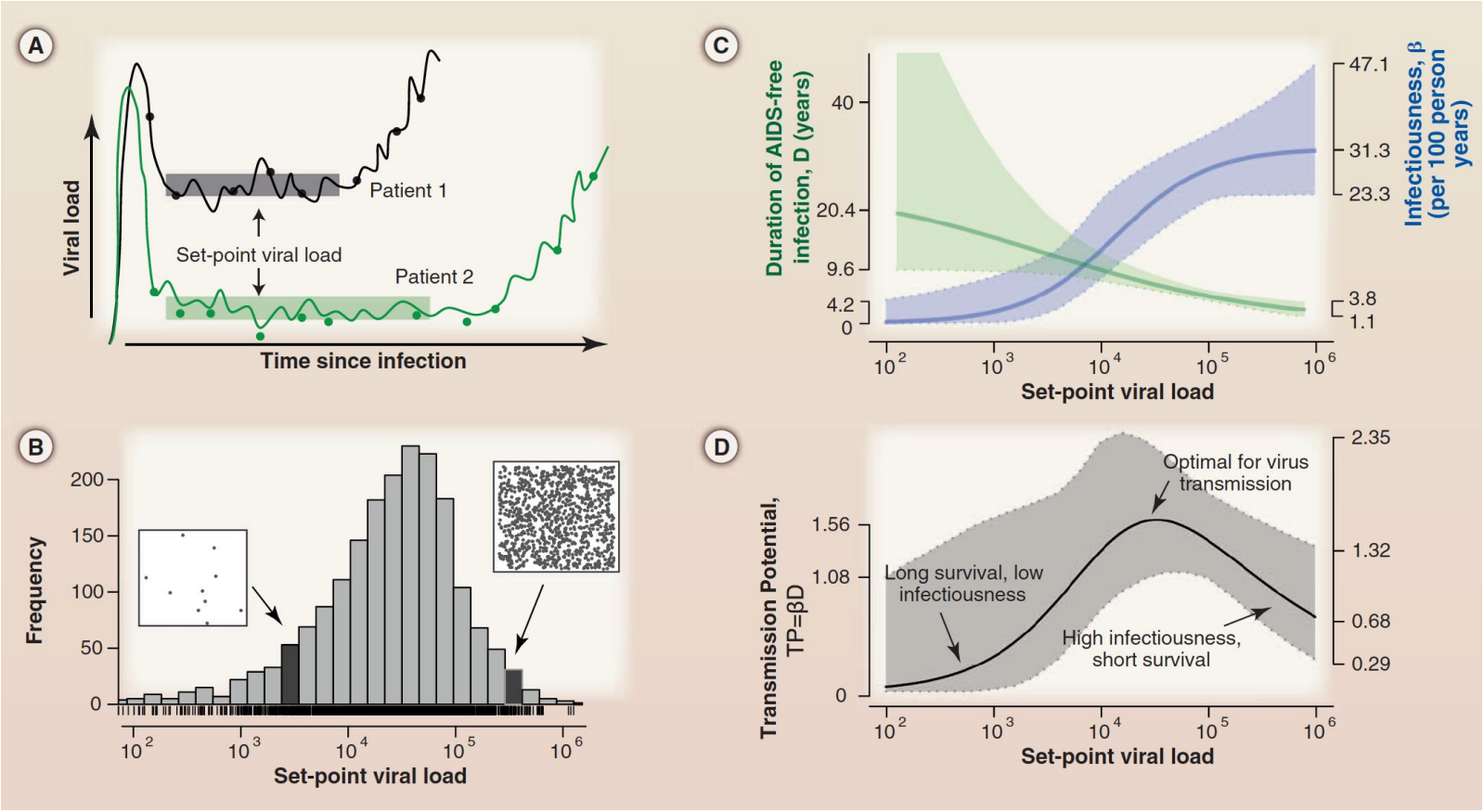
Summary: ART as Prevention

- Initiation of effective ART results in a substantial decrease in HIV infectiousness and transmission risk
- This results was maximized in RCT and heterosexual serodiscordant couples, but has been demonstrated even by observational approach and in MSM population
- ART expansion is associated to a strong reduction of HIV transmission at a population level
- TasP in serodiscordant couples is a cost-effective strategy
- Adherence (with viral suppression) is key to preventive effects of ART
- Prescribing guidelines now include risk of transmission as an indication to initiate ART
- Providers should talk about prevention as part of ART's benefits

Best strategies to increase the access to care

BACKGROUND SLIDES

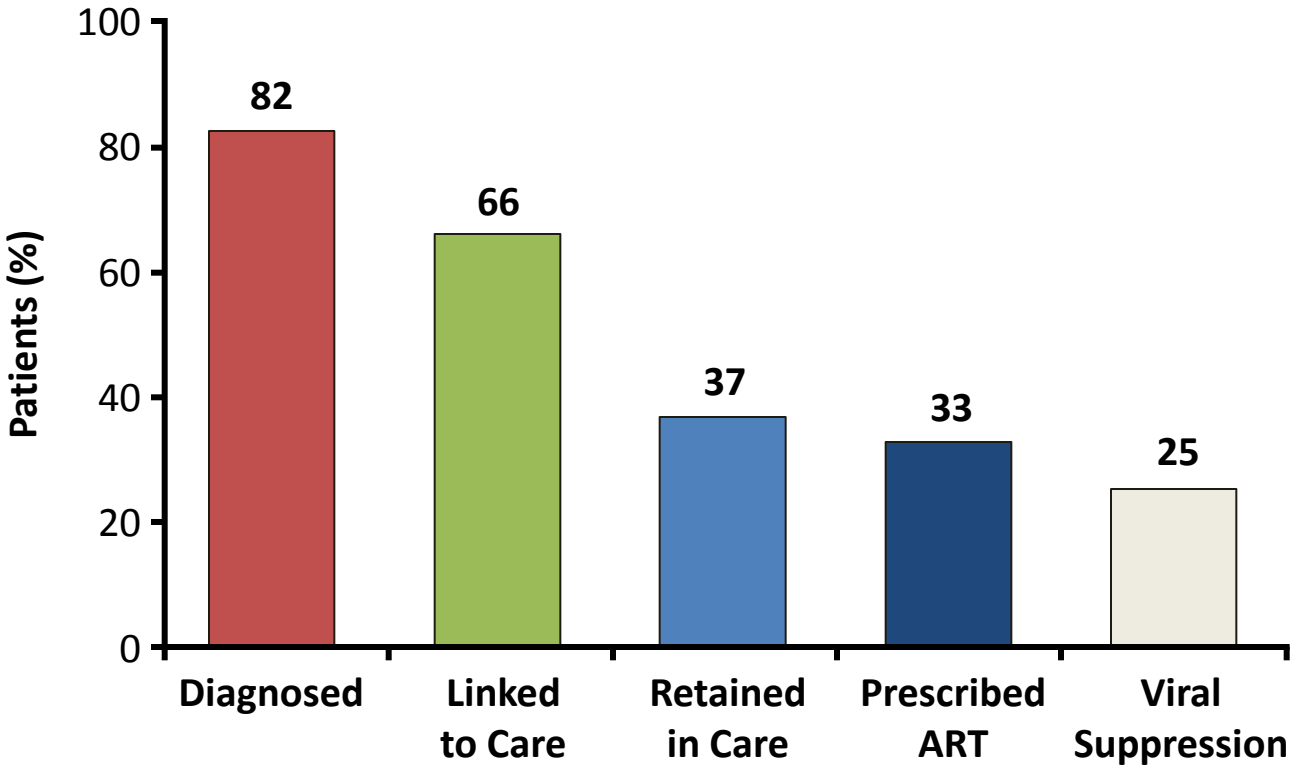
The “evolutionary epidemiology” of HIV-1 viral load



Fraser C, et al. Science, 2014

CDC: Breaks in the Continuum of Care in HIV-Infected Patients in the US

- CDC study shows that only ~ 25% of US patients with HIV have suppressed HIV-1 RNA

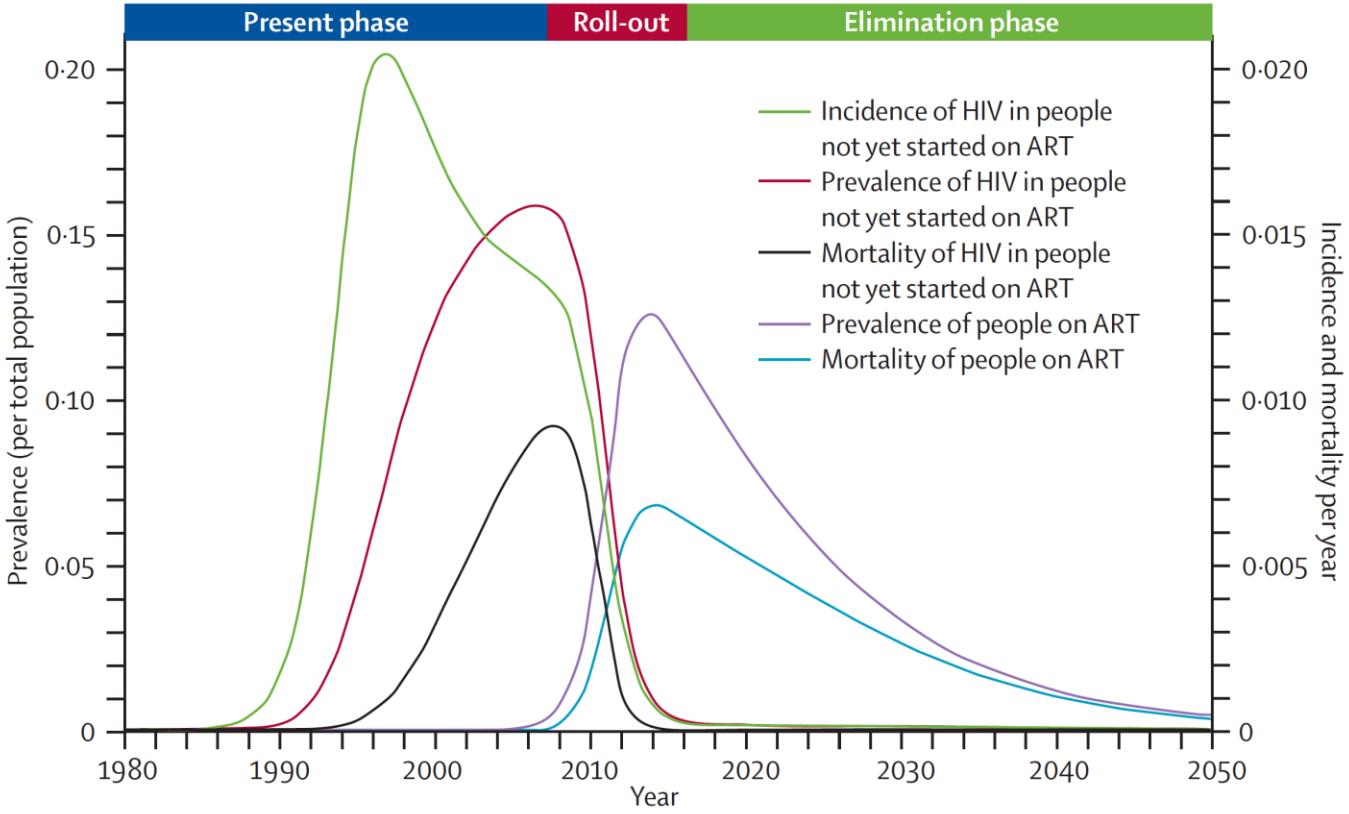


Hall HI, et al. JAMA Intern Med. 2013;17:1-7.

Universal voluntary HIV testing with immediate ART as a strategy for elimination of HIV transmission

A mathematical model

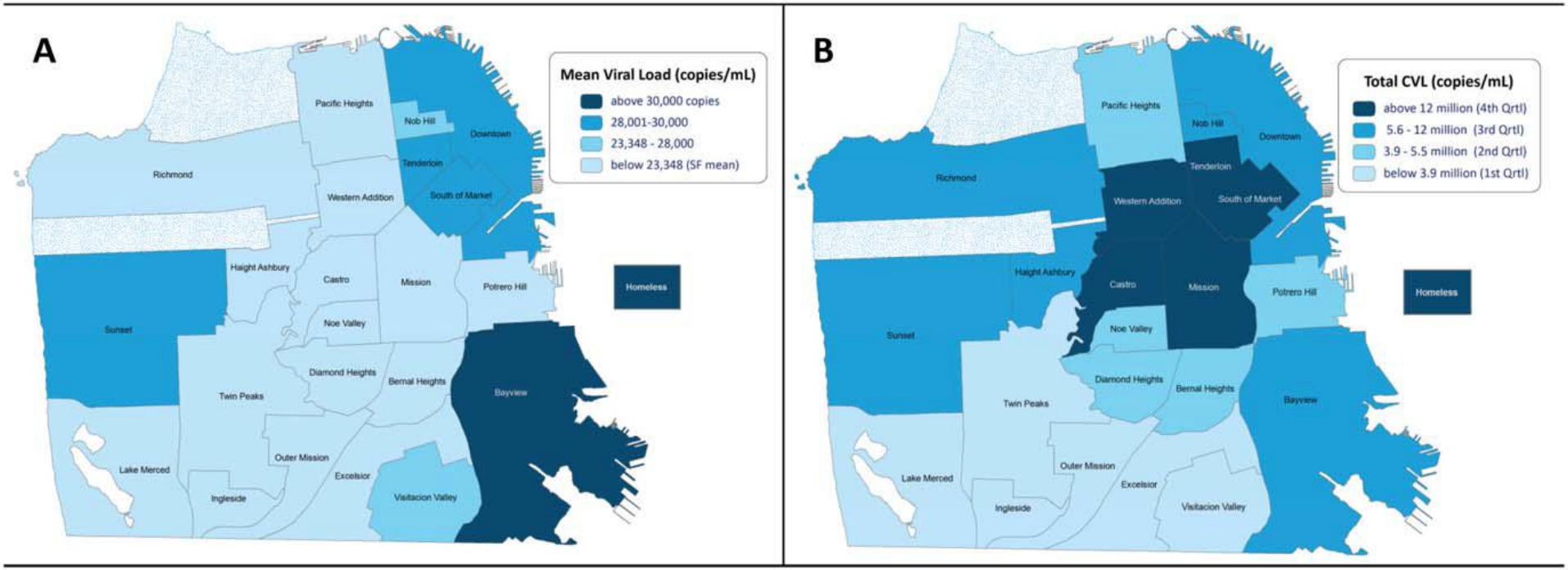
Time trends resulting from application of universal voluntary HIV testing and immediate ART strategy for people who test HIV positive, in combination with other adult prevention interventions that reduce incidence by 40%.



Granich R, et al. Lancet, 2008

Total CVL reflected mean CVL by population with a notable exception of geography

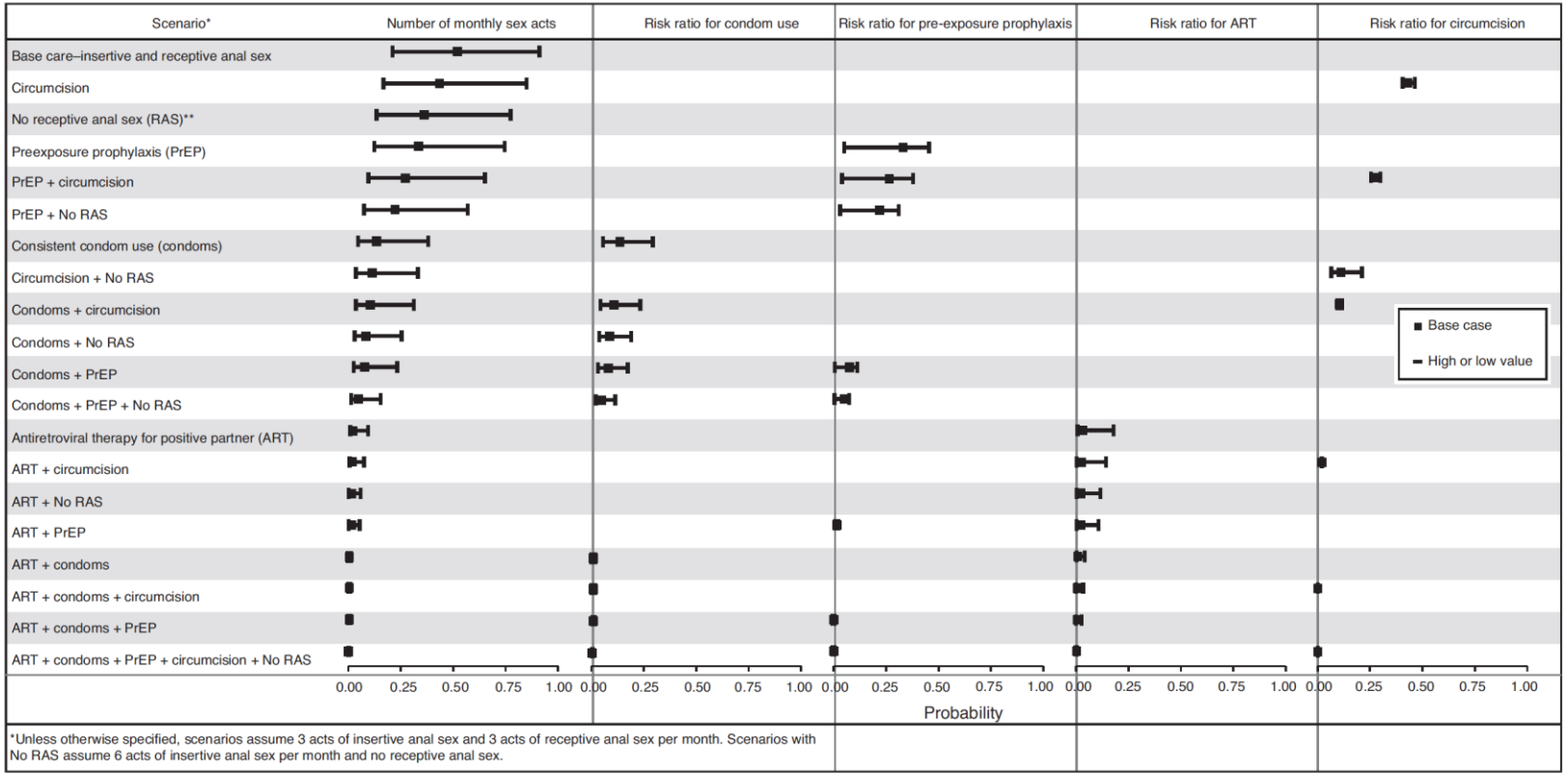
Spatial Distribution of CVL by Neighborhood, 2005–2008. Mean CVL was highest among homeless individuals (38,974copies/mL; N= 775; 6%). The highest mean CVL (38,428 copies/mL; N= 278; 2%) was in the southeast neighborhood of Bayview, which is characterized by lower income and a predominantly African-American population. The highest total CVLs are evident in the Tenderloin, South of Market, Mission, and the Castro, where there are either large numbers of persons living with HIV, many persons with high VLs, or a combination thereof.



Das M, et al. PLoS One, 2010

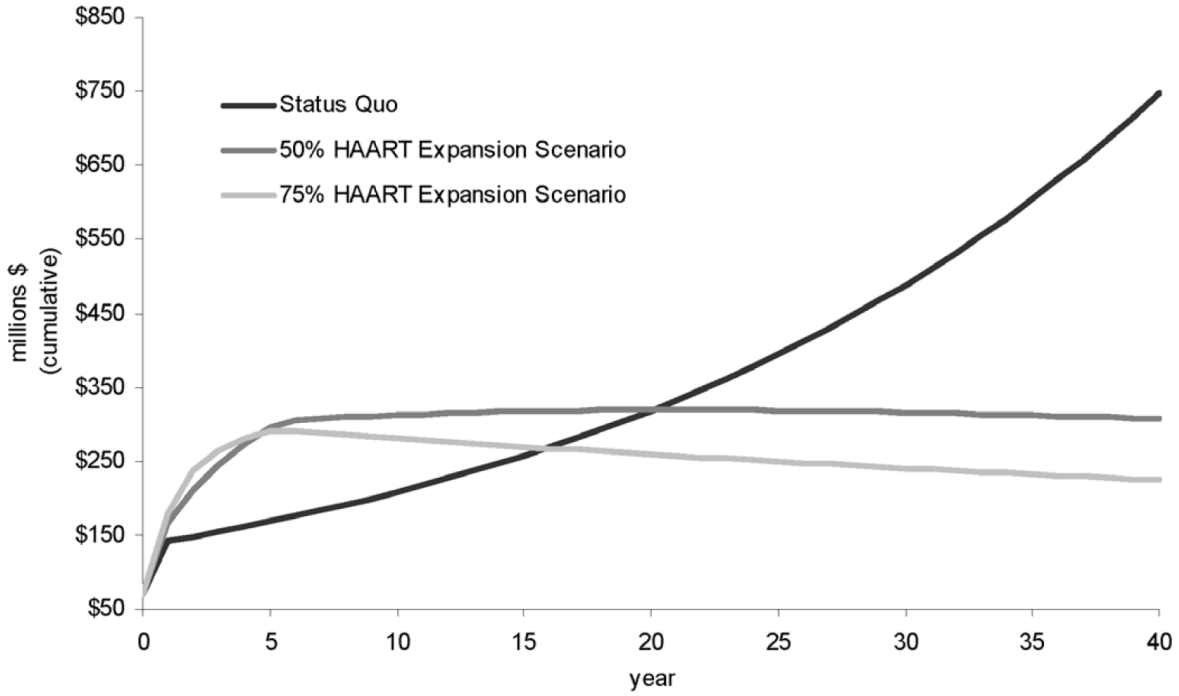
Transmission probabilities to the negative partner in serodiscordant can be substantially reduced with the strategic use of preventive methods, especially those that include ART

We estimated the sexual risk of HIV transmission over 1-year and 10-year periods among male-male and male-female serodiscordant couples. We assumed the following reductions in transmission: **80%** from consistent condom use; **54%** from circumcision in the negative male partner of a heterosexual couple; **73%** from circumcision in the negative partner of a male-male couple; **71%** from PrEP in heterosexual couples; **44%** from PrEP in male-male couples; and **96%** from ART use by the HIV-infected partner.



Lasry A, et al. AIDS, 2014

Return on increased investment resulting from implementation of the Status Quo approach versus expansion scenarios



Within 5 years, increasing HAART coverage decreased yearly new infections by at least 44.8%. In the 50% scenario, in 5 years, DALY decreased by 53% corresponding to 4,155 averted DALYs, and in 25 years it decreased by 66% corresponding to 5,837 averted DALYs. The effect was even stronger if the 75% scenario was chosen instead. Compared to the 100% expansion scenario, we observed an excess in annual direct treatment expenditures at the end of 5 years of approximately 1 million dollars in the 75% scenario, and of approximately 2 million dollars in the 50% scenario.

Lima VD, et al. PLoS One, 2010