Treatment as Prevention in India: What will it take?

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ICAAP 10, Busan, South Korea

HIV IN INDIA

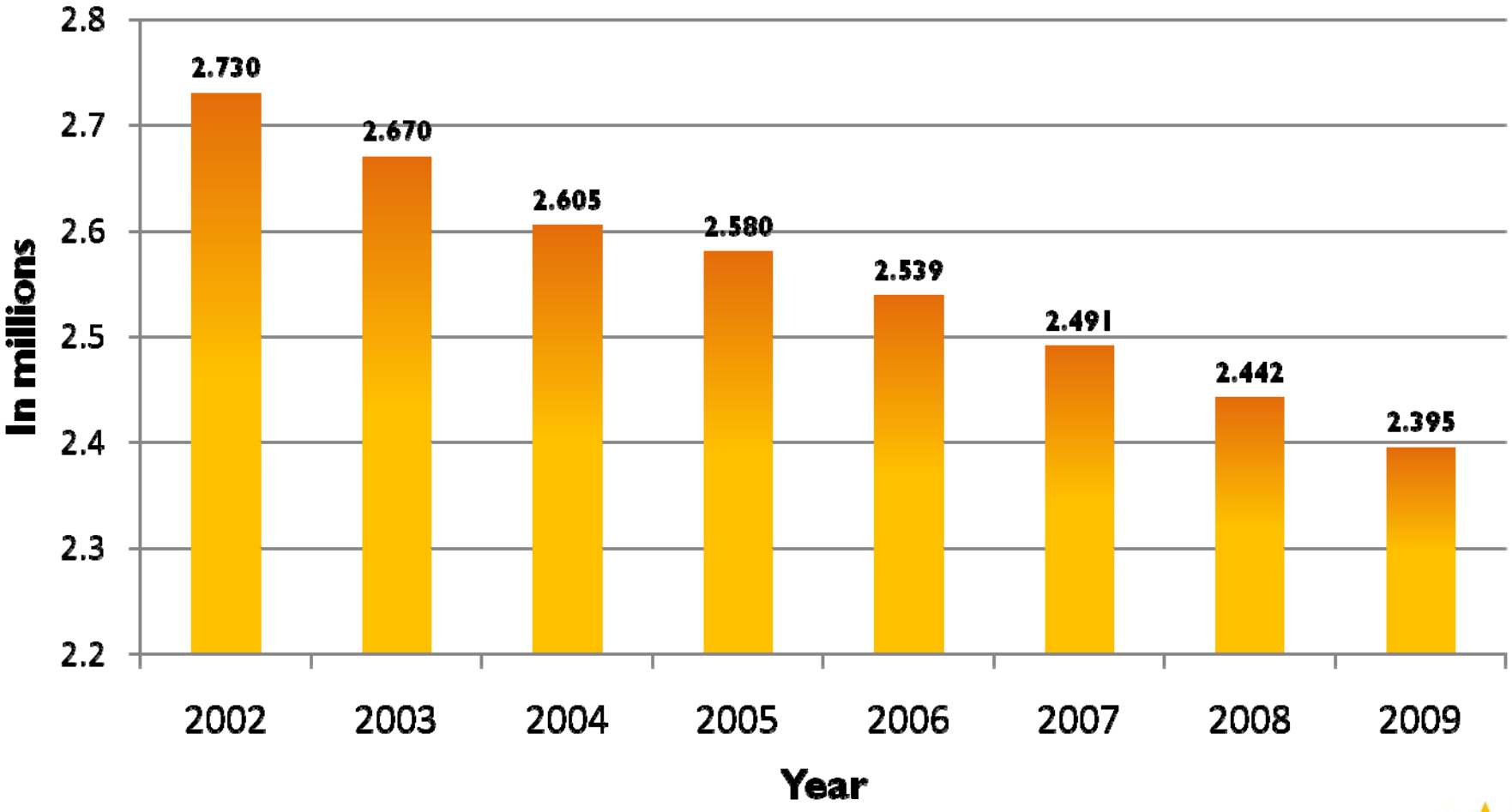
The First Evidence…

AIDS Comes to India

"Evidence for HTLV-III Infection in prostitutes in Tamil Nadu (India)"

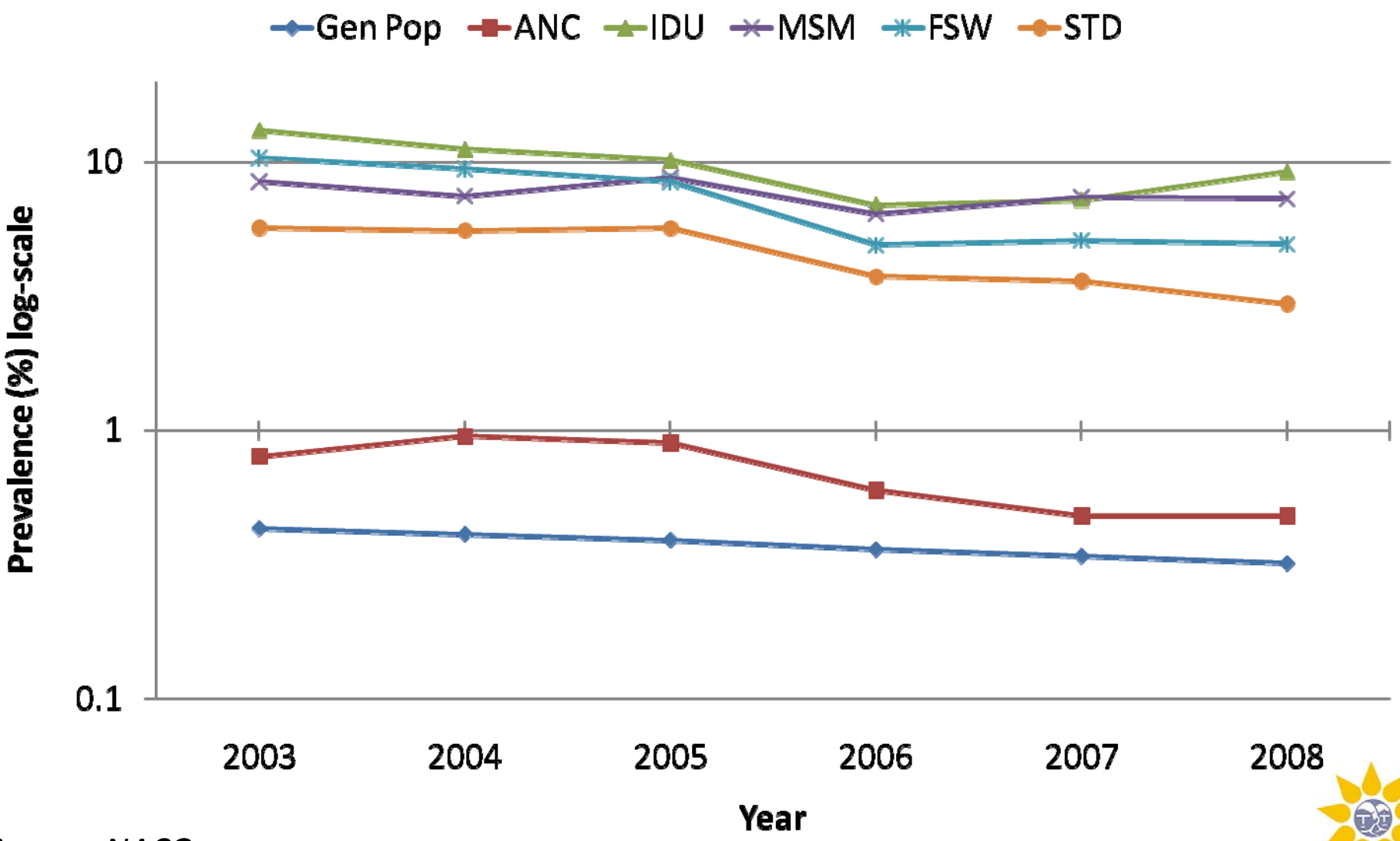
Simoes et al. ***Indian J Med Res 1987; 85:335-8***

The Numbers…..



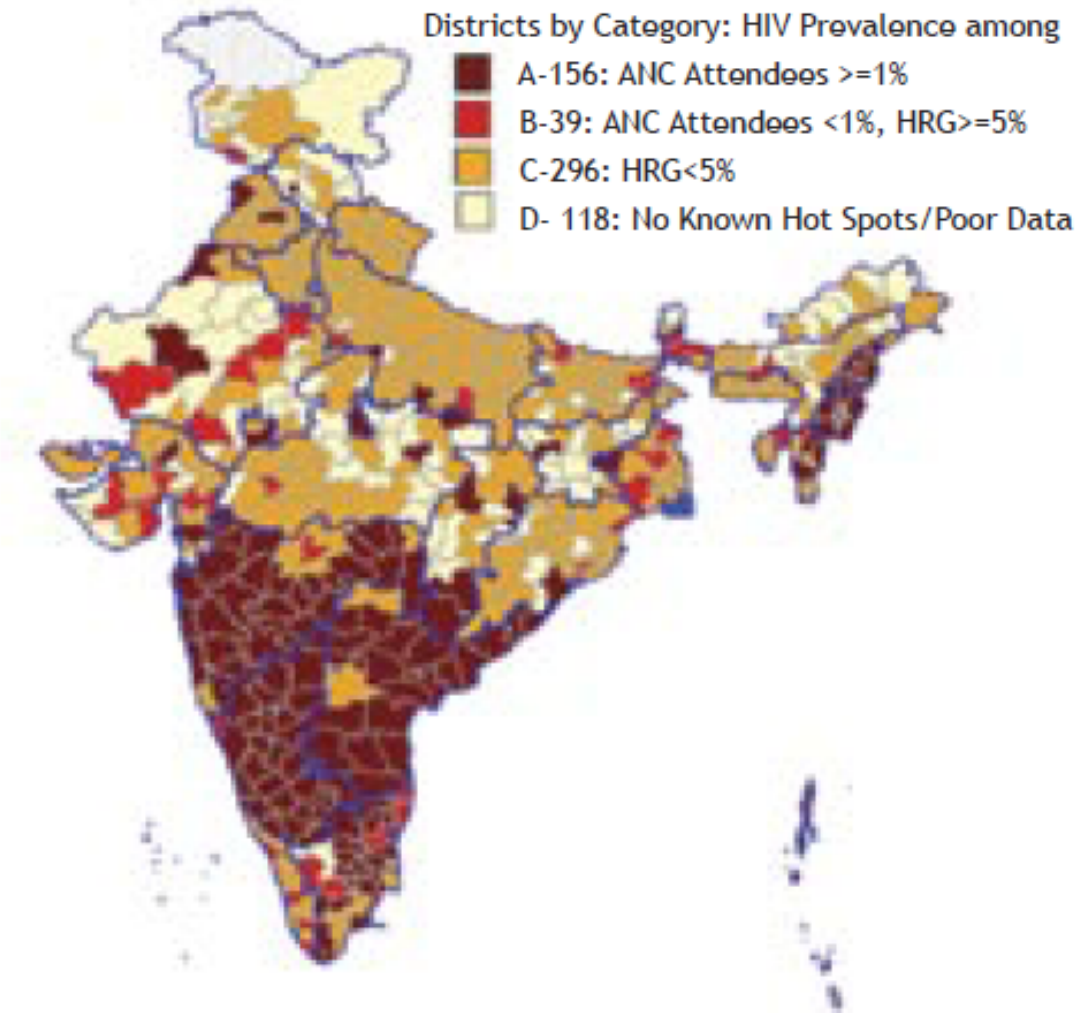
Source: NACO

Prevalence (2003 – 2008)



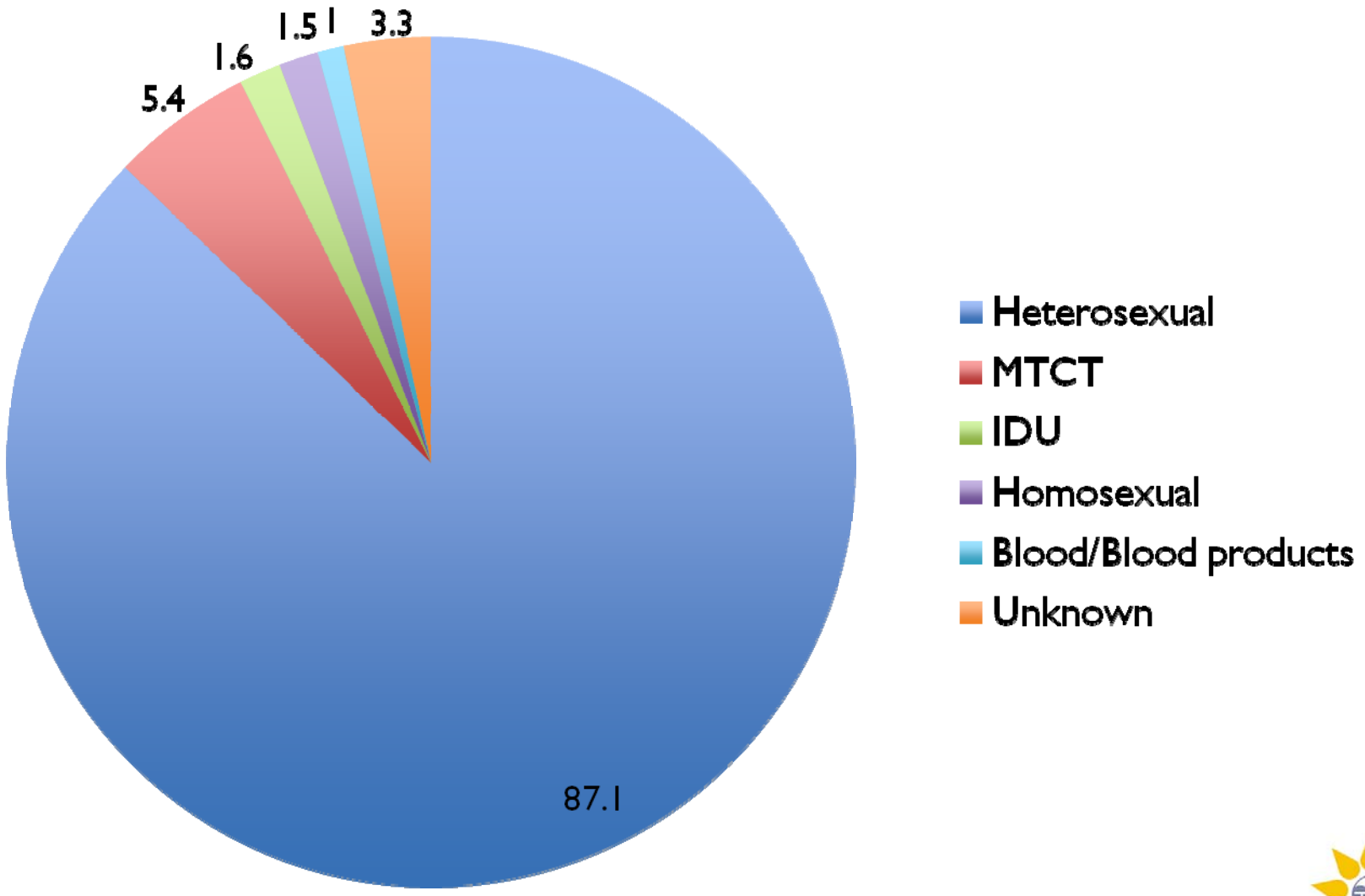
Source: NACO

HIV Prevalence in India



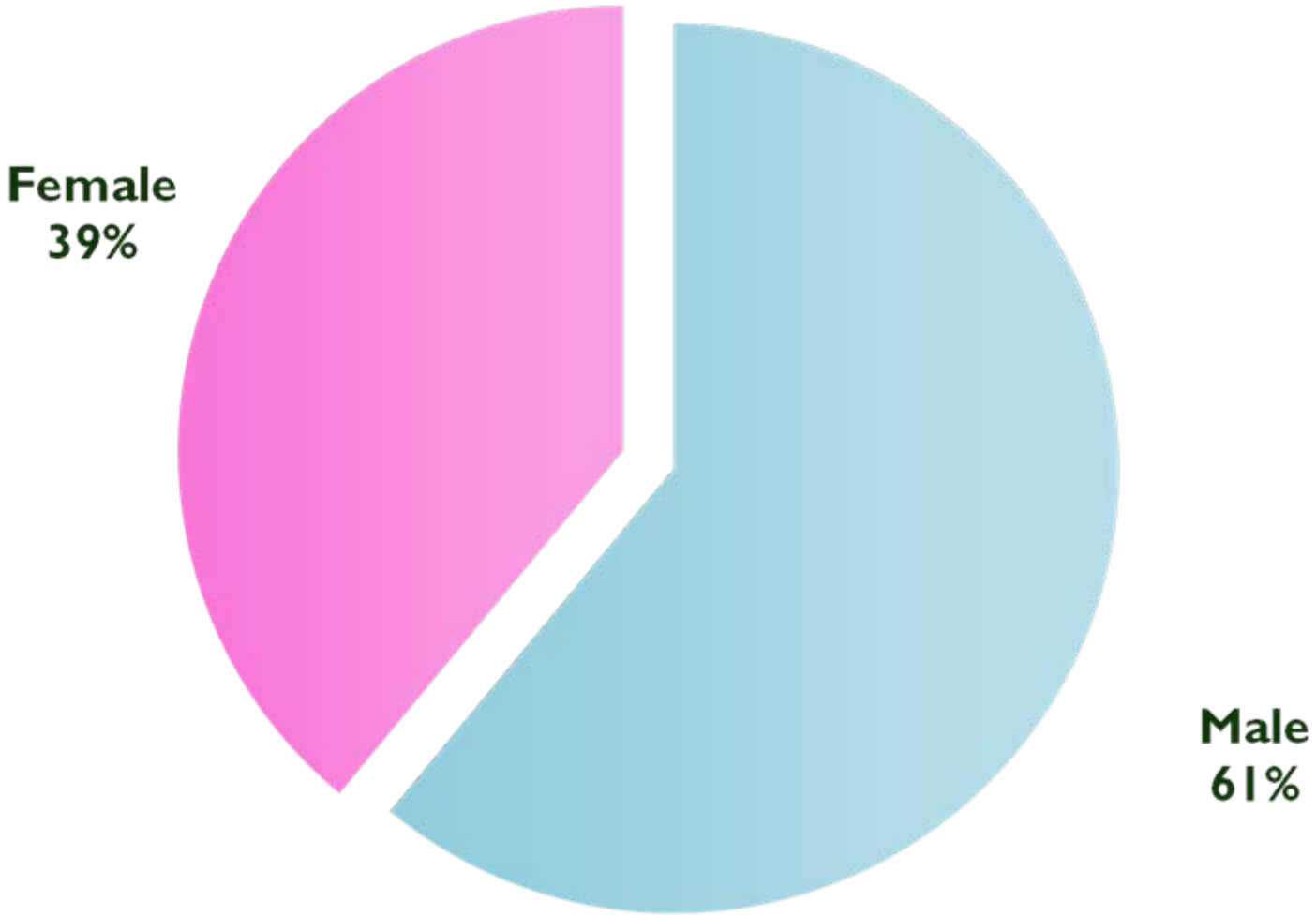
Source: NACO

Modes of transmission in India



Source: NACO

Distribution of HIV in India



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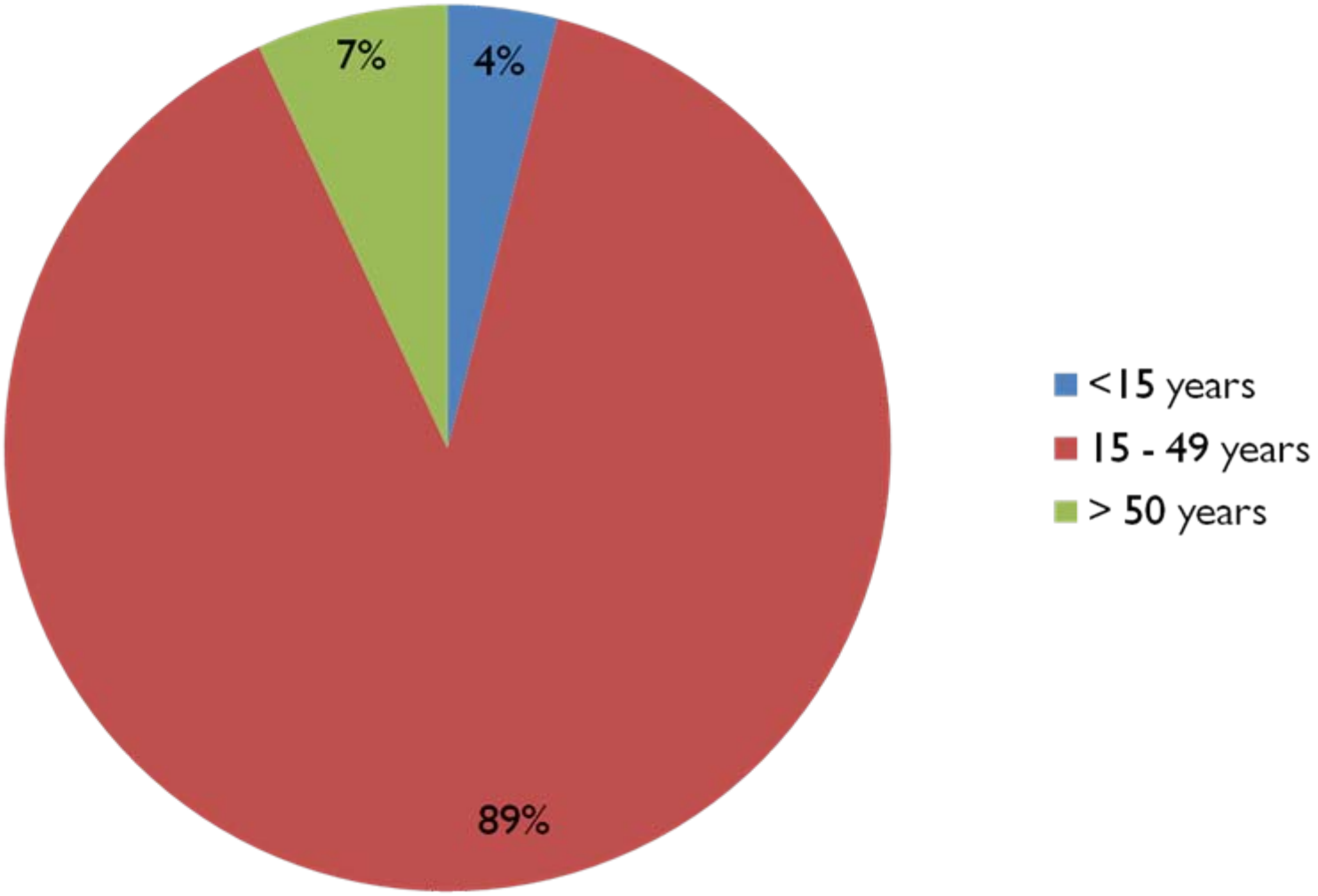
Distribution of HIV in India



Source: NACO

MANAGEMENT OF HIV DISEASE IN INDIA

Natural History of HIV in India

- Predominantly subtype-C except in NE

"Rapid disease progression in HIV type 1 infected seroconverters in India"

Mehendale et al. AIDS Res Hum Retro 2002;18:1175-9

".....the more rapid HIV disease progression described in resource-poor settings may be due to very early virological and host events following primary HIV infection...."

HAART in India

WHEN TO START?

- Currently following WHO guidelines
  - CD4<350 cells/µl
  - AIDS defining illness irrespective of CD4 count

WHAT TO START?

- Generic HAART

HAART in India

"The safety, tolerability and effectiveness of generic antiretroviral drug regimens for HIV-infected patients in south India"

Kumarasamy et al. AIDS 2003;17:2267-9

"Rapid viral load suppression following generic highly active antiretroviral therapy in Southern Indian HIV-infected patients"

Kumarasamy et al. AIDS 2005;19:625-7

HAART in India

WHEN TO START?

- Currently following WHO guidelines
  - CD4<350 cells/µl
  - AIDS defining illness irrespective of CD4 count

WHAT TO START?

- Generic HAART
- d4T + 3TC + NVP is the most common regimen
- d4T/AZT + 3TC + NVP/EFV
- TDF used more in private sector

HAART in India

WHERE IS IT AVAILABLE?

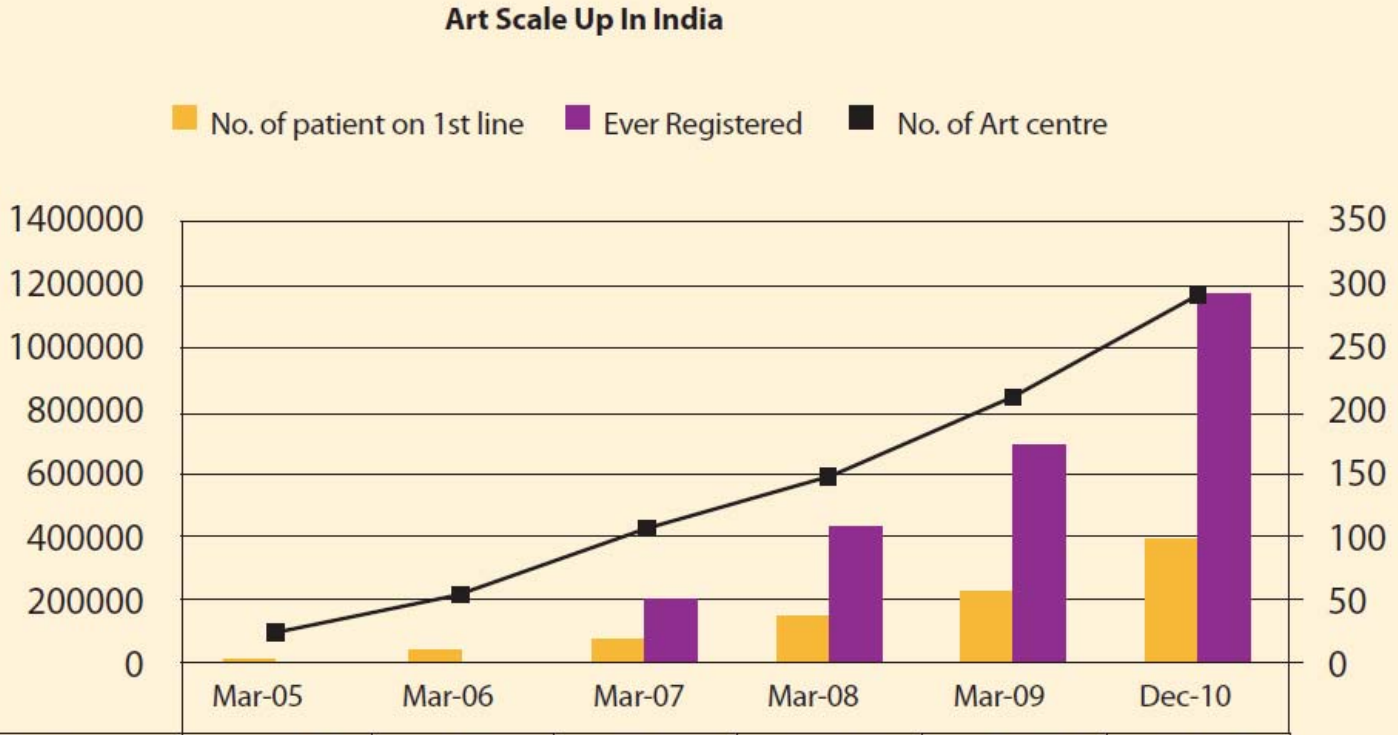
- Government ART centers (292 centers – Dec 2010)
- Private providers
- OTC at pharmacies

HOW MUCH DOES IT COST?

- Government sector: Free
- Private Sector: ~20 USD per month

HOW MANY ON ART?

HAART in India



No. of patient on 1st line	6845	37368	69016	140654	223223	384726
Ever Registered			194,507	428,056	686,913	1169050
No. of ART centre	25	54	107	147	211	292

Source: NACO

HAART in India

WHERE IS IT AVAILABLE?

- Government ART centers (239 centers – Jan 2010)
- Private providers
- OTC at pharmacies

HOW MUCH DOES IT COST?

- Government sector: Free
- Private Sector: ~20 USD per month

HOW MANY ON ART?

- ~50,000 in the private sector

HAART in India

HOW IS ART MONITORED?

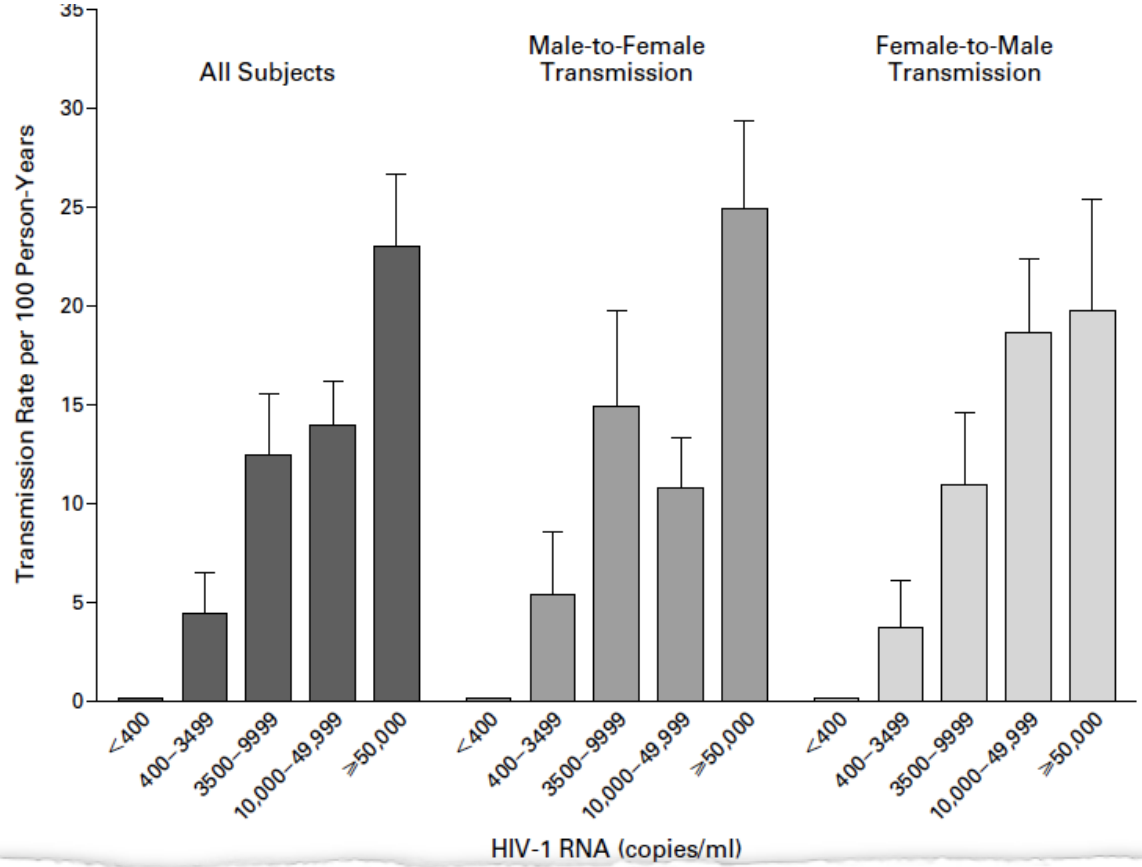
- Only CD4 counts (every 3-6 months when available)
- HIV RNA quantification – private sector

WHAT ABOUT SECOND-LINE TREATMENT?

- Available in both government and private sectors
- More expensive (~USD 100 per month)

EVIDENCE FOR TREATMENT AS PREVENTION

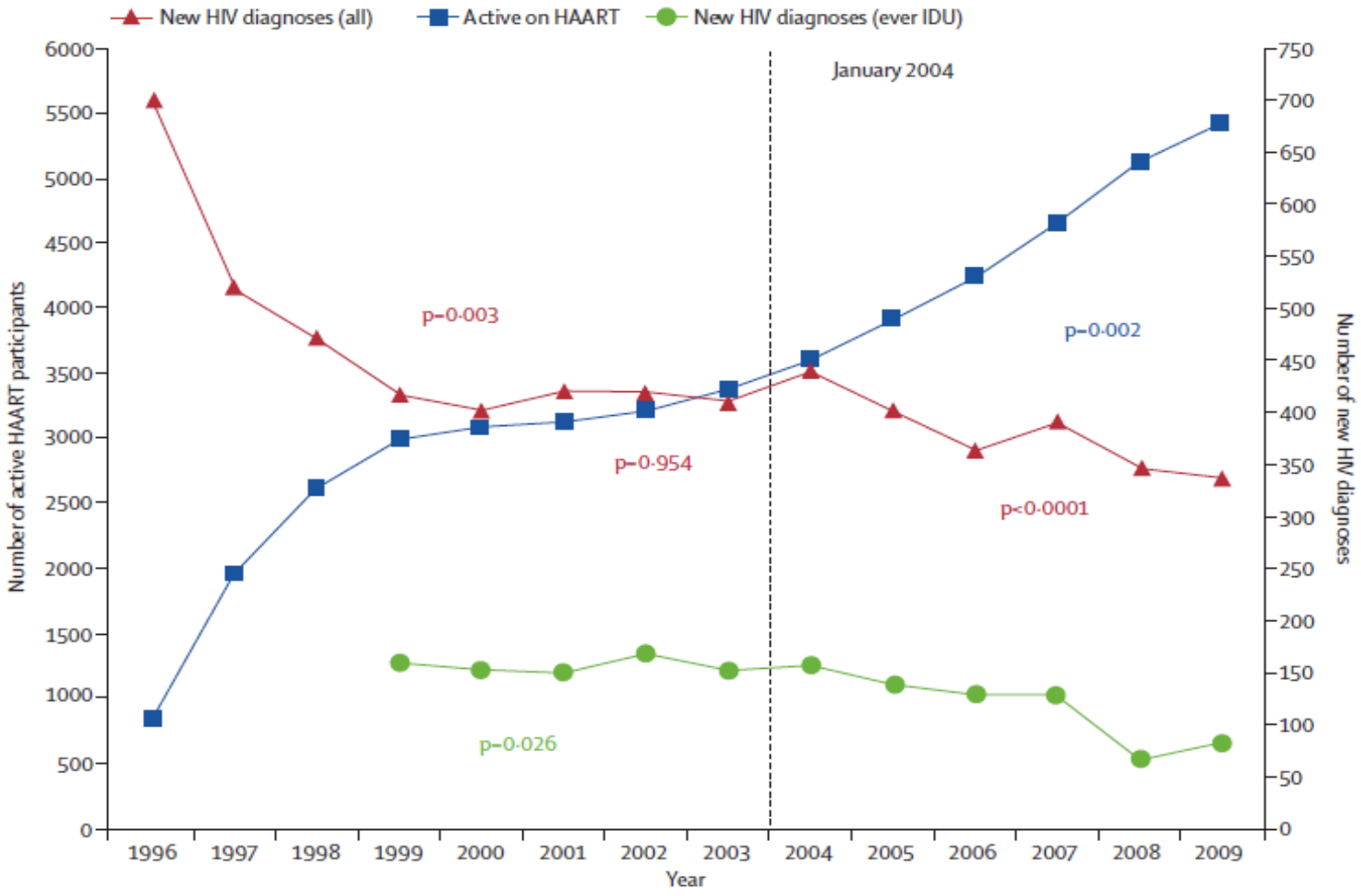
ART = REDUCED TRANSMISSION



"Viral Load and Heterosexual Transmission of Human Immunodeficiency Virus Type 1"

Quinn et al. N Engl J Med 2000;342:921-9

MONTANER ET AL *(Lancet 2010)*



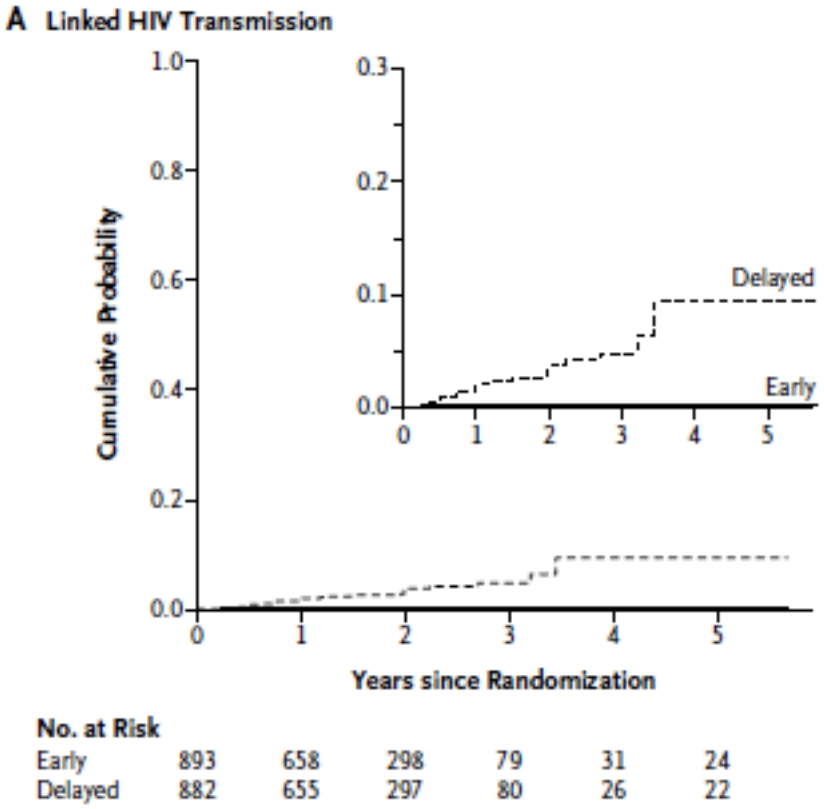
Number at risk														
Active on HAART	837	1960	2597	2994	3079	3120	3211	3356	3585	3913	4255	4654	5123	5413
New HIV diagnoses (all)	702	519	471	416	400	420	418	408	441	400	361	391	346	338
New HIV diagnoses (ever IDU)	NA	NA	NA	159	152	149	168	149	156	137	128	128	65	80
HIV tests done in BC (per 1000)	138	140	137	135	135	135	145	142	154	161	172	176	182	NA

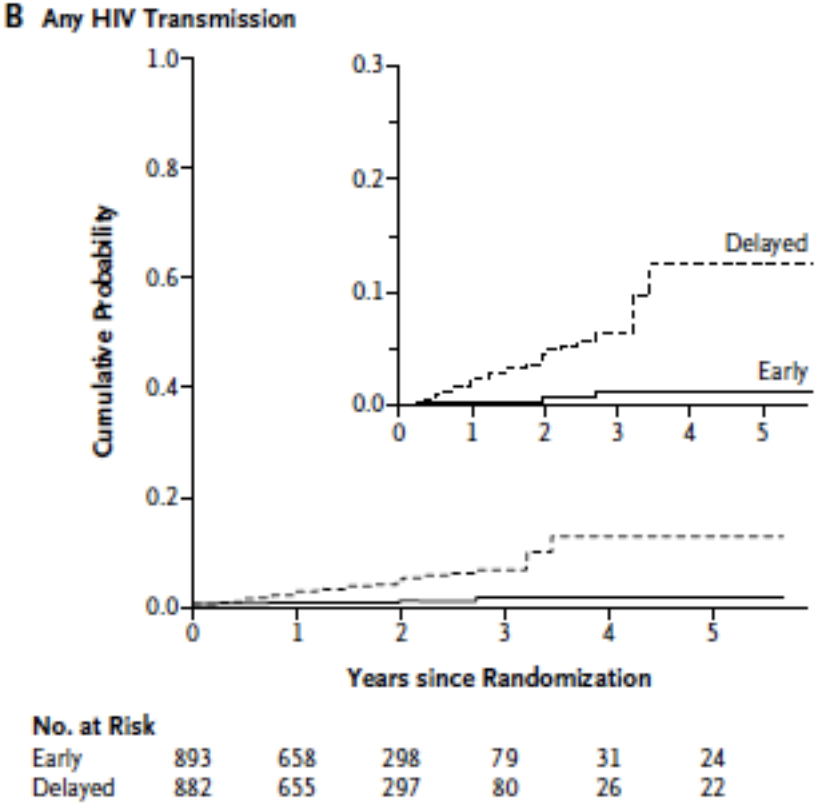
MONTANER ET AL *(Lancet 2010)*

	Individuals who have never injected drugs				Individuals who have ever injected drugs			
	n	Median HIV-1 RNA plasma concentration (copies per mL; IQR)	Patients with <500 copies per mL (%)	Patients with <50 copies per mL (%)	n	Median HIV-1 RNA plasma concentration (IQR)	Patients with <500 copies per mL (%)	Patients with <50 copies per mL (%)
1996	2093	35 000 (6000 to >100 000)	178 (9%)	NA	831	36 000 (7600 to >100 000)	46 (6%)	NA
1997	2848	18 000 (2175 to 93 000)	464 (16%)	NA	1334	37 000 (6100 to >100 000)	120 (9%)	NA
1998	3324	8800 (<500 to 76 000)	1017 (31%)	NA	1558	26 000 (2100 to >100 000)	274 (18%)	NA
1999	3740	6145 (<500 to 72 000)	1368 (37%)	234 (6%)	1707	20 500 (805 to >100 000)	388 (23%)	73 (4%)
2000	4114	6270 (<500 to 76 300)	1572 (38%)	1060 (26%)	1822	18 650 (<500 to >100 000)	481 (26%)	328 (18%)
2001	4535	4260 (<500 to 69 400)	1874 (41%)	1324 (29%)	1936	18 450 (<500 to >100 000)	513 (27%)	370 (19%)
2002	4950	5545 (<500 to 88 000)	2091 (42%)	1529 (31%)	2046	23 550 (<500 to >100 000)	581 (28%)	412 (20%)
2003	5303	4820 (<500 to 76 500)	2270 (43%)	1718 (32%)	2151	22 200 (<500 to >100 000)	636 (30%)	471 (22%)
2004	5848	2355 (<500 to 59 500)	2663 (46%)	2075 (36%)	2230	19 100 (<500 to >100 000)	718 (32%)	533 (24%)
2005	6174	814 (<500 to 51 000)	3013 (49%)	2414 (39%)	2297	13 700 (<500 to 96 400)	803 (35%)	629 (27%)
2006	6426	<500 (<500 to 41 800)	3331 (52%)	2747 (43%)	2330	9015 (<500 to 89 500)	902 (39%)	710 (31%)
2007	6745	<500 (<500 to 34 500)	3675 (55%)	3049 (45%)	2335	5450 (<500 to 80 900)	993 (43%)	789 (34%)
2008	7301	<500 (<500 to 25 000)	4241 (58%)	3283 (45%)	2326	522·5 (<500 to 46 500)	1159 (50%)	807 (35%)
2009	8001	<500 (<500 to 16 092)	4960 (62%)	4040 (51%)	2340	<500 (<500 to 20 035)	1372 (59%)	1038 (44%)
p value			0·0002	0·001			0·001	0·002

Data are n, median (IQR), or n (%).

HPTN 052 *(Cohen et al. NEJM 2011)*



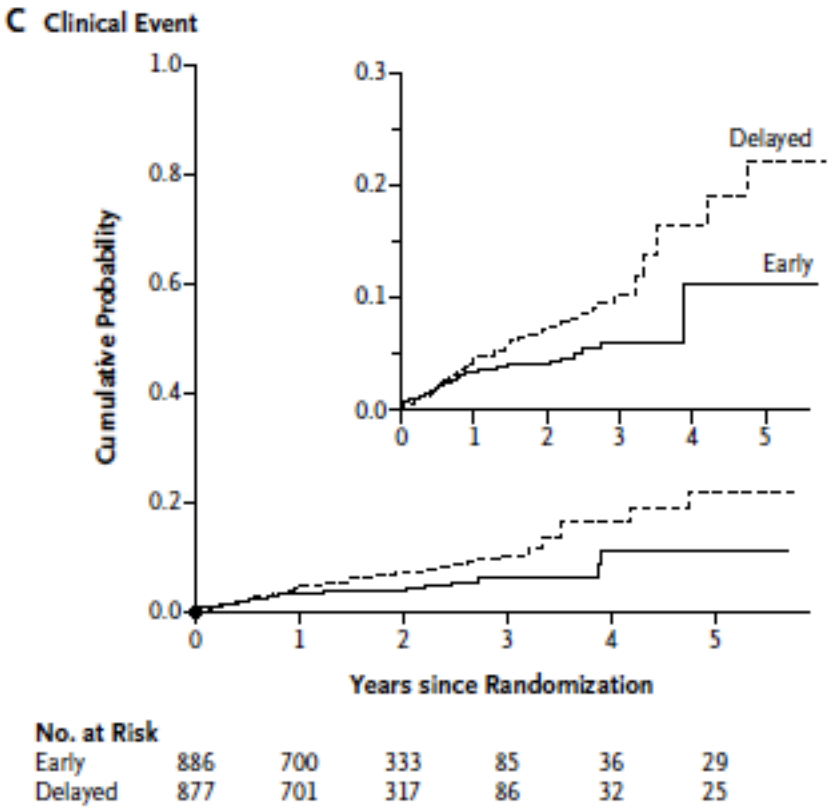


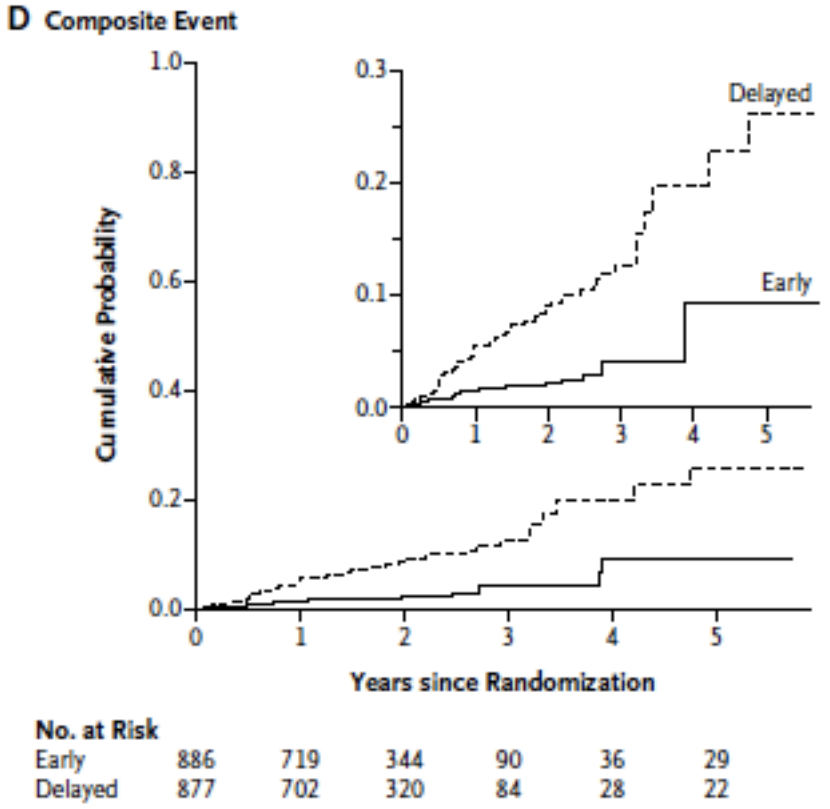
Primary Outcome: Linked Transmissions

27 – delayed arm

1 – early arm

HPTN 052 *(Cohen et al. NEJM 2011)*

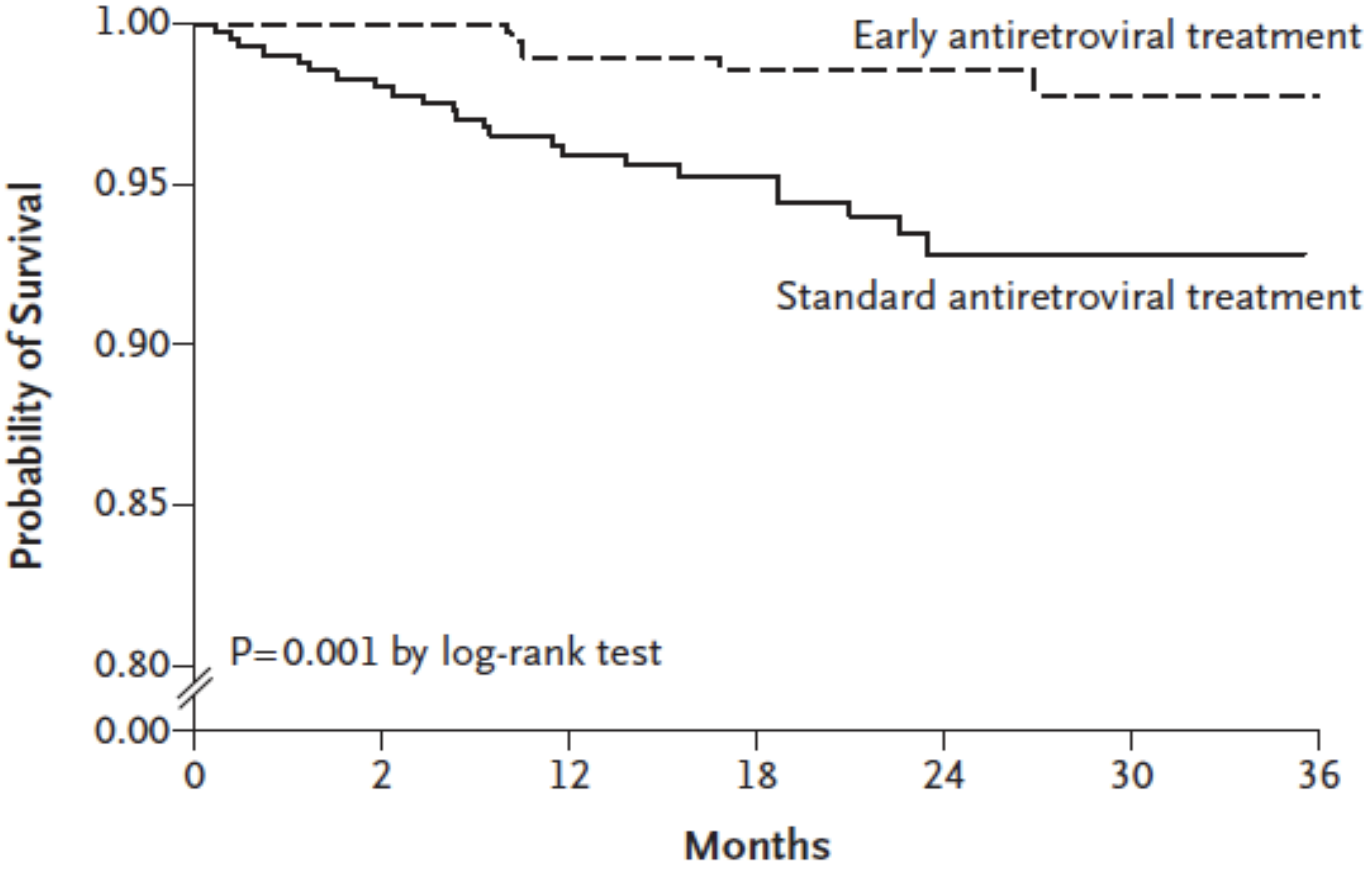




HPTN 052 *(Cohen et al. NEJM 2011)*

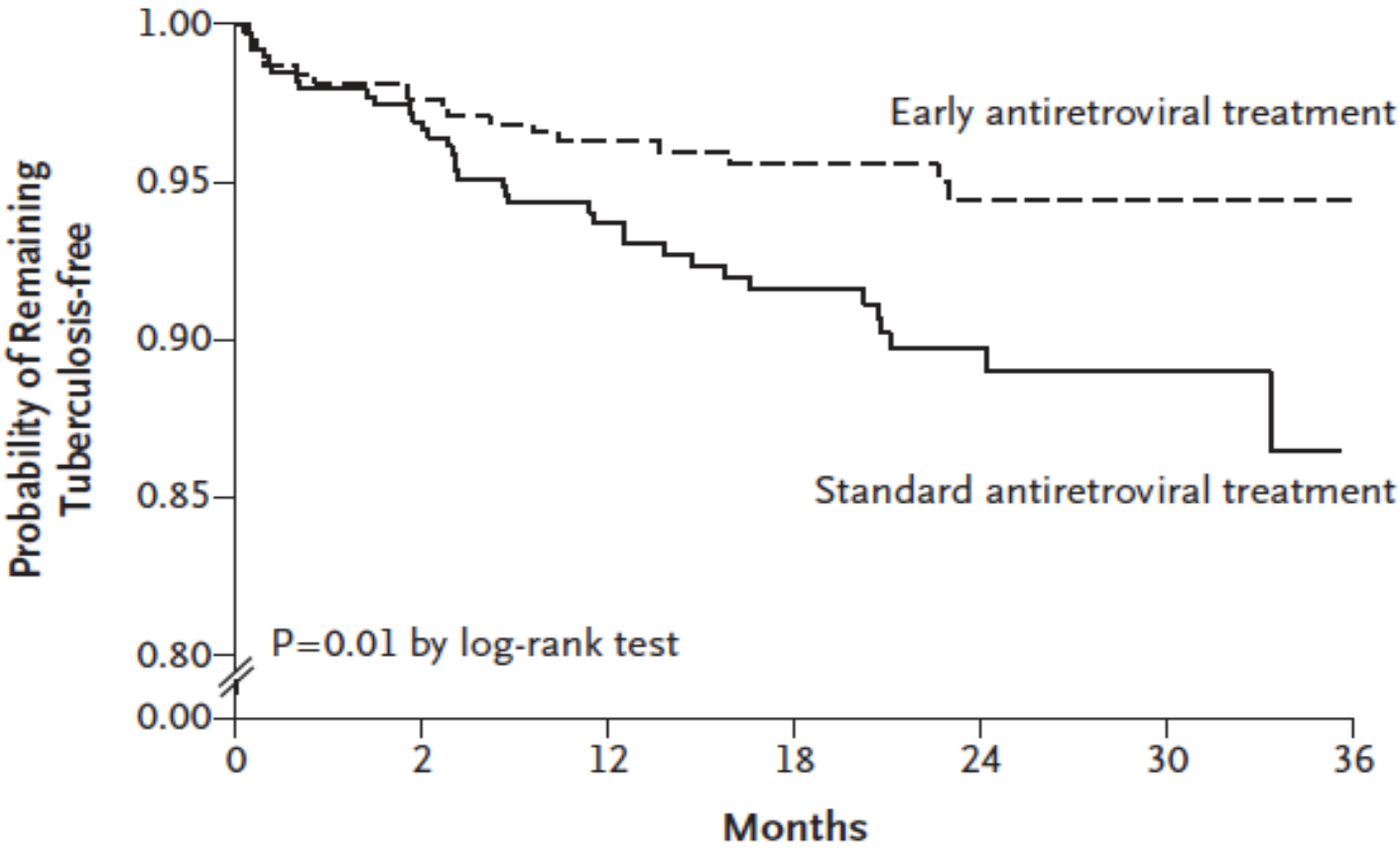
Variable	Linked Transmission	Any Transmission	Clinical Events	Composite Events
	hazard ratio (95% CI)			
Univariate analysis				
Early therapy vs. delayed therapy	0.04 (0.01–0.26)	0.11 (0.04–0.32)	0.60 (0.41–0.90)	0.28 (0.18–0.45)
Baseline CD4 count (per 100 CD4 increment)	1.27 (1.02–1.59)	1.25 (1.02–1.52)	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)

CIPRA HT 001 *(Severe et al. NEJM 2010)*



No. at Risk				
Early treatment	408	327	153	24
Standard treatment	408	309	137	22

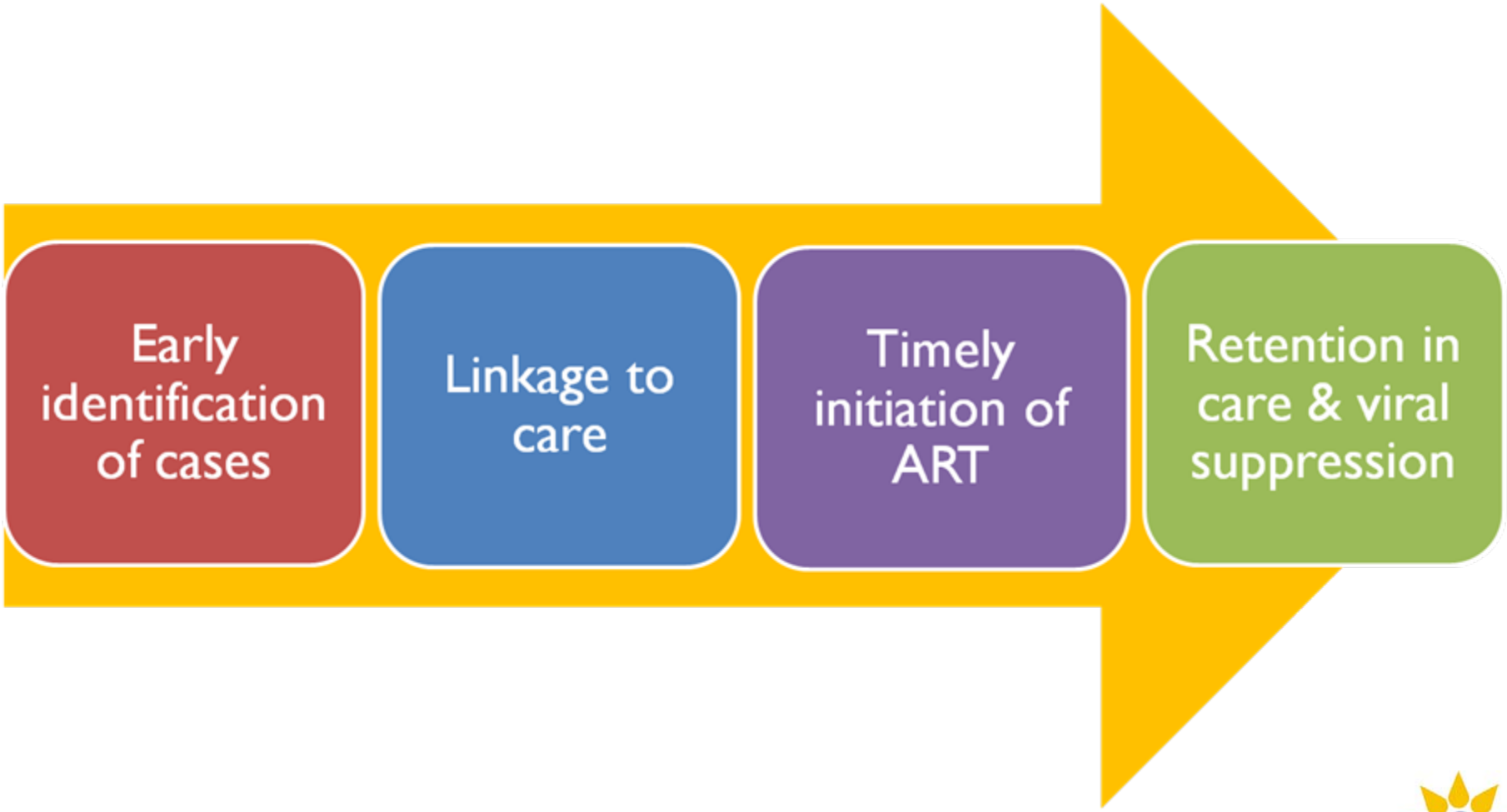
CIPRA HT 001 *(Severe et al. NEJM 2010)*



No. at Risk				
Early treatment	380	302	140	20
Standard treatment	393	288	122	16

IMPLEMENTING TREATMENT AS PREVENTION IN INDIA: WHAT WILL IT TAKE?

Treatment as Prevention in India



Treatment as Prevention in India

EARLY IDENTIFICATION OF CASES:

- In HPTN 052, about 2/3 of transmissions occurred at CD4>350 cells/µl
- In India CD4 at presentation in a clinical setting:

YRGCARE (2004 – 2007) - Unpublished Data	
Median CD4 at presentation	147 cells/µl
Median CD4 at initiation of ART	135 cells/µl
Median time from eligibility to initiation	30 days
Government Centers (Bachani et al. Nat Med J India 2010;23(1):7-12)	
Median CD4 at initiation of ART	119 cells/µl

Treatment as Prevention in India

EARLY IDENTIFICATION OF CASES:

- How do we diagnose HIV infection at an earlier stage?
  - Community based testing strategies
  - Mobile VCT (Project ACCEPT)
  - Social network based sampling strategies especially in high-risk groups

YRGCSAR (Solomon SS et al. Indian J Med Res 2008;127(5):447-52)	
Median CD4 at presentation	395 cells/µl

Treatment as Prevention in India

EARLY IDENTIFICATION OF CASES:

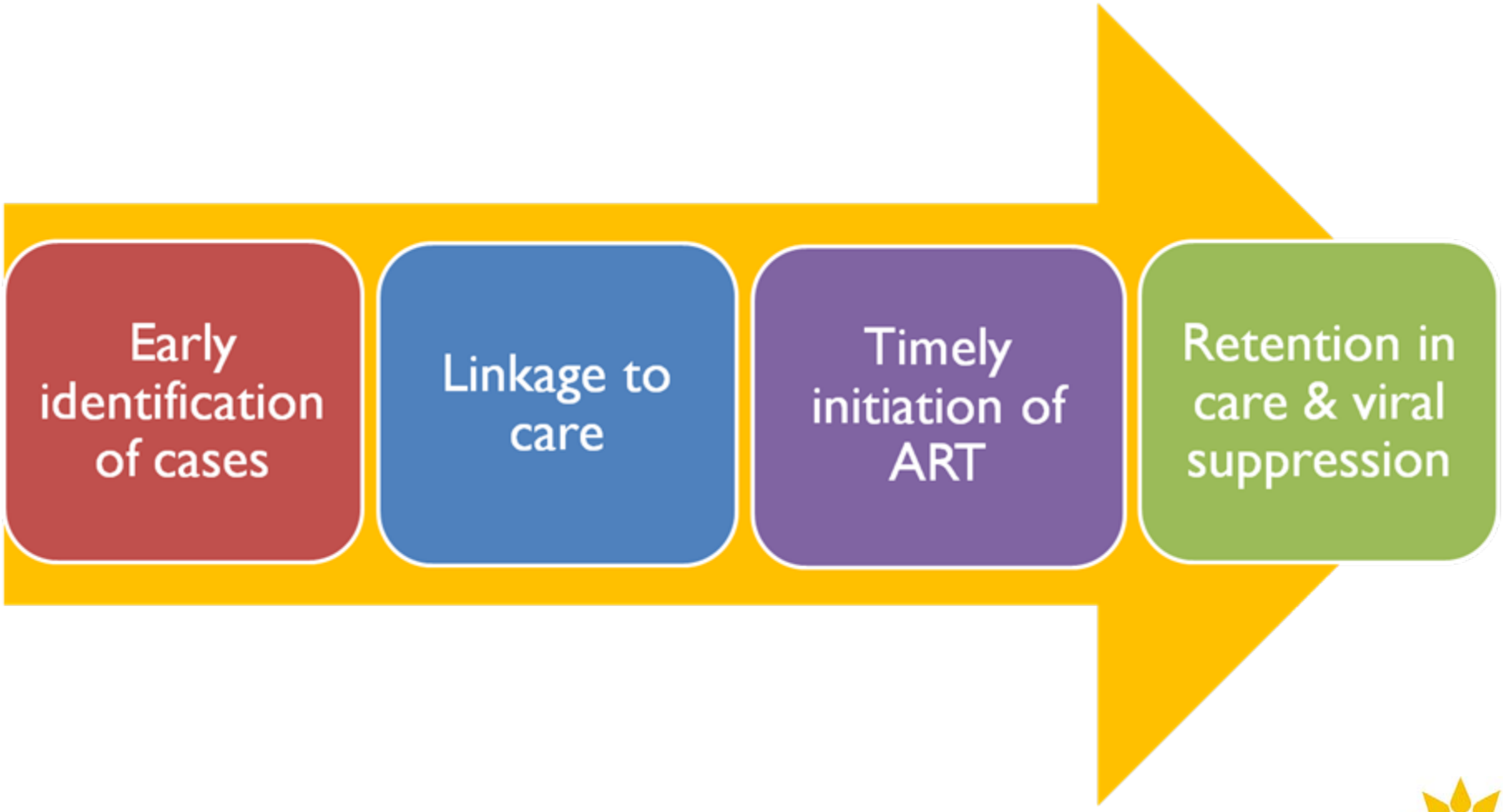
- How do we diagnose HIV infection at an earlier stage?
  - Community based testing strategies
  - Mobile VCT (Project ACCEPT)
  - Social network based sampling strategies especially in high-risk groups
  - Testing of spouses/sexual partners of HIV+ persons
  - Incentive based strategies (Conditional cash transfer)
  - Peer Health Navigators

Treatment as Prevention in India

EARLY IDENTIFICATION OF CASES:

- Cost-effectiveness of these approaches
  - HIV Incidence/Prevalence
  - Cost of the intervention
  - Efficacy of the intervention
  - Number needed to be tested to identify one new infection
  - Modeling exercises are needed

Treatment as Prevention in India



Treatment as Prevention in India

LINKAGE TO CARE:

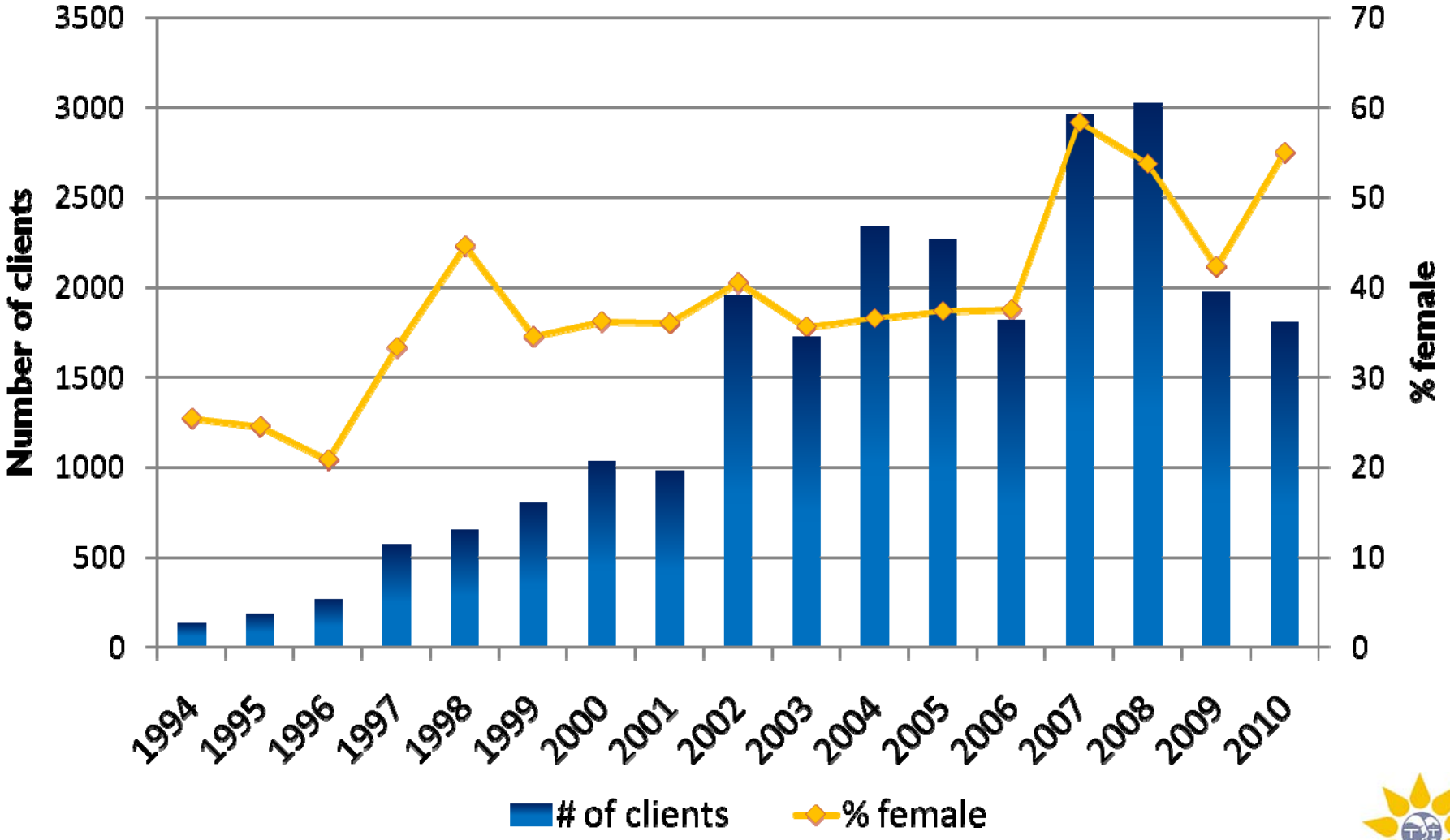
- Over 5,000 stand-alone ICTCs in India
- Many NGOs/CBOs test for HIV infection
- Most private hospitals/labs also perform HIV testing
- What do they do if they find someone infected?
  - Refer to ART centers
  - Treat themselves
  - Not do anything? (Importance of pre- and post-test counseling)

Treatment as Prevention in India

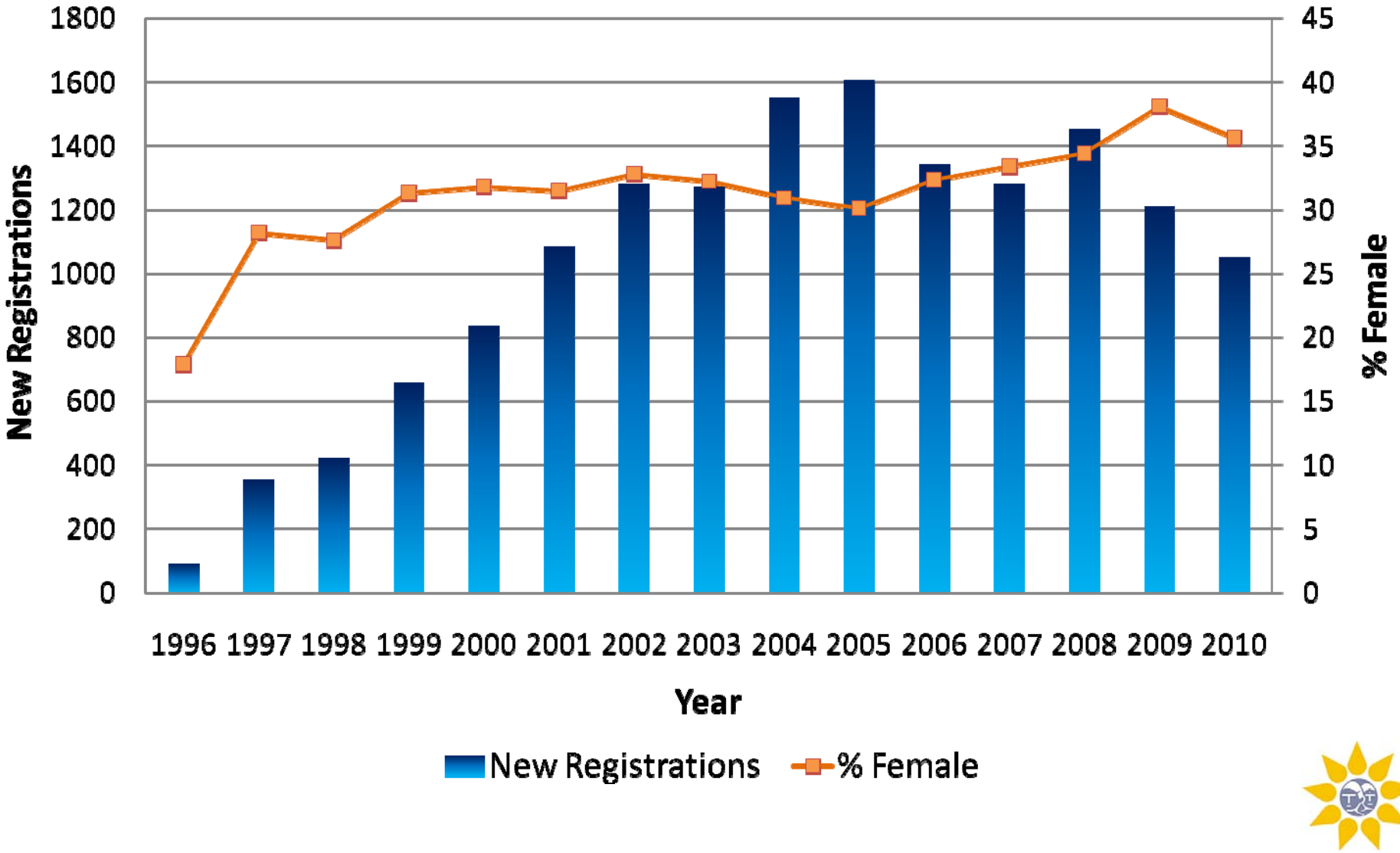
LINKAGE TO CARE:

- How do we improve linkage to care?
  - Identify barriers to accessing care (e.g., discrimination, distance) and develop innovative solutions (e.g., free bus/train passes)
  - Peer health navigators/link workers
  - Incentive based strategies
  - One stop-shop approach (HIV testing and treatment under one roof)

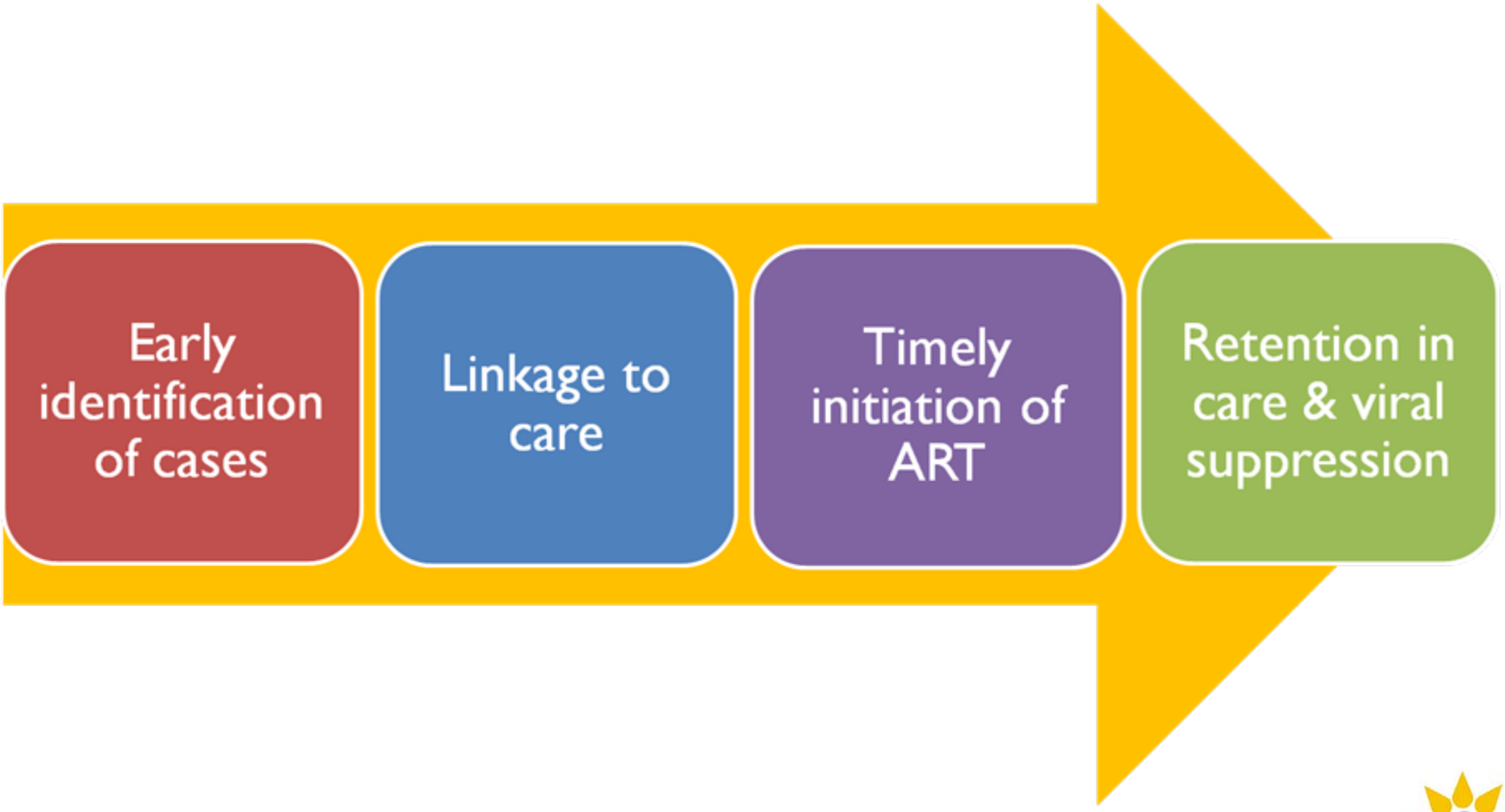
YRGCARE – VCT Trend



YRGCARE – Registered Patients



Treatment as Prevention in India



Treatment as Prevention in India

TIMELY INITIATION OF ART:

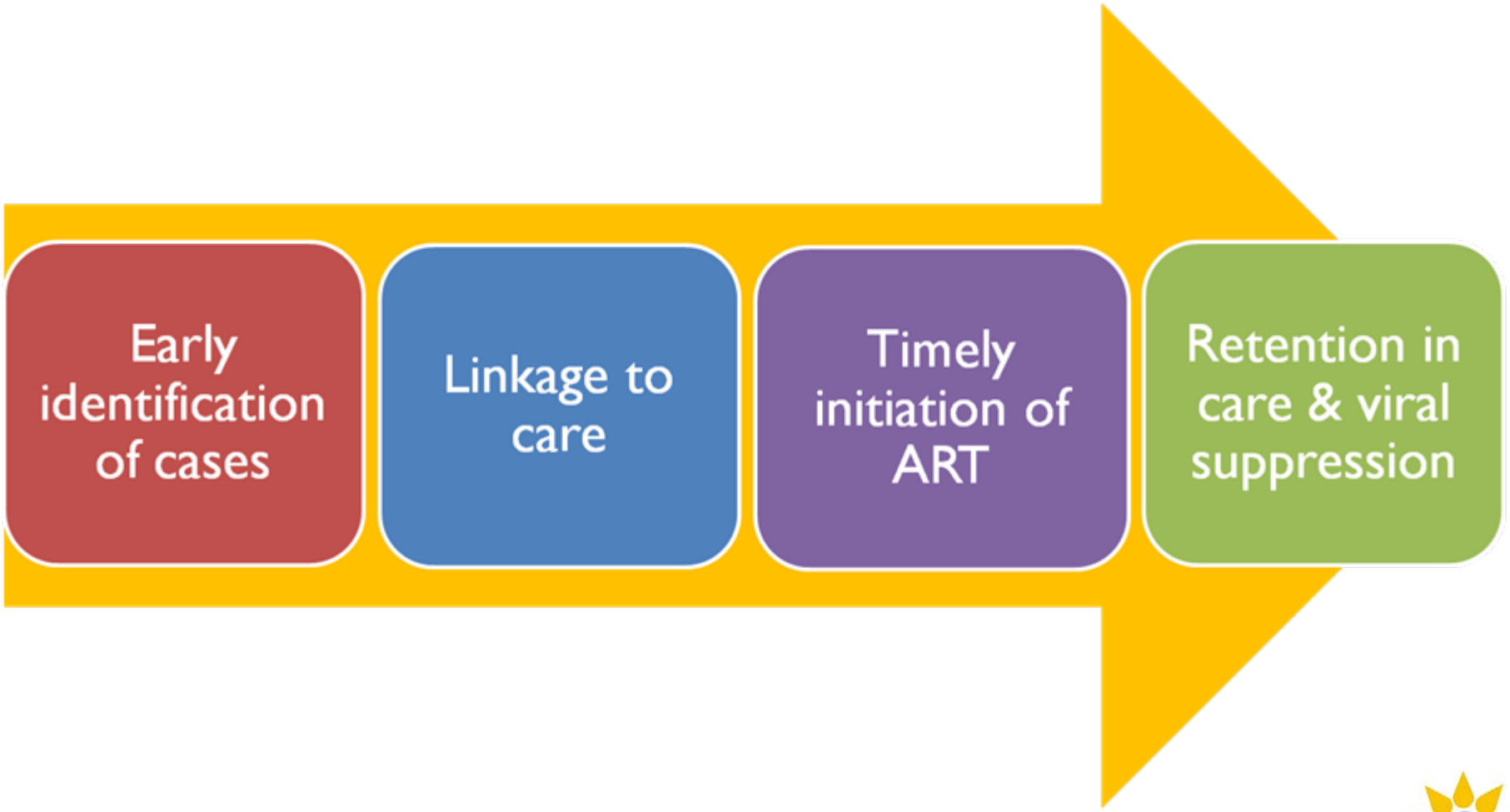
- For this strategy to work, ART needs to be started at CD4 counts greater than what is currently recommended (CD4>350 vs. CD4<350)
- If India does change the guidelines, large number of people will qualify for ART
  - How much will it cost?
  - Do we have the infrastructure in place?
  - Do we have the manpower?

Treatment as Prevention in India

TIMELY INITIATION OF ART:

- What are we going to start them on?
  - Currently, d4T + 3TC + NVP is the most commonly used regimen
  - d4T almost never used in the developed world due to its toxicity profile
  - NVP: black box warning at higher CD4 counts
  - AZT + 3TC + EFV costs almost twice as much
  - Tenofovir still reserved for second-line treatment only (and even more expensive)

Treatment as Prevention in India



Treatment as Prevention in India

RETENTION/VIRAL SUPPRESSION:

- Starting ART is the easy part!
- Maintaining viral suppression is the challenge
- Treatment as prevention works by inducing viral suppression thus minimizing risk of transmission
- Retention in care ≠ viral suppression
  - We need to ensure patients refill their medications in a timely manner
  - Patients need to take their medications

Treatment as Prevention in India

RETENTION/VIRAL SUPPRESSION:

- Retention rates at government ART centers reported to be high (77% actively on ART)
- No systematic studies using an objective measure of treatment failure (HIV RNA)
- In private sector, treatment failure rates as high as 37% have been reported (Mumbai)
- Several ongoing trials to improve adherence

Treatment as Prevention in India

RETENTION/VIRAL SUPPRESSION:

- How do we get patients to refill their medications in a timely manner and induce suppression?
  - Adherence Counseling
    - Individual/Family-based
    - Motivational counseling approaches
  - Reminders (SMS, IVRS, Phone calls, etc.)
    - For refills and to take their doses
  - Peer health workers

Treatment as Prevention in India

RETENTION/VIRAL SUPPRESSION:

- How do we get patients to refill their medications in a timely manner and induce suppression?
  - DOT/mDOT/DAART
    - Using family members/peer health workers as DOT providers
    - Linking to OST programs for IDUs
  - Technology based strategies
    - Wise-Pill/ Sim-PilII
  - Incentive based strategies
    - Incentives for timely refills
    - Incentives for viral suppression

Treatment as Prevention in India

RETENTION/VIRAL SUPPRESSION:

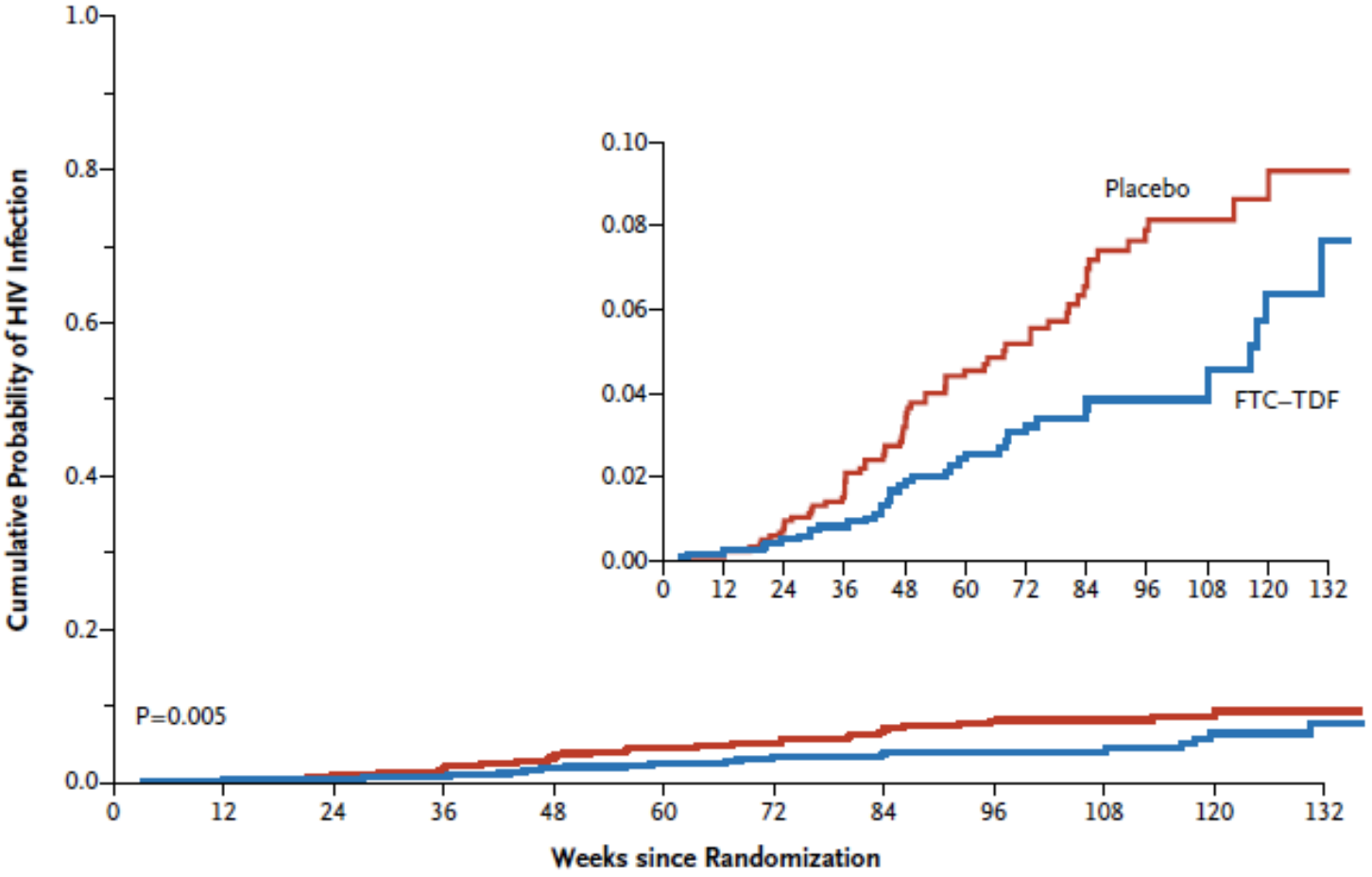
- One important point to consider in the implementation of adherence interventions:
  - Not everyone needs an adherence intervention
- Need a way of identifying persons who need interventions to improve cost-effectiveness
  - Missed refills
  - Self-reported adherence low
  - Unannounced pill counts indicate sub-optimal adherence

Treatment as Prevention in India

- What will I do?
  - I will definitely recommend it (the evidence is there!)
  - Sell both benefits (not everyone is altruistic):
    - Individual as well as public health benefit
  - Resources are limited; so roll out to high-risk populations first (FSWs, MSM with multiple partners, IDUs) and couple them with adherence interventions
    - Inducing viral suppression in an active IDU will result in saving a lot more people from acquiring HIV than in a monogamous MSM couple
  - Push for TDF/AZT + 3TC + EFV to become first-line agent of choice

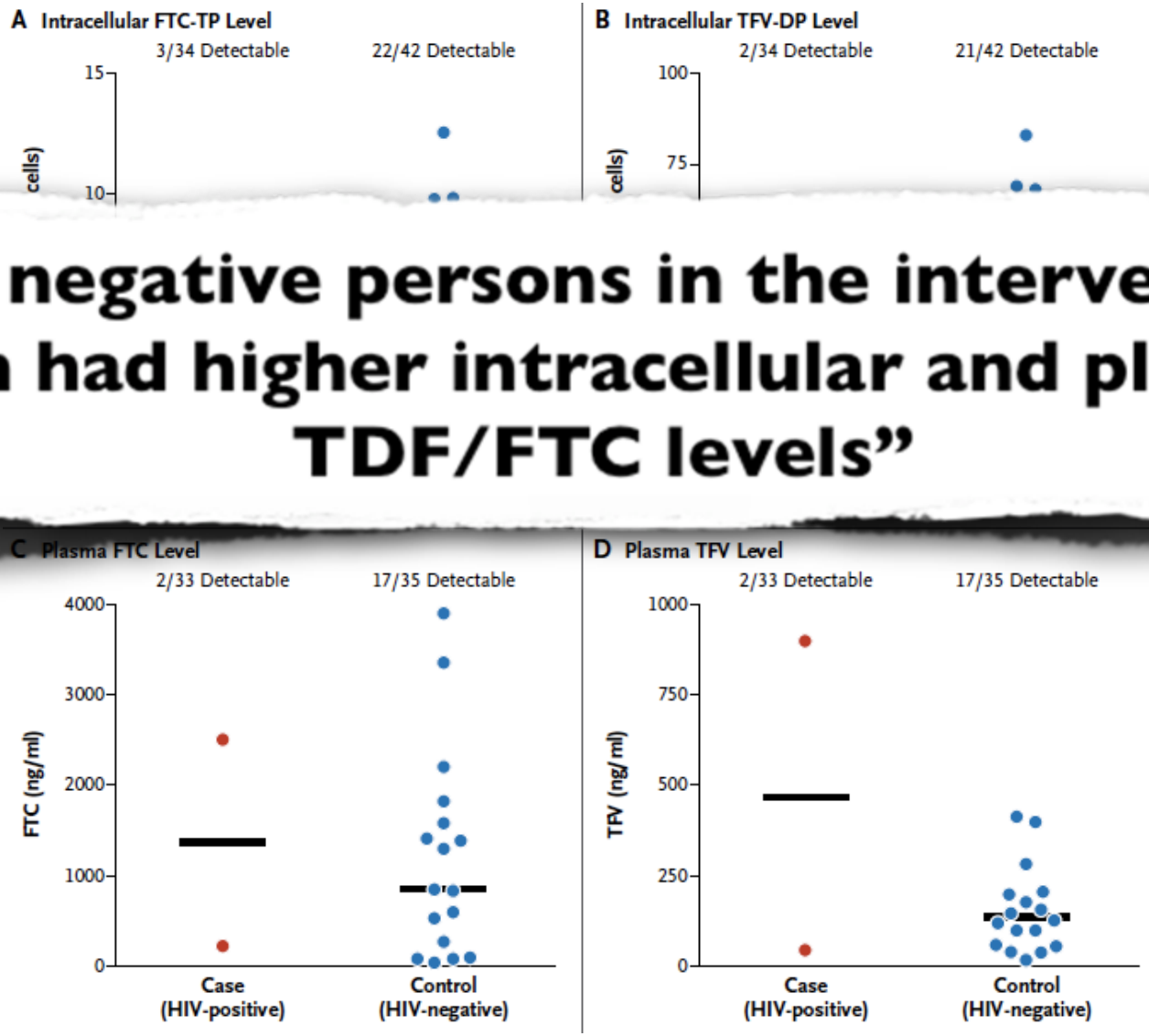
PREP

iPrEX *(Grant RM et al. NEJM 2010)*



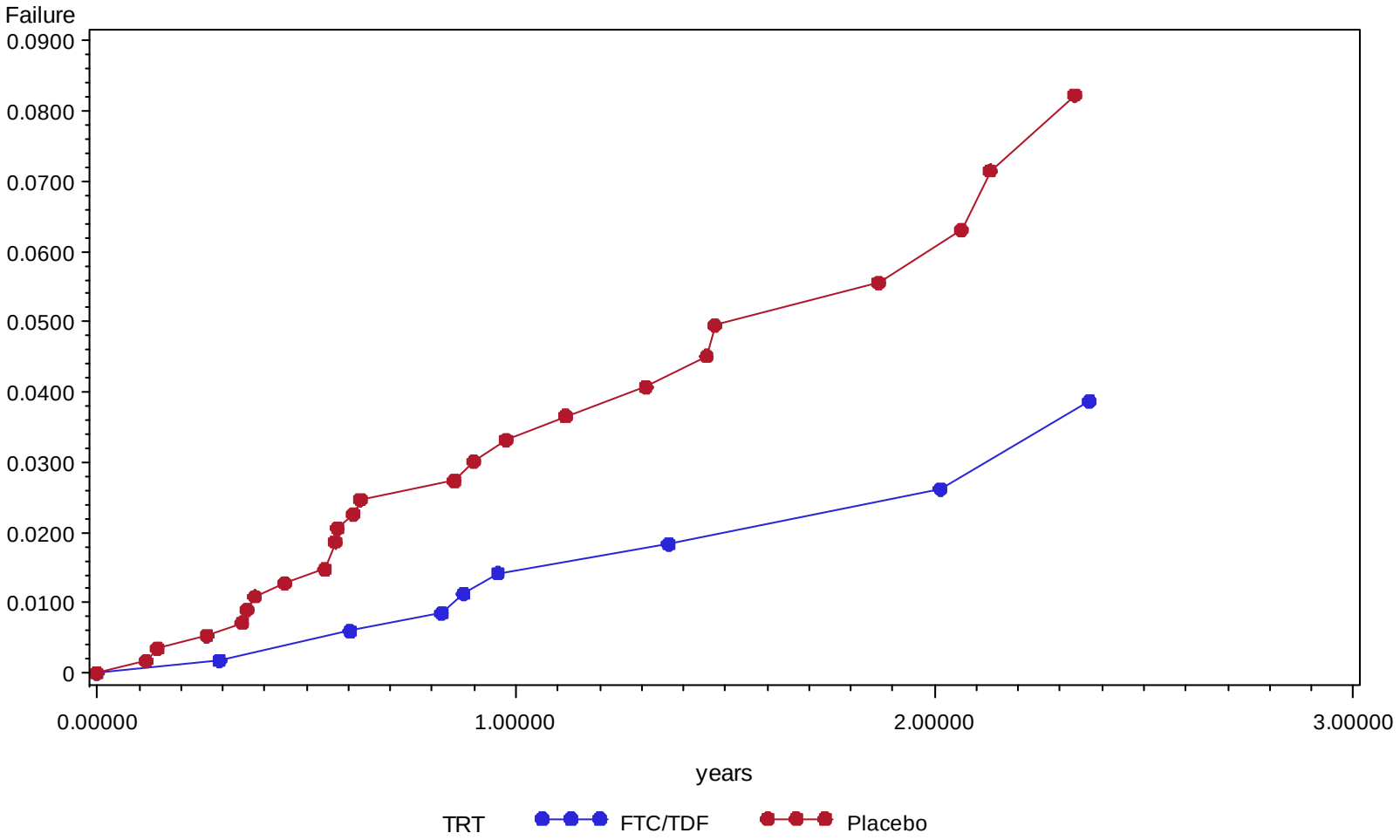
No. at Risk												
Placebo	1248	1194	1108	1005	852	647	546	444	370	258	137	60
FTC–TDF	1251	1188	1097	988	848	693	558	447	367	267	147	65

iPrEX *(Grant RM et al. NEJM 2010)*



"HIV negative persons in the intervention arm had higher intracellular and plasma TDF/FTC levels"

TDF 2 Trial



9 HIV-infected in TDF-FTC group and 24 HIV-infected in placebo group

Overall protective efficacy: 62.6% (95% CI 21.5 to 83.4, p=0.0133)

Partners in PrEP

Modified Intention-to-treat analyses
- Excluded participants who were infected at randomization

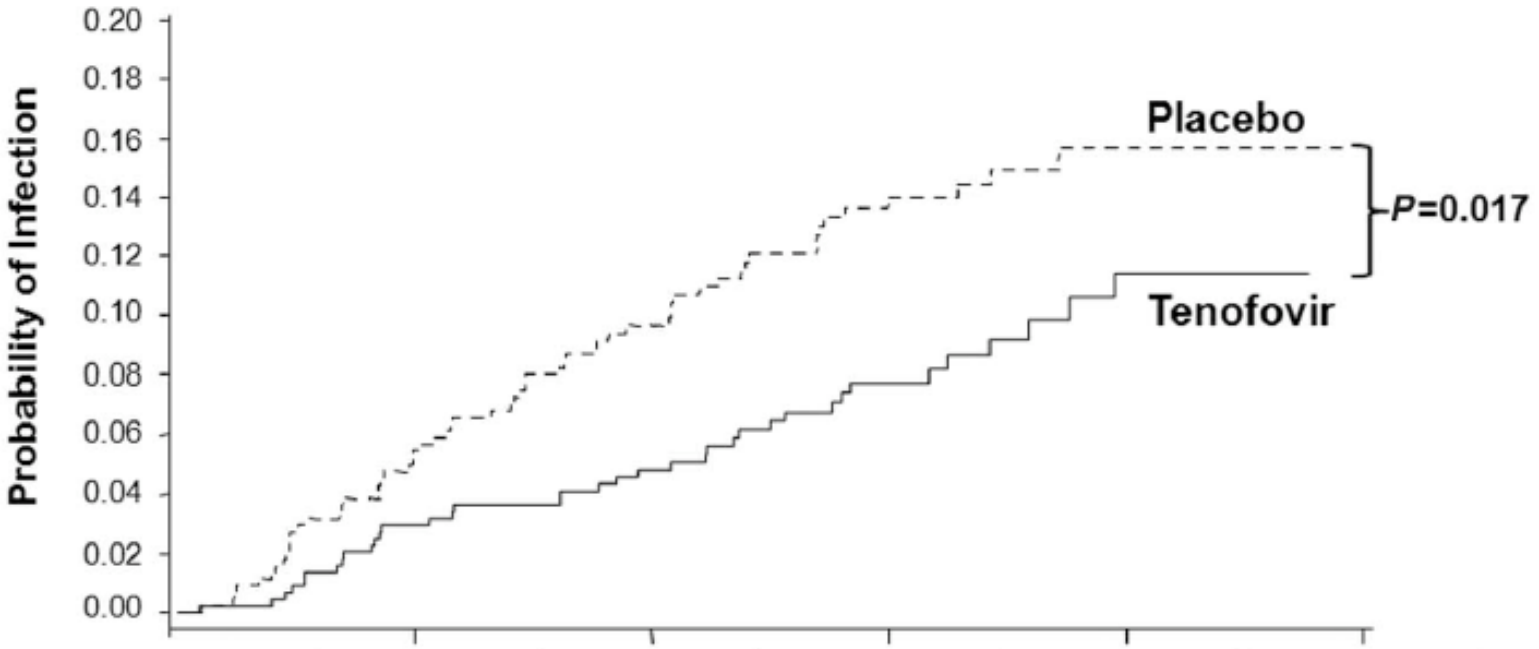
	TDF	FTC/TDF	Placebo
Number of HIV infections	18	13	47
HIV incidence, per 100 person-years	0.74	0.53	1.92
HIV protection efficacy, vs placebo	**62%**	**73%**	
95% CI	(34-78%)	(49-85%)	
p-value	0.0003	<0.0001	
Z-score, vs. H_0=0.7	-2.17	-2.99	

PrEP in India

- Mounting evidence on efficacy of PrEP
- But…..
  - Will it be acceptable/culturally appropriate?
  - Will it be cost-effective?
  - Will the government buy-in?
- In iPrEX, TDF 2 & Partners in PrEP, participants were tested every month
  - Is that feasible in the real world?
- Who will dispense it?
- What about OTC availability?
- Will there be behavior disinhibition?

MICROBICIDES

CAPRISA 004 *(Abdool Karim et al. Science 2010)*



Months of follow-up	6	12	18	24	30
Cumulative HIV endpoints	37	65	88	97	98
Cumulative women-years	432	833	1143	1305	1341
HIV incidence rates (Tenofovir vs Placebo)	6.0 vs 11.2	5.2 vs 10.5	5.3 vs 10.2	5.6 vs 10.2	5.6 vs 9.1
Effectiveness (*P*-value)	**47% (0.064)**	**50% (0.007)**	**47% (0.004)**	**40% (0.013)**	**39% (0.017)**

IMPLICATIONS FOR INDIA

- Microbicides definitely needed in India
- But…..
  - Will it be acceptable/culturally appropriate?
  - Will it be cost-effective?
  - Will government buy-in?
- In CAPRISA, women were tested every month for HIV (remember gel has TDF)
  - Is that feasible in India?
  - Can testing be less frequent without emergence of resistance?

Questions that remain…

- Is there any additional benefit of giving PrEP/microbicide to a discordant couple where the index partner is on ART?
- What about PrEP vs. microbicides? (VOICE trial ongoing)
- Can PrEP be dosed less frequently?
- Should we be focusing our resources on getting people on ART or PrEP and/or Microbicides?
- Do we really believe that we can get all the uninfected people to be adherent to TDF/FTC when we are still struggling to get the HIV-infected people to be adherent?

THANK YOU