

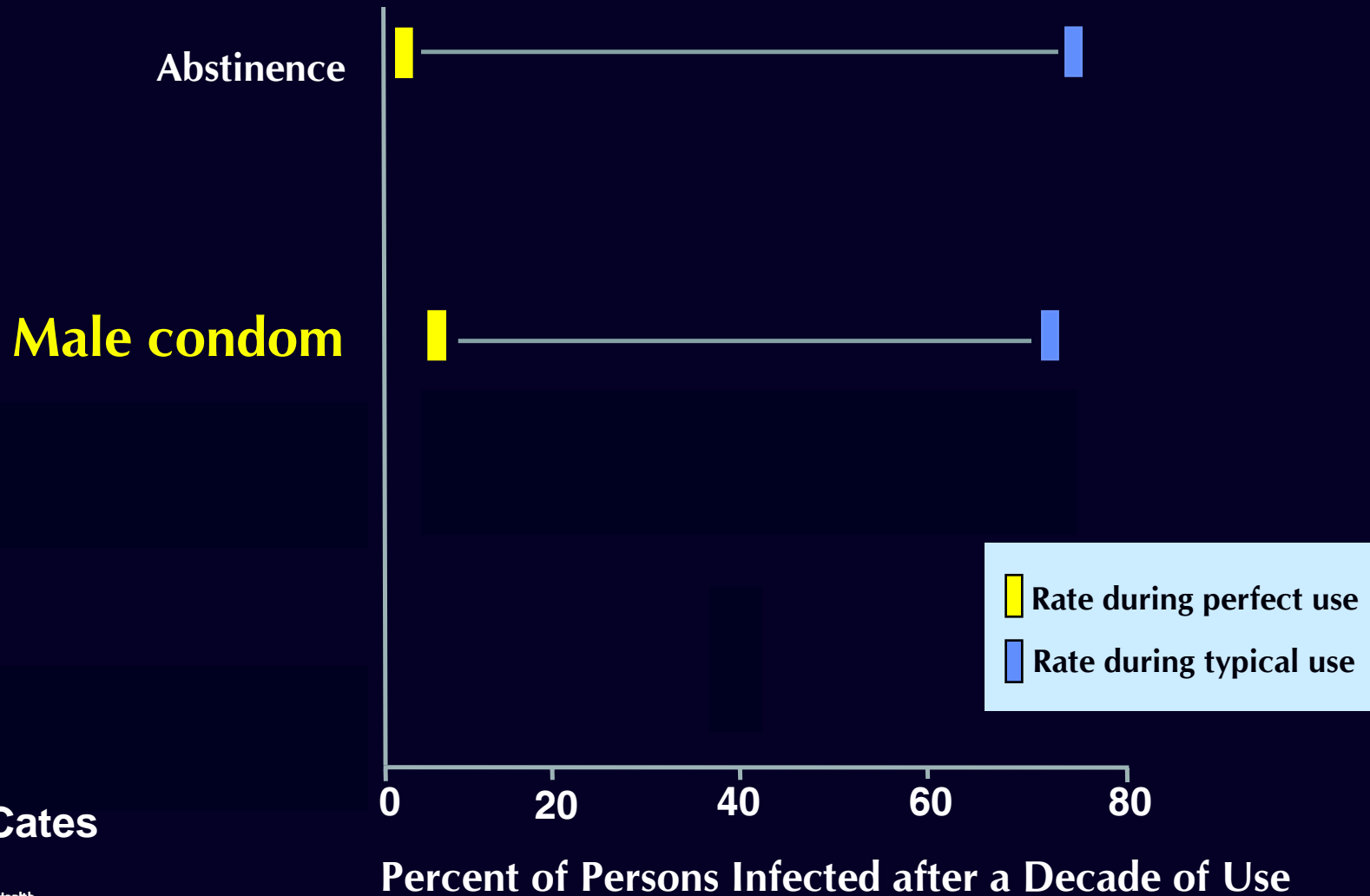
Treatment as Prevention

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Prevention at an Impasse

- **Sexual behaviour**
- **Condoms**
- **Circumcision**
- Vaccine
- Microbicides

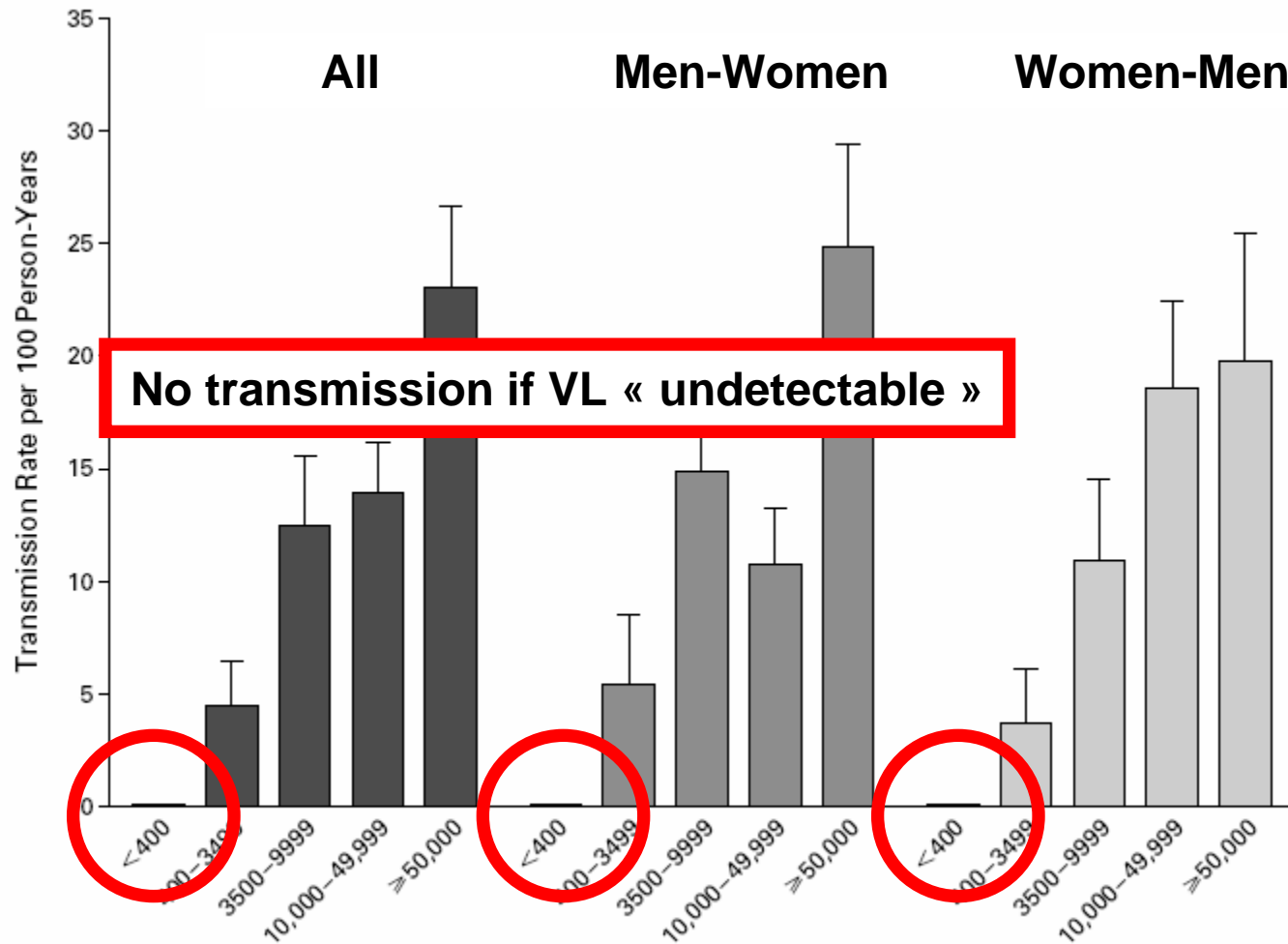
The Gulf Between Theory And Practice



Ward Cates



HAART:
potentially more
efficacious



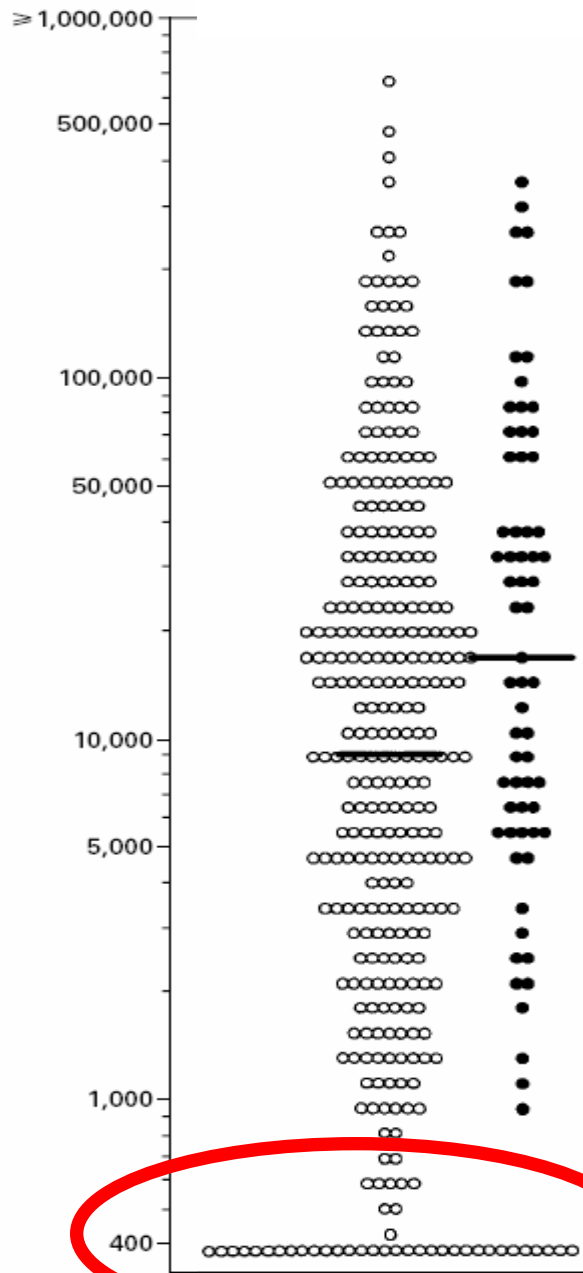
« Rakai » Study: Transmission risk as a function of viral load

N Engl J Med 1999;341:394-402

Maternal levels of plasma HIV RNA and the risk of perinatal transmission

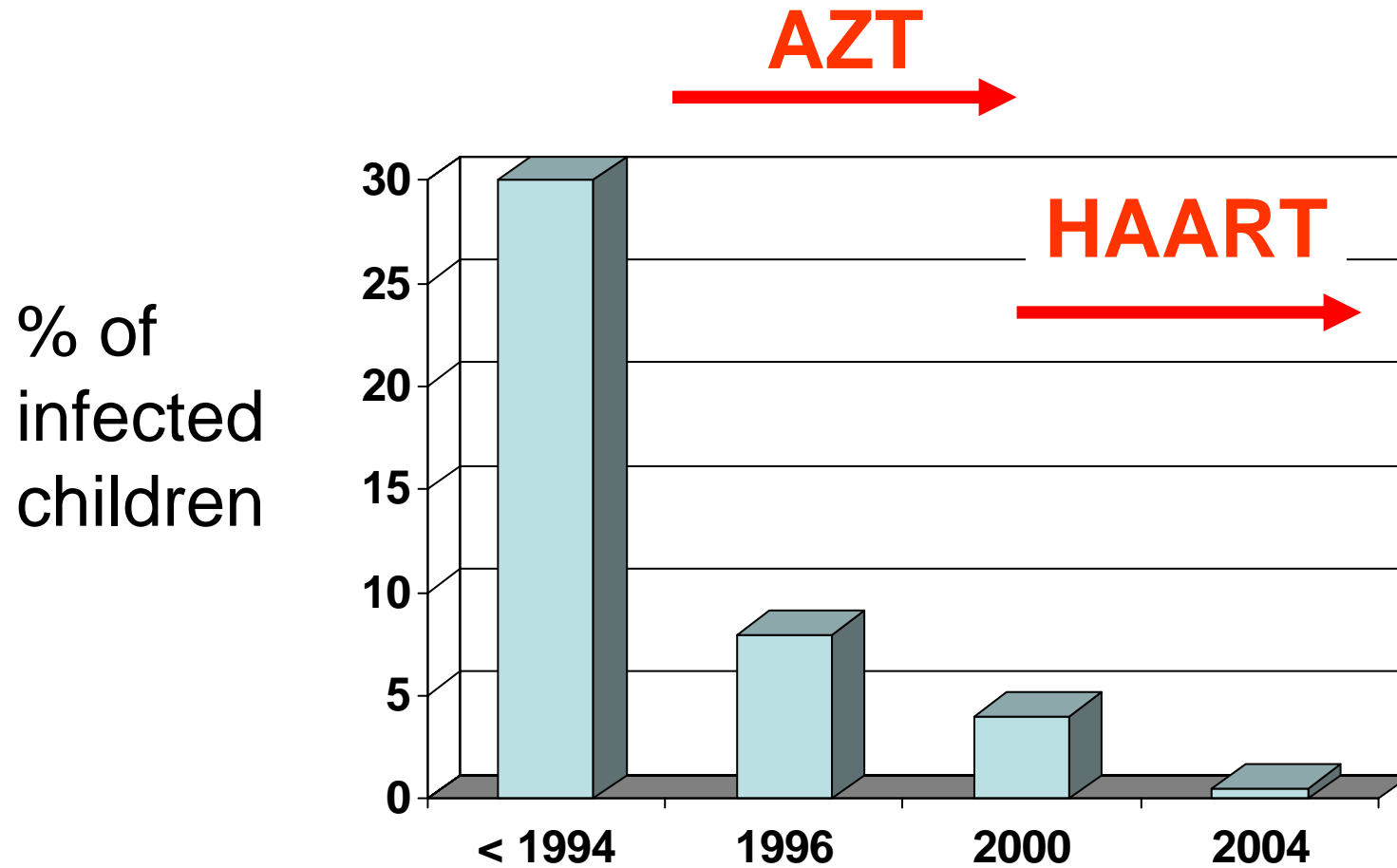
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FOR THE WOMEN AND INFANTS TRANSMISSION STUDY GROUP*

- Mother's viremia of a non infected new born
- Mother's viremia of an infected new born

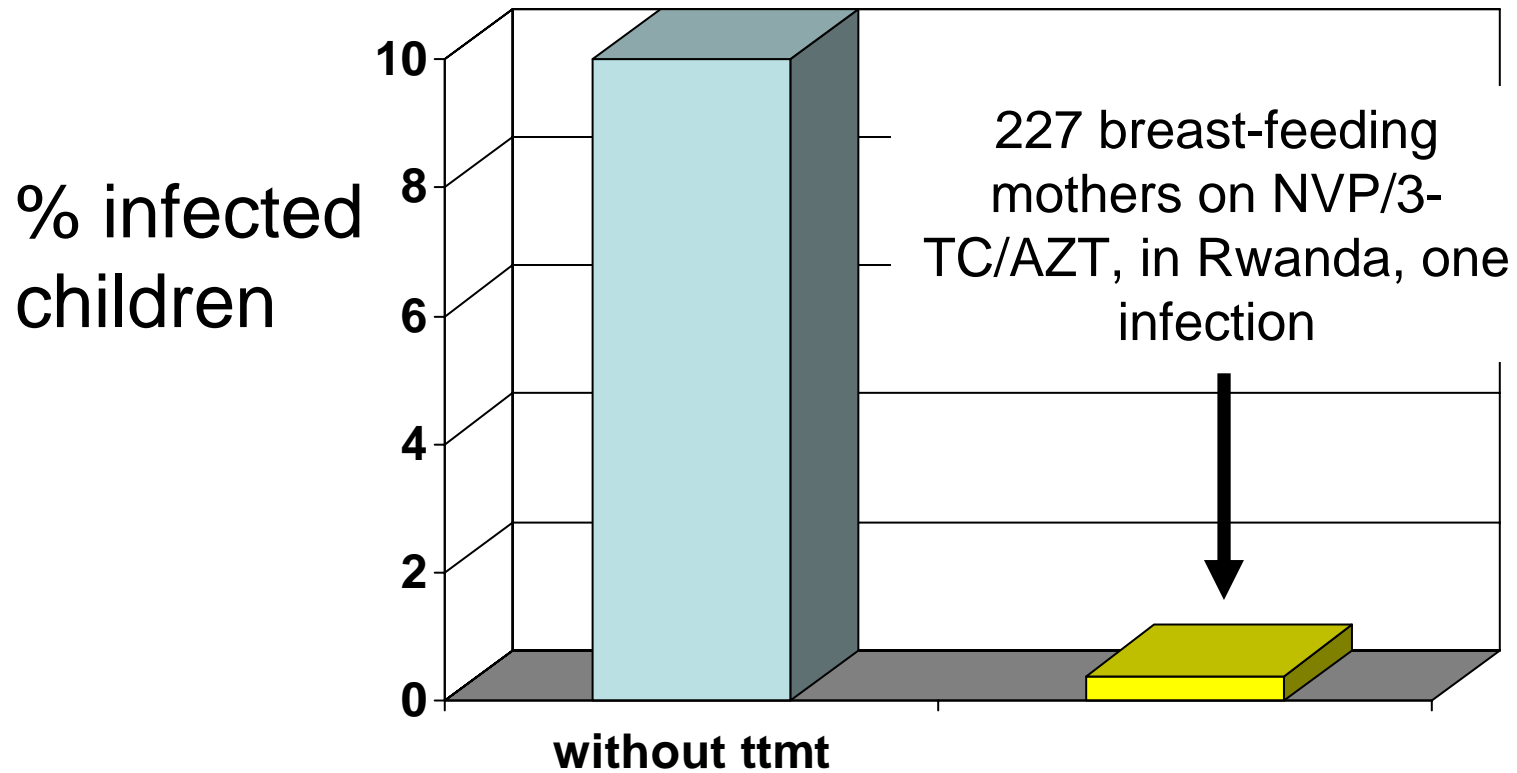


No transmission if maternal viremia < 1000/ml

Mother to Child Transmission



Transmission by breast milk

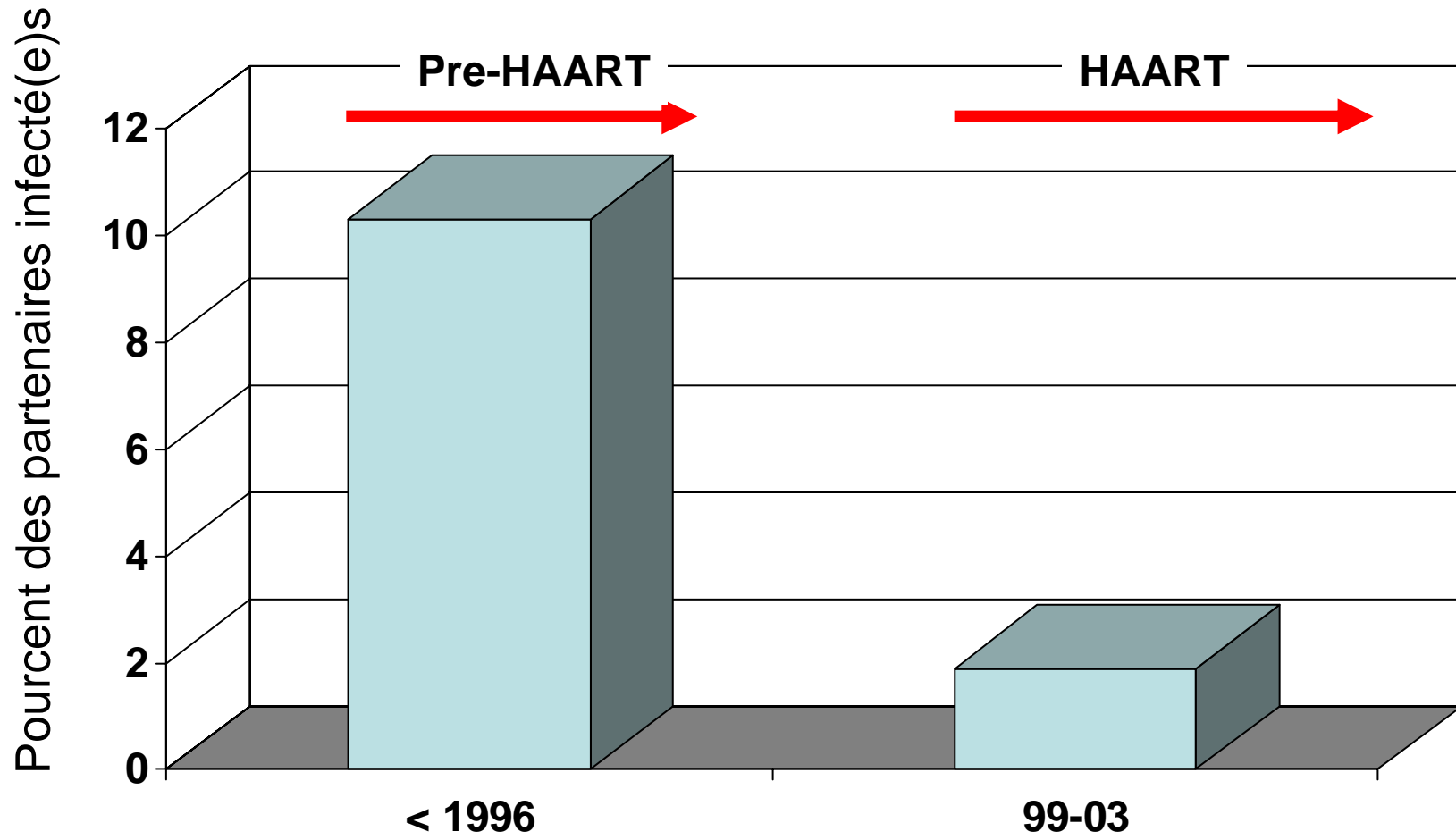


Peltier et al. AIDS 2009, in print

Effect of HAART on heterosexual transmission

- 393 heterosexual couples in Madrid
- The “index” patient was HIV +, and consulted between 1991-2003
- Among their sexual partners, the only risk factor for HIV was exposure to the “index” patient
- All partners tested to establish prevalence of HIV among partners

Prevalence of HIV infection in the partners



Condoms plus HAART in comparison to condoms alone: 2 African studies

What they had in common:

- Transmission in Uganda
- Sero-discordant Couples
- Condom Promotion

How they differed:

- Study A*, without HAART, evaluated the effect of circumcision on male-to-female transmission
- Study B**, with HAART, evaluated transmission both ways

* Wawer M et al. Abstract 33 LB, 15th CROI, Lancet 2009

**Bunnell R et al. Abstract 29, 15th CROI, Boston 2008

Results

	Study A*	Study B**
Condoms	✓	✓
HAART	-	✓
N infections observed 95% CI	12% ppy 9 – 15	0.5 % ppy 0.01-3.0

* Wawer M et al. Abstract 33 LB, 15th CROI, Lancet 2009

**Bunnell R et al. Abstract 29, 15th CROI, Boston 2008, AIDS 2006

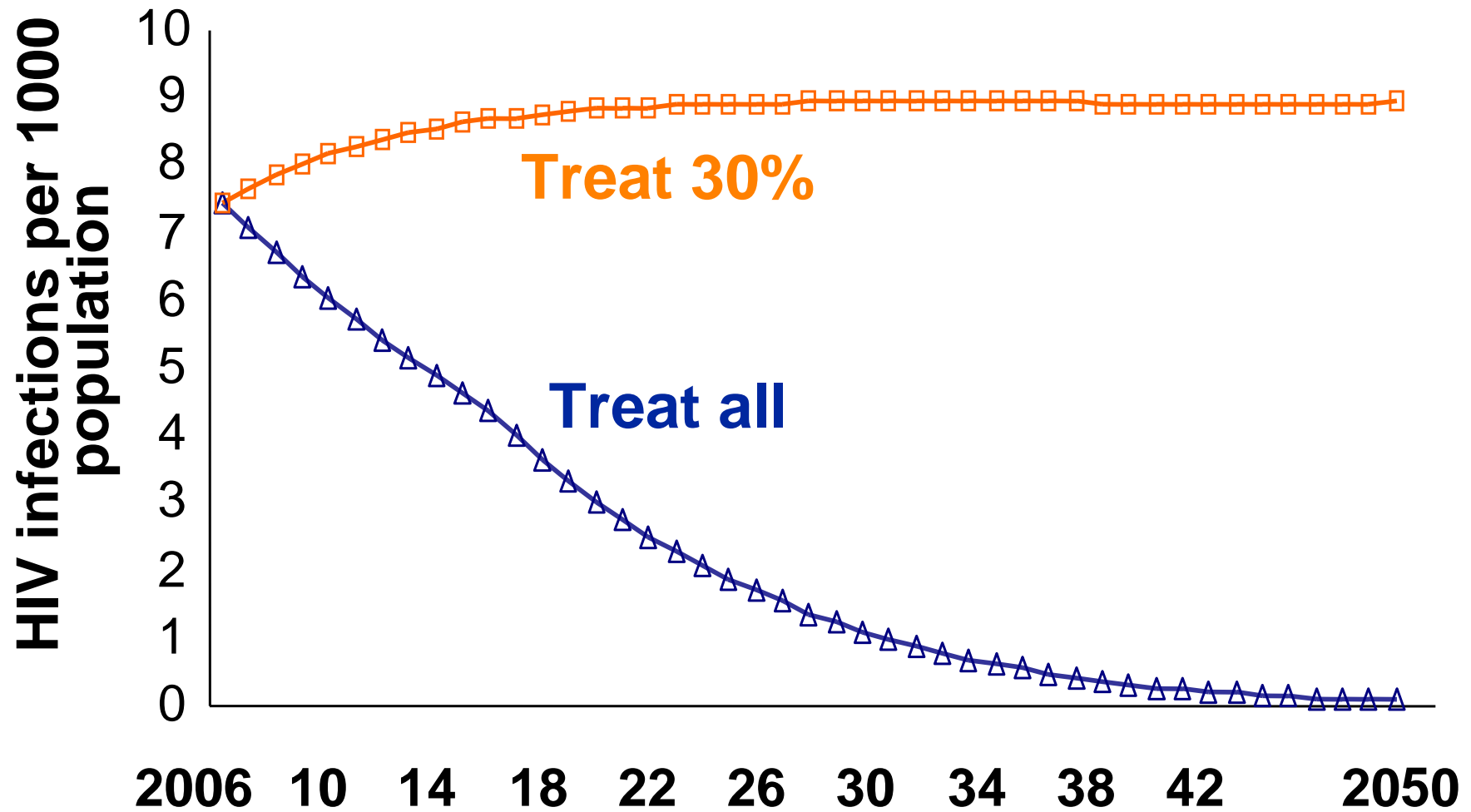
In conclusion

Circumstantial evidence indicates that:

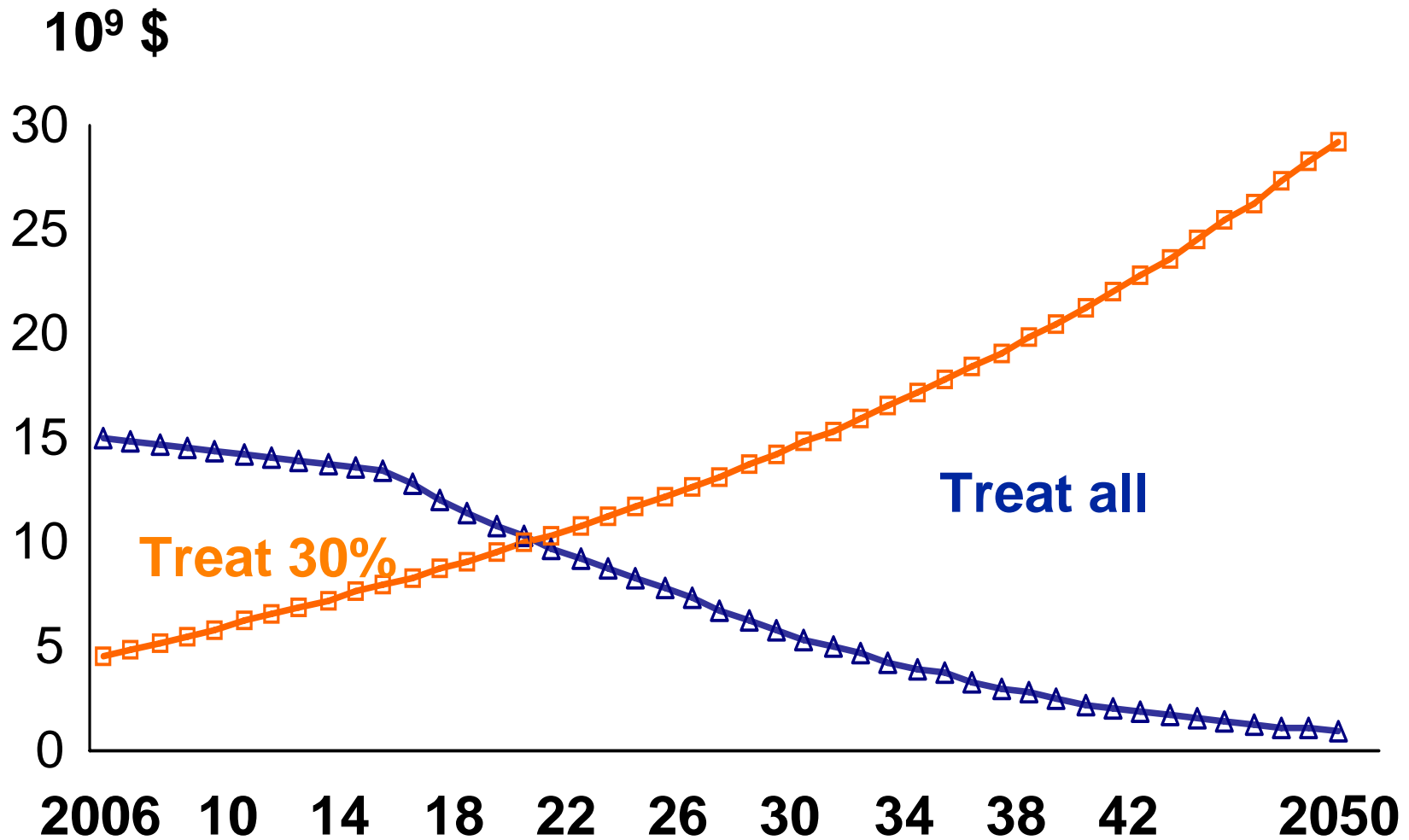
- HAART lowers MTCT
- HAART lowers heterosexual transmission
- HAART appears more efficacious than condoms, in sero-discordant heterosexual couples

What would happen to the epidemic
if more infected persons were
treated?

Projections for British Columbia



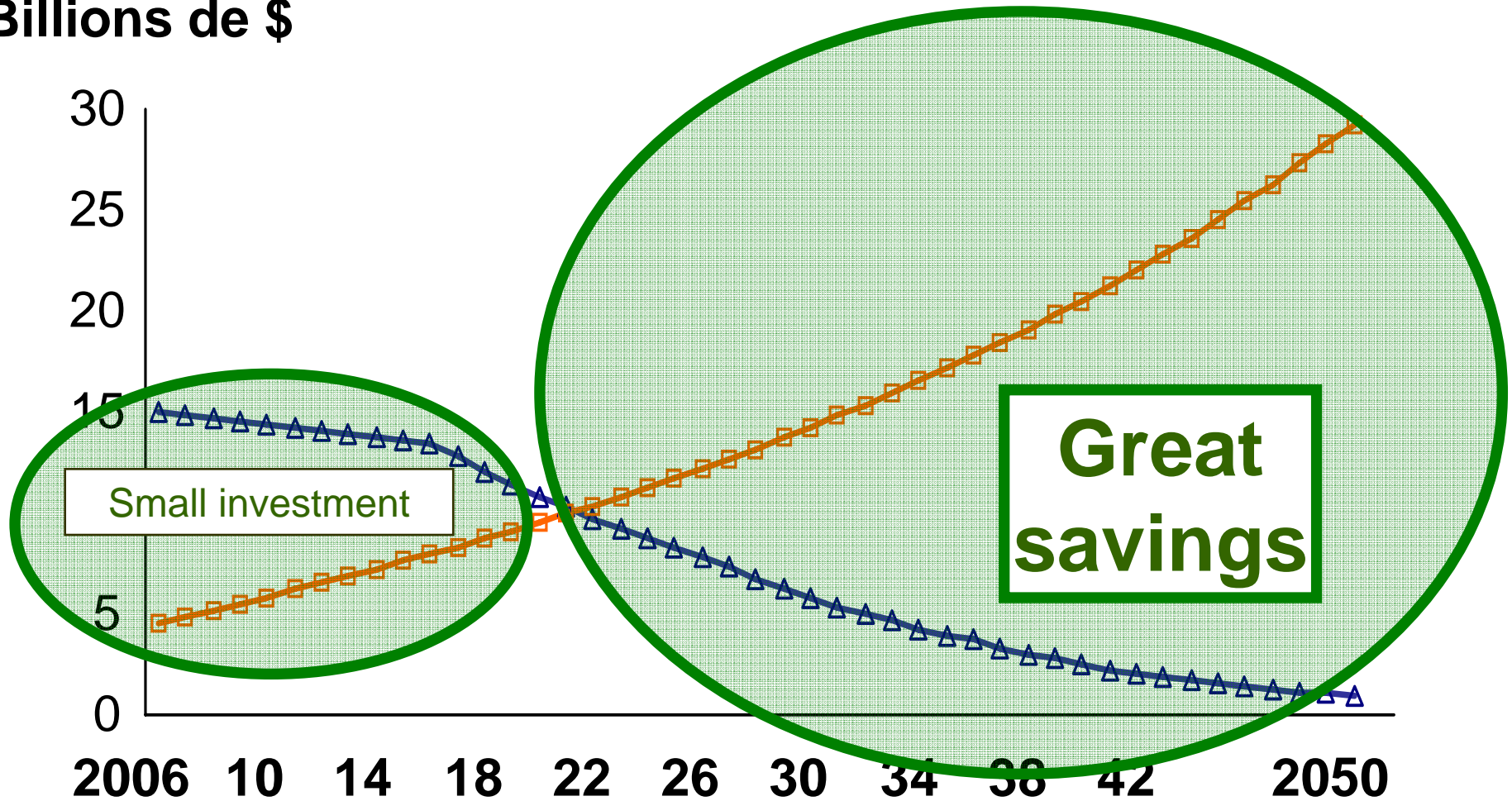
Costs of treatment



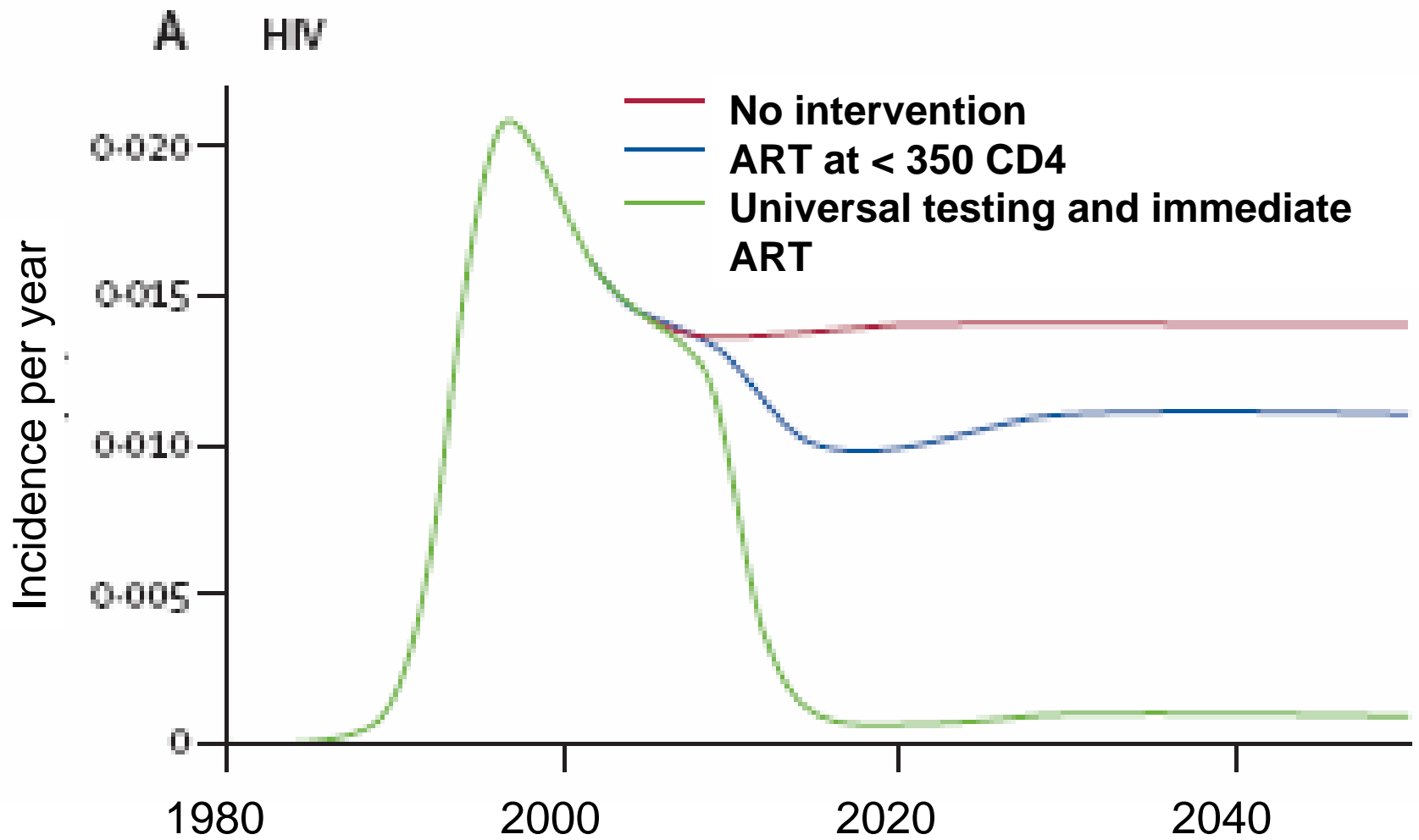
Hogg et al. Unpublished, 2006

Costs of HAART

Billions de \$



- Lima VD et al. Expanded Access to Highly Active Antiretroviral Therapy: A Powerful Strategy to Curb the HIV Epidemic; JID 2008; volume 198, July 1.
- Hogg et al. Unpublished, 2006

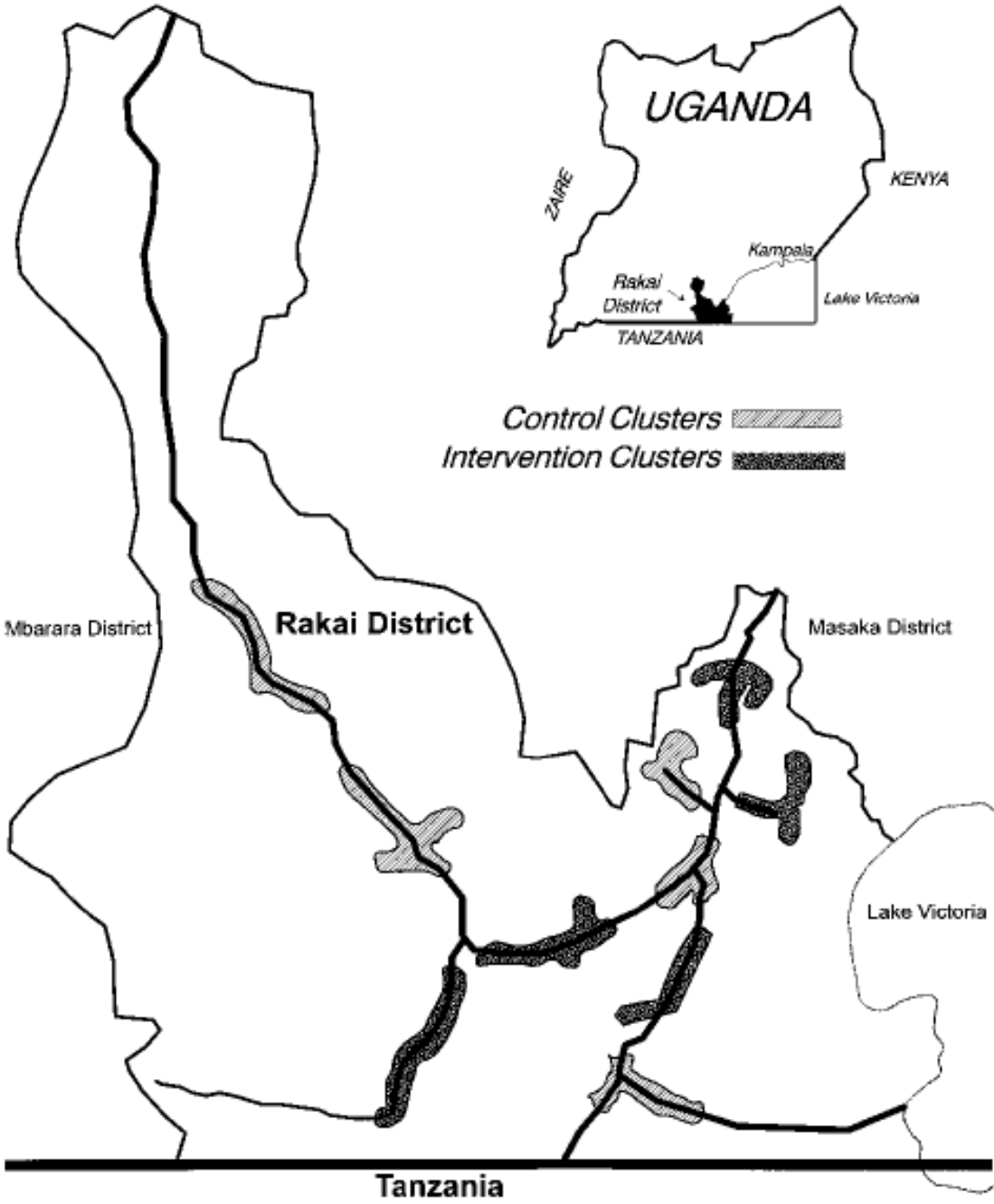


Granich, Lancet 2009: Projections for South Africa

**Alright, there is potential, but
how to prove that it actually
works ?**

The Cluster-Randomized Trial

Where the unit of randomization is not the individual, but a « cluster » of individuals, e.g. the population of a village



Hypothesis: Aggressive treatment of STIs lowers incidence of HIV

- 11000 subjects were recruited
- Condoms and counseling for all
- In case of **symptomatic** MSTs, access to a MST clinic and free treatment for all
- Randomization:
 - In the intervention clusters, all subjects with STIs, even if asymptomatic, received antibiotics
 - In the control clusters, deworming pills, iron and folate

AIDS* 1998, **12:1211–1225

The Rakai Study: Results*

	Intervention	Controls	p
Syphilis	5.6%	6.8%	<.01
Trichomonas	9.3%	14.4%	<0.001
HIV incidence/pa	1.5%	1.5%	NS

A Cluster-Randomized Trial of The Preventive Effect of ART

Study Hypothesis:

Treatment of all HIV-infected individuals regardless of CD4 cell count or viral load in a community will lower HIV incidence in this community

Intervention

- **Screen everybody**
- **2 arms :**
 - Intervention clusters: Treat all adults 15 to 59 (or: see above) who screen HIV+
 - Control clusters: HIV+ with treatment indications according to local guidelines, but using the type of HAART prescribed in the Intervention clusters.

Endpoints

- Primary
 - Incident HIV infections, as measured by repetitive 6-monthly screening
- Secondary
 - Morbidity and mortality in HIV+
 - Also « non-HIV-related? »
 - HAART-related
 - TasP is also a «when-to-start » study

Barring a cluster-randomized trial
of ART-as-prevention: HPTN052

HPTN* 052

- Mike Cohen et al.: Randomised study to evaluate HAART plus primary anti-HIV care, compared to primary care alone, in preventing sexual transmission in sero-discordant couples
- Boston, Rio, Blantyre and Lilongwe in Malawi, Harare in Zimbabwe, Pune et Chennai in India, Chiang Mai in Thailand

* HPTN: Health Prevention and Treatment Network

Inclusion Criteria

- 1750 couples (3500 individuals)
 - 1200 recruited in July 2009
- CD4 = 350-550 cells/mm³
- One partner HIV+, the other HIV-
- Can be heterosexual or homosexual, however, in reality
 - Only 3 percent MSM in pilot study
 - Seropositive woman, seronegative man, and vice versa in approx. Equal proportions
- Endogamous: 93% say that they had only one sex partner during the last six months.

Randomisation

- In the intervention group, ART starts right away, i.e. at a CD4 level between 350 and 550
- In the control group, according to local indication (meaning mostly CD4 = 200 to 250)

Endpoints

1. Transmissions
2. Progression according to WHO, tuberculosis, deaths (this is also a « when to start » study)
3. Toxicity of HAART

Results expected in 2014

Cluster-randomized TasP trial compared to HPTN052

	HPTN 052	TasP
Target Population	Disc. Couples (HIV- partners)	General population
Sample size	2 * 1750	2 * 15000 ?
Randomisation unit	Couple	Village
Baseline Incidence of HIV	3 à 10 %	1-3 % ?
Indication for HAART in intervention group	CD4 350-550	HIV+
Indication for HAART in control group	usual care	usual care
Follow-up	5 years	2 years



Hurdles

1. Attrition
2. Risk compensation
3. Harm (to the individual) versus benefit (to the community)
4. Cost and sustainability

Attrition...

Intervention Group

- Not all will be tested
- Of those who are tested, some will not receive their results
- Of those who receive results and are HIV+, not all will be treated
- Of those who are treated, not all will have effective treatment
- Of those with effective treatment, not all will continue

Attrition...

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Control Group

- Some already on ART
- Proportion on ART expected to increase:
 - Expansion of access
 - Revision of indications (limit of 350 CD4 cells instead of 200)
- Of those who remain off treatment, many will use other prevention methods:
 - Condoms
 - Microbicides
 - Circumcision

Attrition: Example from MTCT

	Observed	Ideal	Obs/Ideal
• Pregnant women	40000		
• Received counseling	17263	40000	43%
• Tested	12438	40000	31%
• Received test results	12065	40000	30%
• Positive	2924	9403	30%
• Received nevirapine			
– Mothers	1654	9403	18%
– Children	1157	9403	12%
• Partners tested	86	9403	0.9%

Source: Stringer EM et al. AIDS 2003; 17:3077 (Lusaka, Zambia)

Risk Compensation

- Increased sexual risk taking in intervention clusters
 - May, or may not matter while patients are on HAART
 - Has to be considered in the local context (where infection rates at times have been shockingly high even in trial settings with condom promotion)
 - Some reassurance provided by the circumcision trials, where there was no increase in sexual risk taking in intervention groups

Harm versus Benefit

- On balance, the trial offers little potential for benefit to the individual, but considerable potential for benefit to the community
- Health benefits and risks
 - Persons in intervention clusters will probably have less HIV-related diseases. This will be a secondary endpoint in the trial.
 - Nonetheless, asymptomatic individuals with intact immune systems may derive little or no benefit, and probable side effects, from HAART
- The general move towards earlier treatment will attenuate this conflict (but may make it more difficult to distinguish intervention from control clusters)

Resources and Sustainability

- If successful, TasP will increase pool of people potentially eligible for HAART
 - Will increase pressure for availability of ARVs
 - Will increase costs
 - Long-term sustainability and resistance is certainly an issue. « TasP2 » would provide years follow-up and surveillance of infection, without randomisation

Follow-up

TasP1: Years 1 and 2:



Evaluation



TasP2: Years 3 to 5 (to 10?)

TasP1 compared to Tasp2

	TasP1	TasP2
Target Population	General population	General population
Randomisation unit	Cluster	No randomisation
Indication for HAART in intervention group	All HIV+	All HIV+
Indication for HAART in control group	usual care	No control group
Follow-up	2 years	3-8 years
Focus on	efficacy	sustainability







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