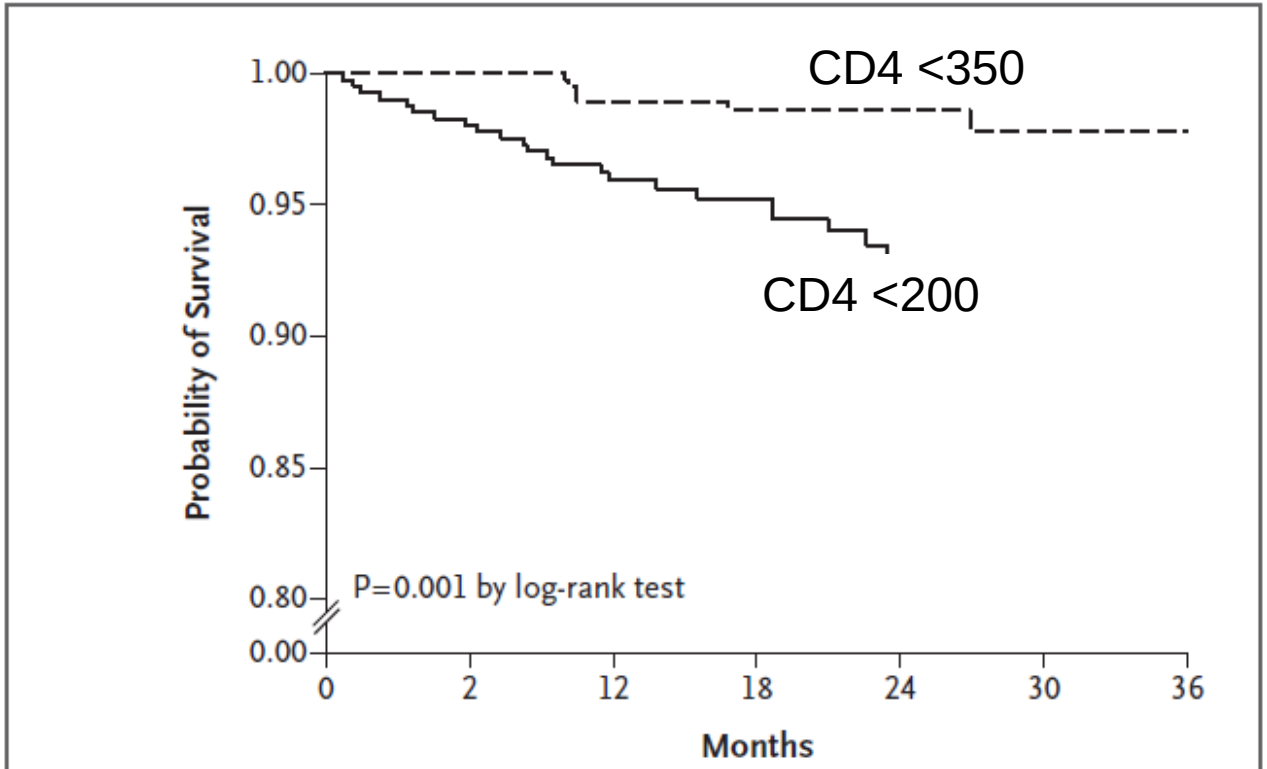
We can't treat ourselves out of the HIV epidemic

Gary Maartens

Clinical benefit of early ART: Only one RCT informing when to start



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

Figure 2. Kaplan–Meier Estimates of Survival in the Early-Treatment and Standard-Treatment Groups.

NEJM 2010;363:257

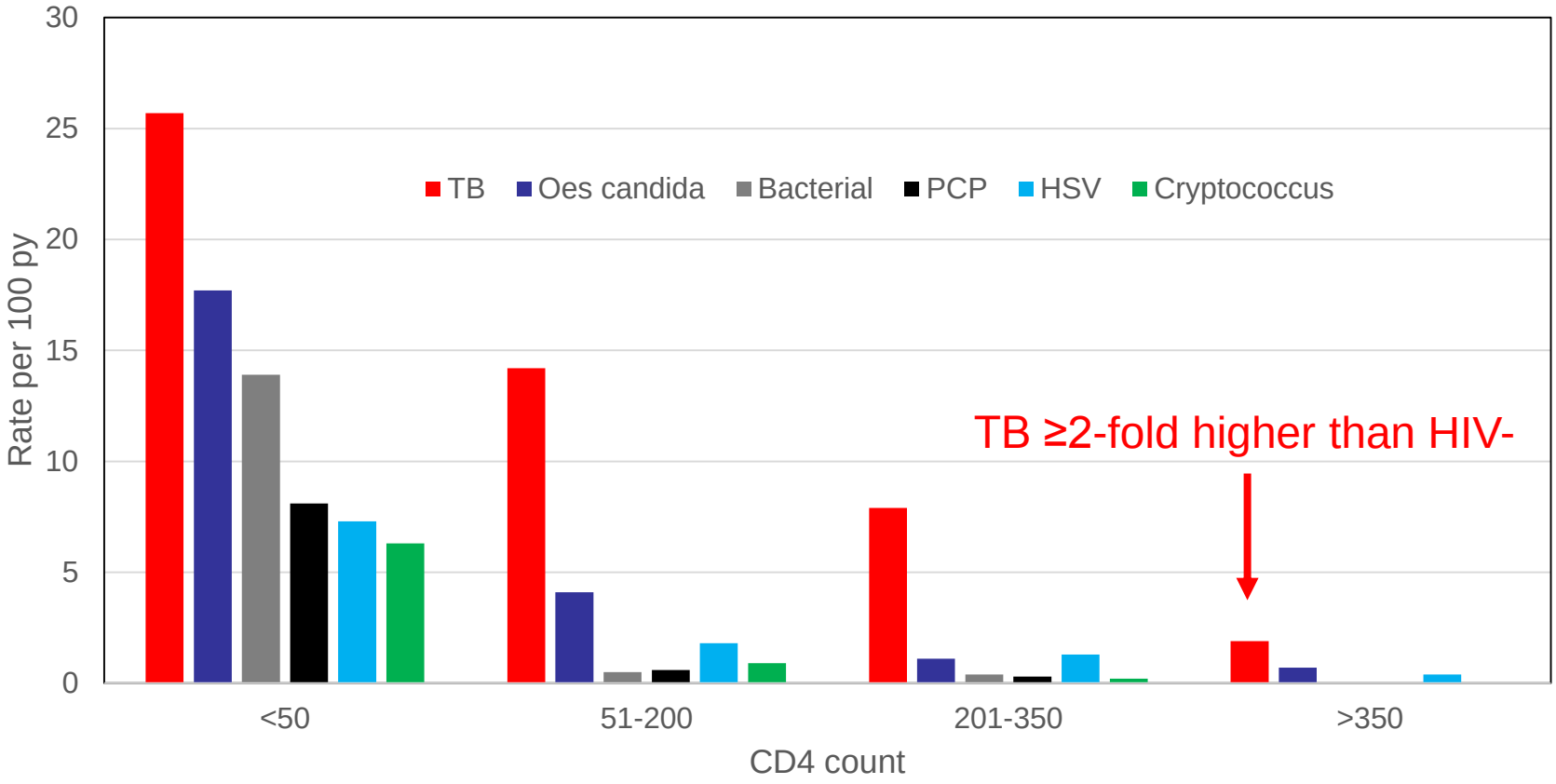
Post hoc analysis HTPN 052

RCT to assess effect of ART on HIV transmission in serodiscordant couples

- CD4 350-550
- ART start immediate vs delayed (CD4 <250 twice)
- No difference in death
- Reduction in AIDS (HR 0.64 95%CI 0.43-0.96), mostly driven by TB
- Only 52/1763 received IPT

Grinsztejn Lancet ID 2014

Incidence of OIs Cape Town: pre-ART era



JAIDS 2006;42:464
JID 2005;191:150

Cohorts of when to start ART

Study	CD4 bands	Death	AIDS + death
When to start	351-450 vs 451-550	0.93 (0.60, 1.44)	0.99 (0.76, 1.29)
	251-350 vs 351-450	1.13 (0.80, 1.60)	**1.28 (1.04, 1.57)**
CASCADE	350-499 vs 500-799	0.98 (0.47, 2.04)	0.91 (0.56, 1.49)
	200-349 vs 350-499	**1.96 (1.25, 3.03)**	1.33 (0.88, 2.04)
HIV-CAUSAL	200-350 vs 350-500	1.01 (0.84, 1.22)	**1.38 (1.23, 1.56)**

Lancet 2009; 373: 1352–63
Arch Intern Med. 2011;171(17):1560
Ann Intern Med. 2011;154:509-515
Sabin AIDS 2013

ART tolerability

- HIV-related morbidity and ART side effects can both impair QoL
- Treating asymptomatic patients with high CD4 counts could worsen QoL
- Severe ART adverse drug reactions are rare with newer regimens, but unclear whether the very small clinical benefits with early ART outweigh risks

Value Health. 2008;11(7):1144-53

Healthcare costs

- Discounted 10 year costs SA public sector (Khayelitsha) $7,688

  $184,512 to prevent one case of AIDS (CASCADE NNT=48 for 5 years)

- Earlier ART would reduce TB incidence, but IPT is effective & much cheaper
- Donor funding has plateaued
- Reducing transmission will save healthcare costs, but need data to estimate NNT long term

Ann Intern Med. 2011;154:509-515
PLoS ONE 2013;8(2):e53570

Won't all need ART soon? CD4 count decline Cape Town

TABLE 2. CD4 Cell Count Declines by CD4 Count Stratum

CD4 Cell Count Stratum (cells/μL)	CD4 Cell Count Decline (cells/μL) (95% CI)*
>500	47.1 (40.0–54.2)
351–500	30.6 (23.4–37.8)
201–350	20.5 (13.7–27.3)

500 to 350 will take 3.97-6.41 years

750 to 500 will take 4.61-6.25 years

JAIDS 2006;42:464

ART for preventing transmission

Observational studies of serodiscordant couples show ART ↓transmission by 64%

HTPN 052 RCT in serodiscordant couples

- 96% (73-99%) reduction in transmission
- Median follow up 1.7 yrs

RCTs of “test & treat” strategy underway

Cochrane Database Syst Rev. 2013 Apr 30;4:CD009153
N Engl J Med 2011;365:493-505

“all models are wrong, but some are useful”

GEORGE BOX

Models of HIV in SA with test & treat

- Start universal test & treat (UTT) 2012 & scale up to 90% coverage by 2019
- Elimination = <1 per 1000 person years
- Model D: elimination reached in 2029 with UTT vs 2041 starting ART with CD4 <350
- Dropout rate of 8.5% in the first year of treatment and 1.5% in subsequent years (“rather optimistic”). Sensitivity analysis if dropout increased to 5% in subsequent years:

Elimination UTT 2048 vs 2041 starting ART CD4 <350

PLoS Med 10(10): e1001534

Despite “rather optimistic” assumptions*:

“Although we show that the universal test & treat intervention proposed is highly cost-effective, the required number of health workers and financial resources for such a strategy far exceeds the current availability in South Africa.”

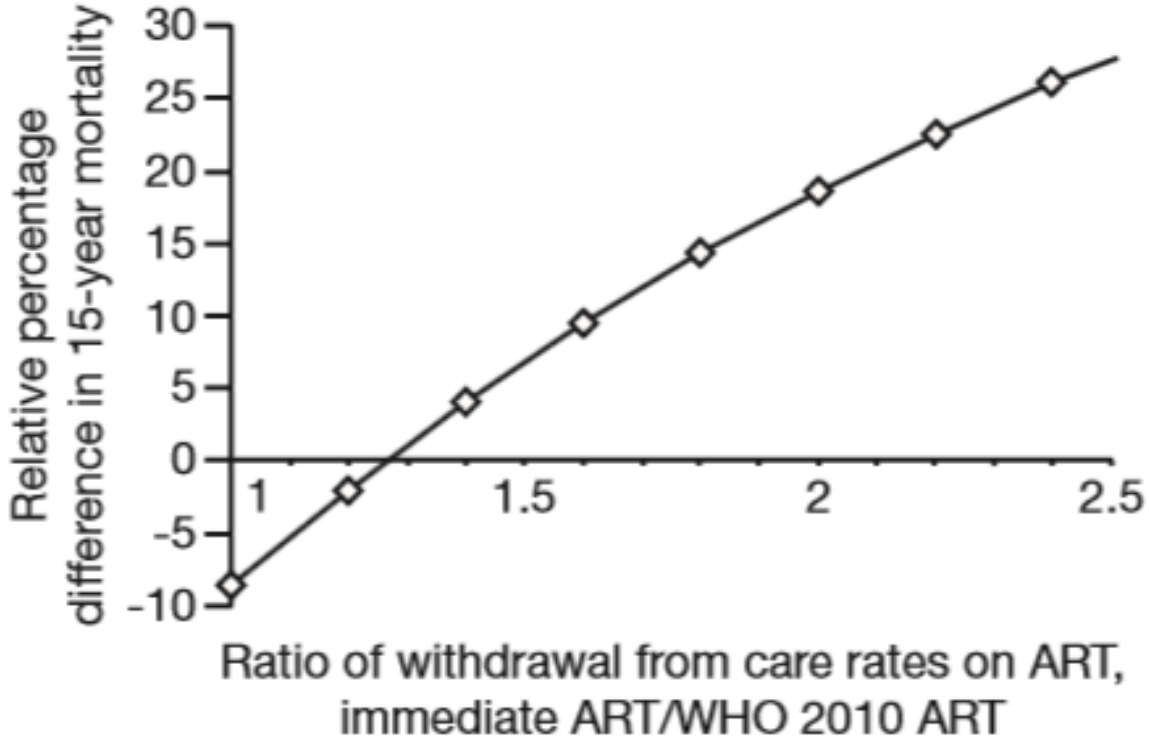
*LTFU 8.5% year 1 then 1%

90% tested and treated

90% transmission reduction with ART

PLoS Med 10(10): e1001534

Start ART CD4 >500 vs <350 in Africa



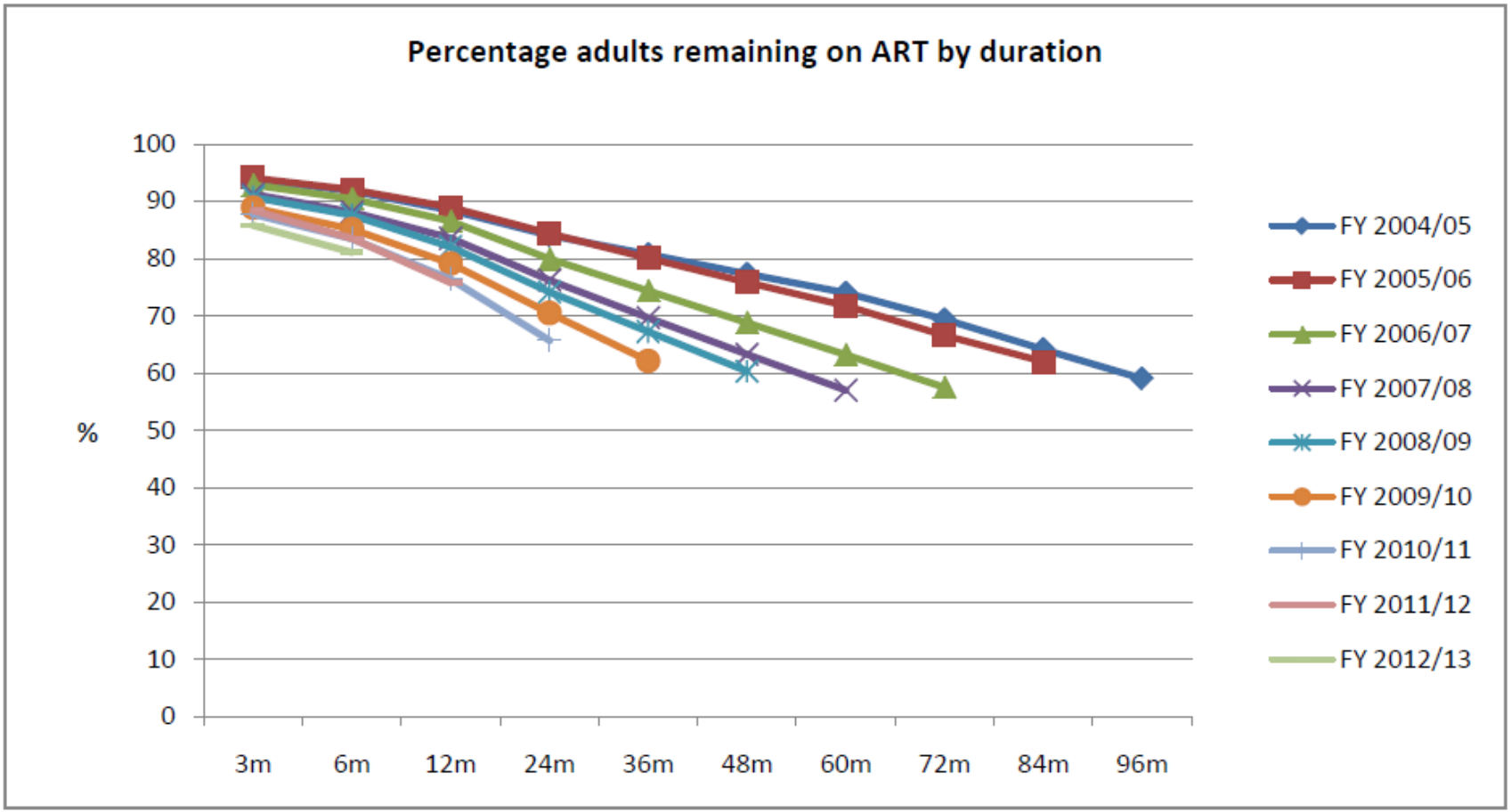
LTFU assumed 11.6% in 1st year, then 9.2% per year

↑ Mortality if withdrawal >1.2 fold higher on immediate ART

Antivir Ther 2013;18:45

SA retention in ART care

Figure 18: Adult remaining in care by year started ART (cohort)



http://www.health.gov.za/docs/reports/2013/ARTProgramme.pdf#sthash.zqUZlUpO.dpuf

Consequences of LTFU

- 42% resume ART within 3 years of defaulting
- 3-fold higher rate of failure & switching to 2nd line ART after defaulting
- Model of test & treat in Los Angeles estimates increasing primary ARV resistance

JAIDS 2010;55:e17–e23
Leisegang PLoS ONE 2013
CID 2013;56:1789

How many on ART are suppressed?

- Sample of 10% all adults in Masiphumele, research site with high HIV testing and ART coverage
- 30.4% of those on ART had VL>1,500
- Community VL based on routine VL monitoring are over estimates

JAIDS 2013;63:498

Conclusions

- Main clinical benefit of early ART is reducing TB, which IPT does very well
- Massive scale up needed to test & treat – donor funding plateau
- Models of test & treat sensitive to LTFU, which will likely worsen with implementation. This undermines transmission benefit & may increase long term mortality
- Community VL studies over estimated transmission benefit
- ↑ risk of resistance with ↑ ART use
- Need good evidence - RCT results pending, but need long term follow up to assess intervention
- When we are treating those who need it and retaining them in care test & treat could be considered