Partners, START and a model

Simon Briggs

Outline

- Partners
- START
- UK Modelling

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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*

- Enrolled HIV serodiscordant couples in nine countries (Botswana, Kenya, Malawi, South Africa, Zimbabwe, Brazil, India, Thailand and USA) starting in 2005
- CD4 count between 350 and 550 cells/mm^3
- Randomly assigned to immediate or delayed antiretroviral treatment (started when two CD4 count <250 cells/mm^3 or development of an AIDS-defining illness)

- The uninfected partners were encouraged to attend all study visits
- Both groups received
  - counselling on risk reduction and the use of condoms
  - treatment of STIs
- 1763 serodiscordant couples were enrolled
- 886 immediate treatment group
- 877 delayed treatment group

- 97% of couples were heterosexual
- Participants in both groups were similar in educational status, self-reported sexual behaviour and rate of condom use
- In 2011 the Data Safety Monitoring Board recommended that the results of the study be released

Table 2. Incidence of Partner-Linked and Any HIV-1 Transmission and Clinical and Composite Events.

Variable	Early Therapy			Delayed Therapy			Hazard or Rate Ratio (95% CI)*
	Events	Person-yr	Rate (95% CI)	Events	Person-yr	Rate (95% CI)	
		no.	%		*no.*	%	
Linked transmission							
Total	1	1585.3	0.1 (0.0–0.4)	27	1567.3	1.7 (1.1–2.5)	0.04 (0.01–0.27)
1 yr	1	819.0	0.1 (0.0–0.7)	16	813.3	2.0 (1.1–3.2)	0.06 (0.00–0.40)
2–3 yr	0	686.5	0.0 (0.0–0.5)	9	682.8	1.3 (0.6–2.5)	0.00 (0.00–0.50)
>3 yr	0	79.9	0.0 (0.0–4.6)	2	71.2	2.8 (0.3–10.1)	0.00 (0.00–4.75)
Any transmission†							
Total	4	1585.3	0.3 (0.1–0.6)	35	1567.3	2.2 (1.6–3.1)	0.11 (0.04–0.32)
1 yr	2	819.0	0.2 (0.0–0.9)	18	813.3	2.2 (1.3–3.5)	0.11 (0.01–0.46)
2–3 yr	2	686.5	0.3 (0.0–1.1)	14	682.8	2.1 (1.1–3.4)	0.14 (0.02–0.62)
>3 yr	0	79.9	0.0 (0.0–4.6)	3	71.2	4.2 (0.9–12.3)	0.00 (0.00–2.16)

- Relative risk reduction of 96% in the number of linked transmissions resulting from immediate treatment
- The only linked transmission in the immediate treatment group was identified 3 months after the infected partner started treatment

- “These results support the use of antiretroviral treatment as a part of a public health strategy to reduce the spread of HIV infection”

Partners updated 2015

- In 2011 all couples in the delayed group were offered antiretroviral treatment
- The study continued until 2015 when 1,171 couples remained in follow-up
- The final results show “a sustained 93% reduction of HIV transmission within couples where the HIV-infected partner was given antiretroviral treatment”

- There were only 8 linked transmissions within couples where the partner was given antiretroviral treatment
- Four of these occurred shortly after treatment started
- Four occurred later when the partner had a detectable HIV viral load
- There were no partner to partner transmissions when the partner with HIV infection had a suppressed HIV viral load

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Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection

The INSIGHT START Study Group*

- Randomly assigned treatment naïve adults with HIV infection with CD4 counts >500 cells/mm^3 to immediate treatment or delayed treatment (treatment once the CD4 count < 350 cells/mm^3 or the development of an AIDS-defining illness)
- Primary composite end point was an AIDS-defining illness, a non AIDS-defining illness or death from any cause

- Enrolled patients from 2009 to 2013
- 4685 patients were followed for a mean of 3 years
- At the time the study ended, patients received antiretroviral treatment for 94% of the time (immediate group) and 28% of the time (delayed group)
- Again the Data Safety Monitoring Board stopped the study early

Table 1. Characteristics of the Patients at Baseline.*

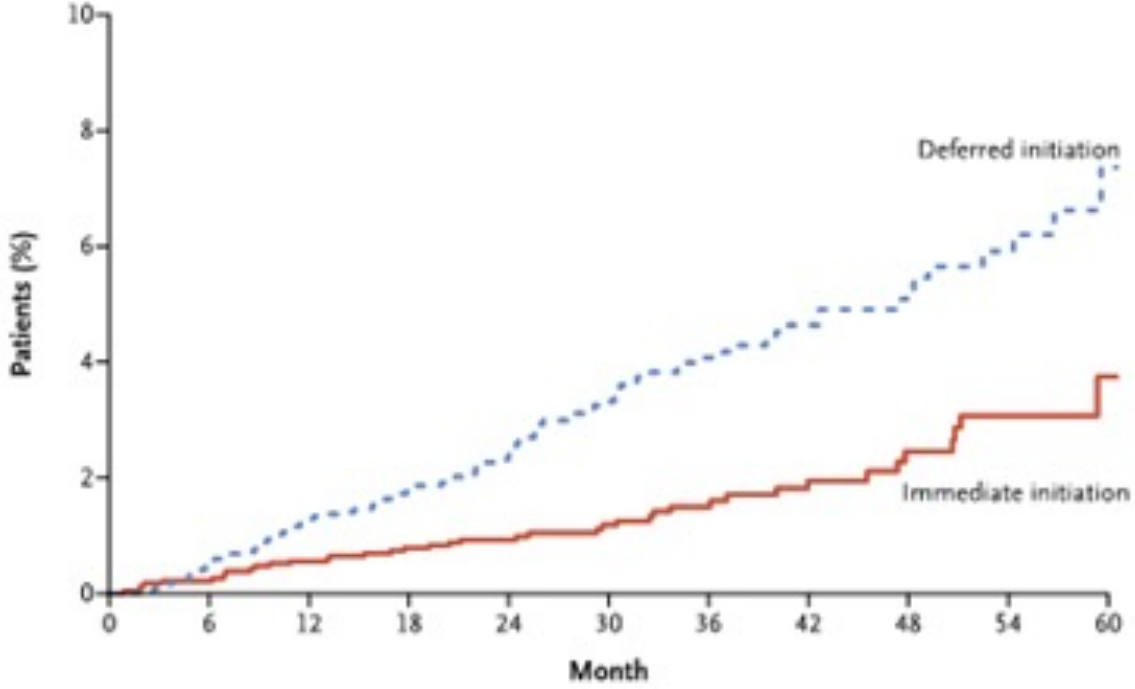
Characteristic	Immediate-Initiation Group (N = 2326)	Deferred-Initiation Group (N = 2359)	All Patients (N = 4685)
Median age (IQR) — yr	36 (29–44)	36 (29–44)	36 (29–44)
Female sex — no. (%)	624 (26.8)	633 (26.8)	1,257 (26.8)
Race or ethnic group — no. (%)†			
Asian	198 (8.5)	190 (8.1)	388 (8.3)
Black	702 (30.2)	708 (30.0)	1,410 (30.1)
Latino or Hispanic	320 (13.8)	318 (13.5)	638 (13.6)
White	1,015 (43.6)	1,071 (45.4)	2,086 (44.5)
Other	91 (3.9)	72 (3.1)	163 (3.5)
Geographical region — no. (%)			
Africa	499 (21.5)	501 (21.2)	1,000 (21.3)
Asia	179 (7.7)	177 (7.5)	356 (7.6)
Australia	56 (2.4)	53 (2.2)	109 (2.3)
Europe and Israel	763 (32.8)	776 (32.9)	1,539 (32.8)
North America	248 (10.7)	259 (11.0)	507 (10.8)
South America and Mexico	581 (25.0)	593 (25.1)	1,174 (25.1)
Mode of infection with HIV — no. (%)			
Sexual contact			
Men having sex with men	1,300 (55.9)	1,286 (54.5)	2,586 (55.2)
With person of opposite sex	873 (37.5)	917 (38.9)	1,790 (38.2)
Injection-drug use	37 (1.6)	27 (1.1)	64 (1.4)
Blood products, other, or unknown	116 (5.0)	129 (5.5)	245 (5.2)
Median time since HIV diagnosis (IQR) — yr	1.0 (0.4–3.0)	1.1 (0.4–3.1)	1.0 (0.4–3.1)
Median CD4+ count (IQR) — cells/mm^3‡	651 (585–765)	651 (582–764)	651 (584–765)
Median HIV RNA (IQR) — copies/ml	13,000 (3133–43,808)	12,550 (2963–42,567)	12,759 (3019–43,391)
Current smoker — no. (%)	730 (31.4)	766 (32.5)	1,496 (31.9)
Median CHD risk at 10 yr (IQR) — %§	1.9 (0.5–5.0)	1.9 (0.5–5.3)	1.9 (0.5–5.1)

Table 2. Primary and Secondary End Points.*

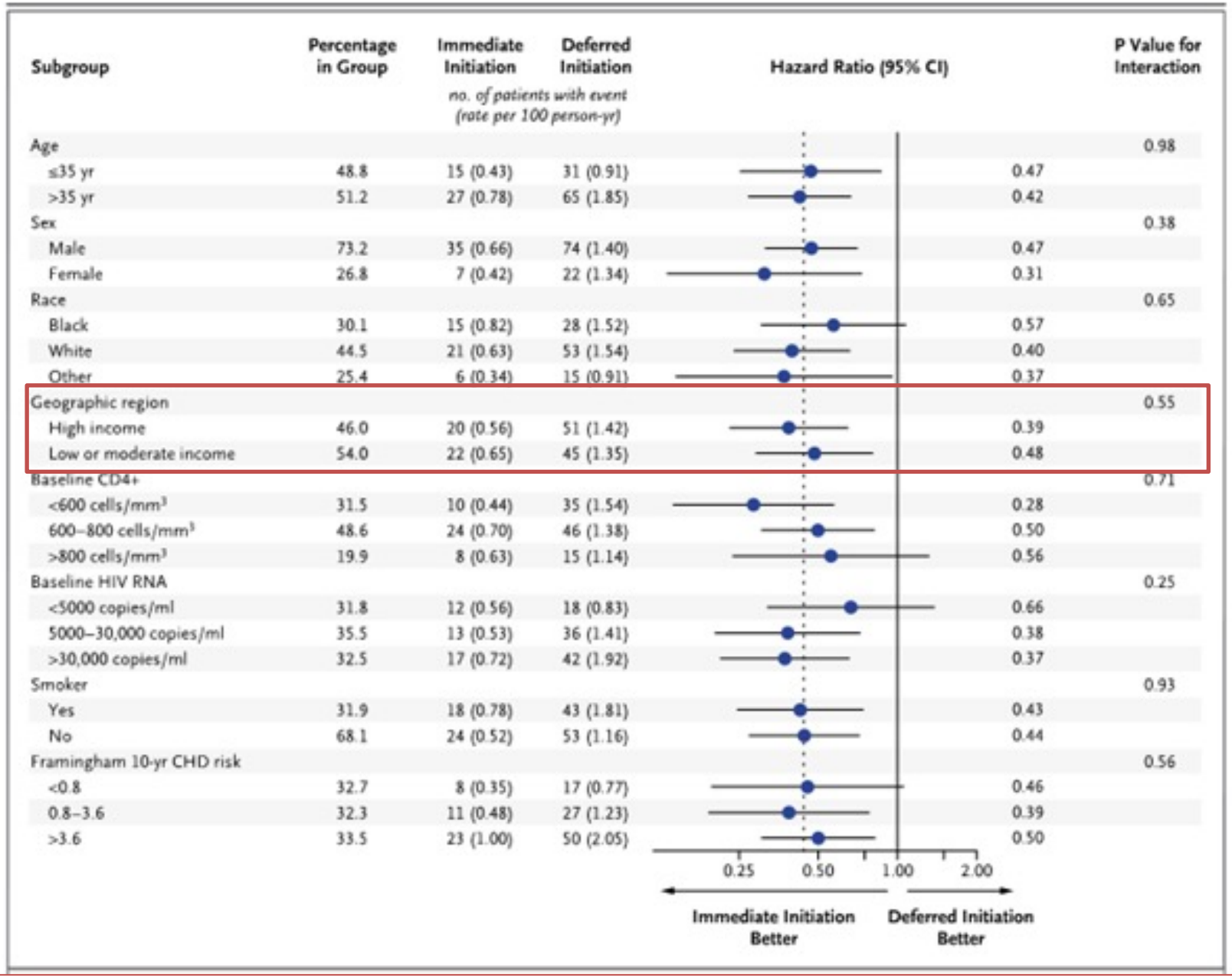
End Point	Immediate-Initiation Group (N=2326)		Deferred-Initiation Group (N=2359)		Hazard Ratio (95% CI)†	P Value
	no.	*no./100 person-yr*	*no.*	*no./100 person-yr*		
Composite primary end point	42	0.60	96	1.38	0.43 (0.30–0.62)	<0.001
Components of the primary end point						
Serious AIDS-related event	14	0.20	50	0.72	0.28 (0.15–0.50)	<0.001
Serious non–AIDS-related event	29	0.42	47	0.67	0.61 (0.38–0.97)	0.04
Death from any cause	12	0.17	21	0.30	0.58 (0.28–1.17)	0.13
Tuberculosis	6	0.09	20	0.28	0.29 (0.12–0.73)	0.008
Kaposi's sarcoma	1	0.01	11	0.16	0.09 (0.01–0.71)	0.02
Malignant lymphoma	3	0.04	10	0.14	0.30 (0.08–1.10)	0.07
Cancer not related to AIDS	9	0.13	18	0.26	0.50 (0.22–1.11)	0.09
Cardiovascular disease	12	0.17	14	0.20	0.84 (0.39–1.81)	0.65

- Although the relative risk reduction was 57% the absolute risk reduction was 0.78 events per 100 person years

A Time to First Primary Event



No. at Risk											
Immediate initiation	2326	2302	2279	2163	1801	1437	1031	757	541	336	110
Deferred initiation	2359	2326	2281	2135	1803	1417	1021	729	520	334	103
Estimated Percentage											
Immediate initiation		0.2	0.6	0.8	0.9	1.2	1.5	2.0	2.5	3.1	3.7
Deferred initiation		0.5	1.2	1.8	2.4	3.3	4.1	4.6	5.3	5.9	7.4


Subgroup
Percentage in Group
Immediate Initiation
Deferred Initiation
no. of patients with event (rate per 100 person-yr)
Hazard Ratio (95% CI)
P Value for Interaction
Age 0.98
≤35 yr 48.8 15 (0.43) 31 (0.91) 0.47
>35 yr 51.2 27 (0.78) 65 (1.85) 0.42
Sex 0.38
Male 73.2 35 (0.66) 74 (1.40) 0.47
Female 26.8 7 (0.42) 22 (1.34) 0.31
Race 0.65
Black 30.1 15 (0.82) 28 (1.52) 0.57
White 44.5 21 (0.63) 53 (1.54) 0.40
Other 25.4 6 (0.34) 15 (0.91) 0.37
Geographic region 0.55
High income 46.0 20 (0.56) 51 (1.42) 0.39
Low or moderate income 54.0 22 (0.65) 45 (1.35) 0.48
Baseline CD4+ 0.71
<600 cells/mm³ 31.5 10 (0.44) 35 (1.54) 0.28
600–800 cells/mm³ 48.6 24 (0.70) 46 (1.38) 0.50
>800 cells/mm³ 19.9 8 (0.63) 15 (1.14) 0.56
Baseline HIV RNA 0.25
<5000 copies/ml 31.8 12 (0.56) 18 (0.83) 0.66
5000–30,000 copies/ml 35.5 13 (0.53) 36 (1.41) 0.38
>30,000 copies/ml 32.5 17 (0.72) 42 (1.92) 0.37
Smoker 0.93
Yes 31.9 18 (0.78) 43 (1.81) 0.43
No 68.1 24 (0.52) 53 (1.16) 0.44
Framingham 10-yr CHD risk 0.56
<0.8 32.7 8 (0.35) 17 (0.77) 0.46
0.8–3.6 32.3 11 (0.48) 27 (1.23) 0.39
>3.6 33.5 23 (1.00) 50 (2.05) 0.50
0.25
0.50
1.00
2.00
Immediate Initiation Better
Deferred Initiation Better

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Kaposi's sarcoma	1	0.01	11	0.16	0.09 (0.01–0.71)	0.02
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Cardiovascular disease	12	0.17	14	0.20	0.84 (0.39–1.81)	0.65
Other secondary end points						
Grade 4 event‡	73	1.06	73	1.05	1.01 (0.73–1.39)	0.97
Unscheduled hospitalization§	262	4.02	287	4.40	0.91 (0.77–1.08)	0.28
Grade 4 event, unscheduled hospitalization, or death from any cause	283	4.36	311	4.78	0.91 (0.77–1.07)	0.25
Most common grade 4 events, unscheduled hospitalization, or death from any cause¶						
Bacterial infectious disorder	14	0.20	36	0.52	0.38 (0.20–0.70)	0.002
Bone or joint injury	17	0.24	11	0.16	1.55 (0.73–3.31)	0.26
Depressed mood disorder or disturbance	12	0.17	9	0.13	1.34 (0.57–3.19)	0.50
Infection with unspecified pathogen	64	0.93	65	0.94	0.99 (0.70–1.40)	0.96
Injury not elsewhere classified	11	0.16	22	0.31	0.50 (0.24–1.03)	0.06
Suicidal or self-injurious behavior not elsewhere classified	27	0.39	24	0.34	1.15 (0.66–1.99)	0.63
Viral infectious disorder	12	0.17	15	0.21	0.81 (0.38–1.72)	0.58
Grade 4 event, unscheduled hospitalization, or primary end point	295	4.56	355	5.52	0.82 (0.71–0.96)	0.01

Cost-Benefit analysis

Group	Patients	Follow up (years) (mean follow up 3 years)	Receiving ART (years)	Events
Immediate group	2326	6978	6559 (94%)	42
Deferred group	2359	7077	1982 (28%)	96

- Treat with ART for 4577 years to prevent 54 events
- NNT: 85 patients for one year to prevent one event
- Assuming cost of ART is $15,000 per year, it would cost $1.3 million to prevent one event

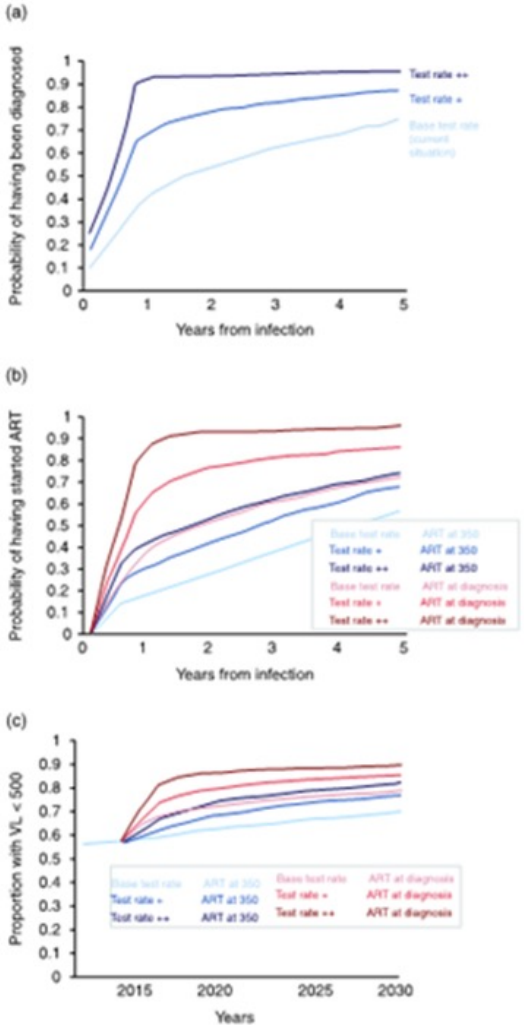
Potential impact on HIV incidence of higher HIV testing rates and earlier antiretroviral therapy initiation in MSM

Andrew N. Phillips[a], Valentina Cambiano[a], Alec Miners[b], Fiona C. Lampe[a], Alison Rodger[a], Fumiyo Nakagawa[a], Alison Brown[c], O. Noel Gill[c], Daniela De Angelis[c], Jonathan Elford[d], Graham Hart[a], Anne M. Johnson[a], Jens D. Lundgren[e], Simon Collins[f] and Valerie Delpech[c]

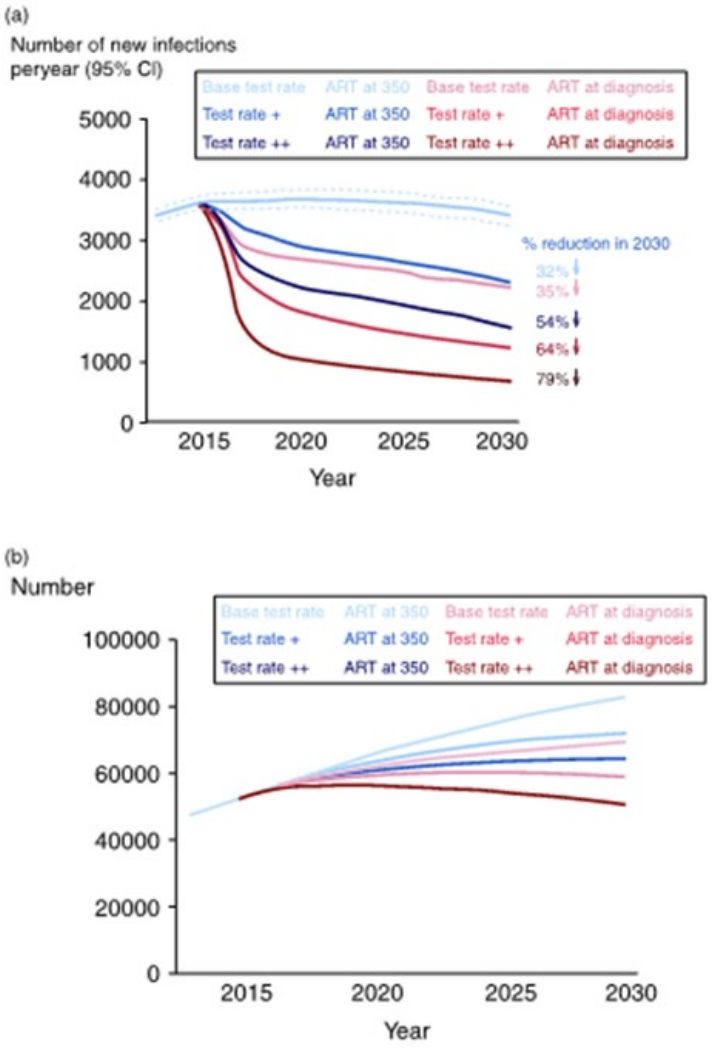
AIDS 2015, **29**:1855–1862

- Modelled HIV in the UK MSM population since 1980
- Projected future outcomes 2015 to 2030
- Modelled current annual rate of testing (19%) and increased testing rates of 38 and 65%
- Antiretroviral treatment (ART) initiation criteria was also changed from a CD4 count of 350 cells/mm^3 to initiation at diagnosis
- Current HIV incidence in MSM population is 6/1000 person-years
- Aimed to address what it would take to reduce this to 1/1000 person-years

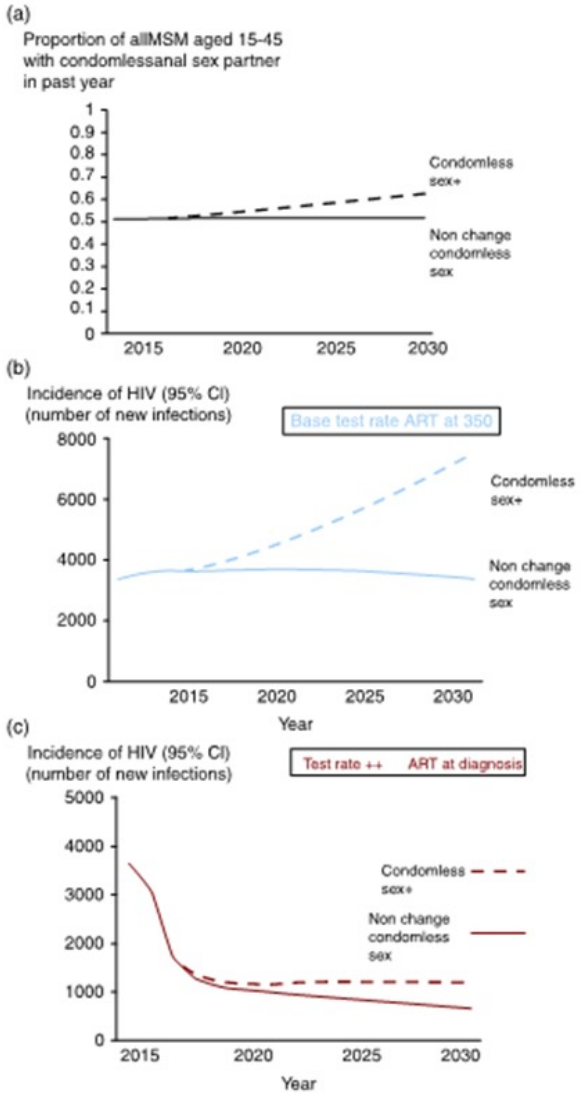
Potential changes in testing and treatment initiation and effect on proportion with viral suppression



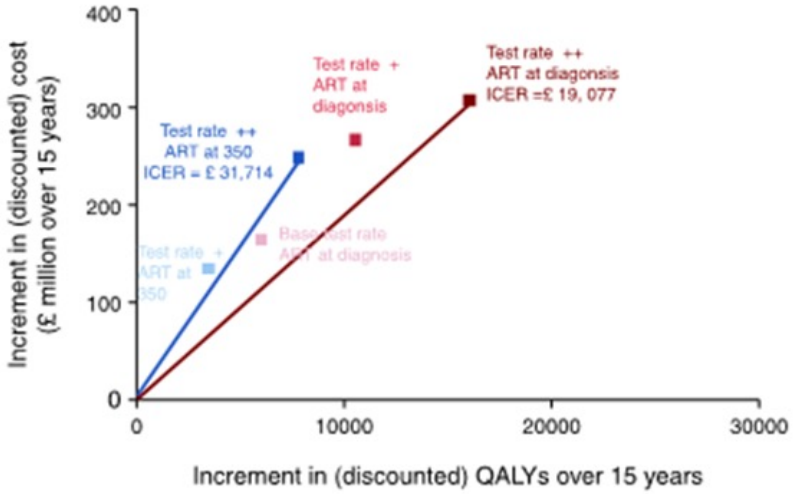
Projected HIV incidence and men living with HIV infection



Possible increases in condomless sex and their impact on HIV incidence



Cost-effectiveness analysis



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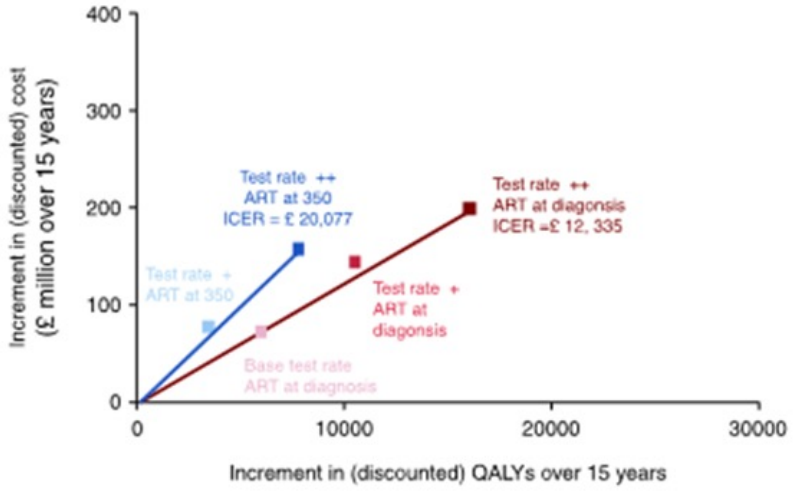

- To reduce incidence to below 1/1000 person-years
  - need to increase the number of MSM with HIV who are receiving ART and who have viral suppression from 60 to 90%
  - this would involve 90% of men being diagnosed within a year of infection and assumes no increase in codomless sex
- This reduction in incidence to below 1/1000 person-years is required to reduce the total number of MSM with HIV infection
- Assuming a threshold of £20,000 per QALY, increased testing and ART at diagnosis are cost effective

Summary

- Partners has shown that treatment prevents transmission
- START has shown that early treatment prevents morbidity and mortality
- UK modelling shows that very high testing rates and immediate ART would result in lower numbers of MSM living with HIV infection and that this would be cost effective