Treatment as prevention: the experience from HIV

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Looking back…

1980s

- 1983: Discovery of HIV
- 1987: Introduction of AZT

1990s

- 1995: Introduction of PI
- 1995: “Discovery” of HAART (IDV/r+2NRTI)
- 1996: Introduction of NNRTI

2000s

- 2003: development of FI
- 2006: 1st STR
- 2007: CCR5 antagonists
- 2007: INSTI

However…

- Side effects
- Resistances/Failure
- Daily pill burden
- Drug-drug interactions
- Costs
- Stigma
- Availability
- Lack of experience/knowledge

Table_5

Note: To print large tables and graphs users may have to change their printer settings to landscape and use a small font size.

TABLE 5. Indications for the initiation of antiretroviral therapy in the chronically HIV-infected patient

Clinical category	CD4+ T cell count and HIV RNA	Recommendation
Symptomatic (i.e., AIDS, thrush, unexplained fever)	Any value	Treat
Asymptomatic	CD4+ T Cells <500/mm3 or HIV RNA >10,000 (bDNA) or >20,000 (RT-PCR)	Treatment should be offered. Strength of recommendation is based on prognosis for disease-free survival as shown in Table 4 and willingness of the patient to accept therapy. *
Asymptomatic	CD4+ T Cells >500/mm3 and HIV RNA <10,000 (bDNA) or <20,000 (RT-PCR)	Many experts would delay therapy and observe; however, some experts would treat.

* Some experts would observe patients whose CD4+ T cell counts are between 350-500/ mm3 and HIV RNA levels <10,000 (bDNA) or <20,000 (RT-PCR).

Stanley SK. MMWR 1998

Table 3. Risk of Death Associated with Deferral of Antiretroviral Therapy, According to CD4+ Count at Baseline, with Adjustment for HIV RNA Level, Age, and Sex.*

Variable	351-to-500 CD4+ Count		More-Than-500 CD4+ Count	
	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
Without inclusion of HIV RNA data				
Deferral of antiretroviral therapy	1.69 (1.26–2.26)	<0.001	1.94 (1.37–2.79)	<0.001
Female sex	1.21 (0.89–1.64)	0.24	1.85 (1.33–2.59)	<0.001
Older age (per 10-yr increment)	1.68 (1.48–1.91)	<0.001	1.83 (1.62–2.06)	<0.001
Baseline CD4+ count (per 100 cells/mm^3)	1.13 (0.72–1.78)	0.59	0.93 (0.87–0.99)	0.03
With inclusion of HIV RNA data				
Deferral of antiretroviral therapy	1.63 (1.21–2.19)	0.002	1.85 (1.20–2.86)	0.006
Female sex	1.47 (1.02–2.12)	0.04	1.35 (0.85–2.15)	0.20
Older age (per 10-year increment)	1.89 (1.69–2.11)	<0.001	1.81 (1.58–2.07)	<0.001
Baseline CD4+ count (per 100 cells/mm^3)	0.74 (0.55–1.00)	0.06	0.97 (0.89–1.05)	0.45
Baseline HIV RNA level (per $\log_{10}$ copies/ml)	1.11 (0.96–1.28)	0.15	1.13 (0.96–1.33)	0.14

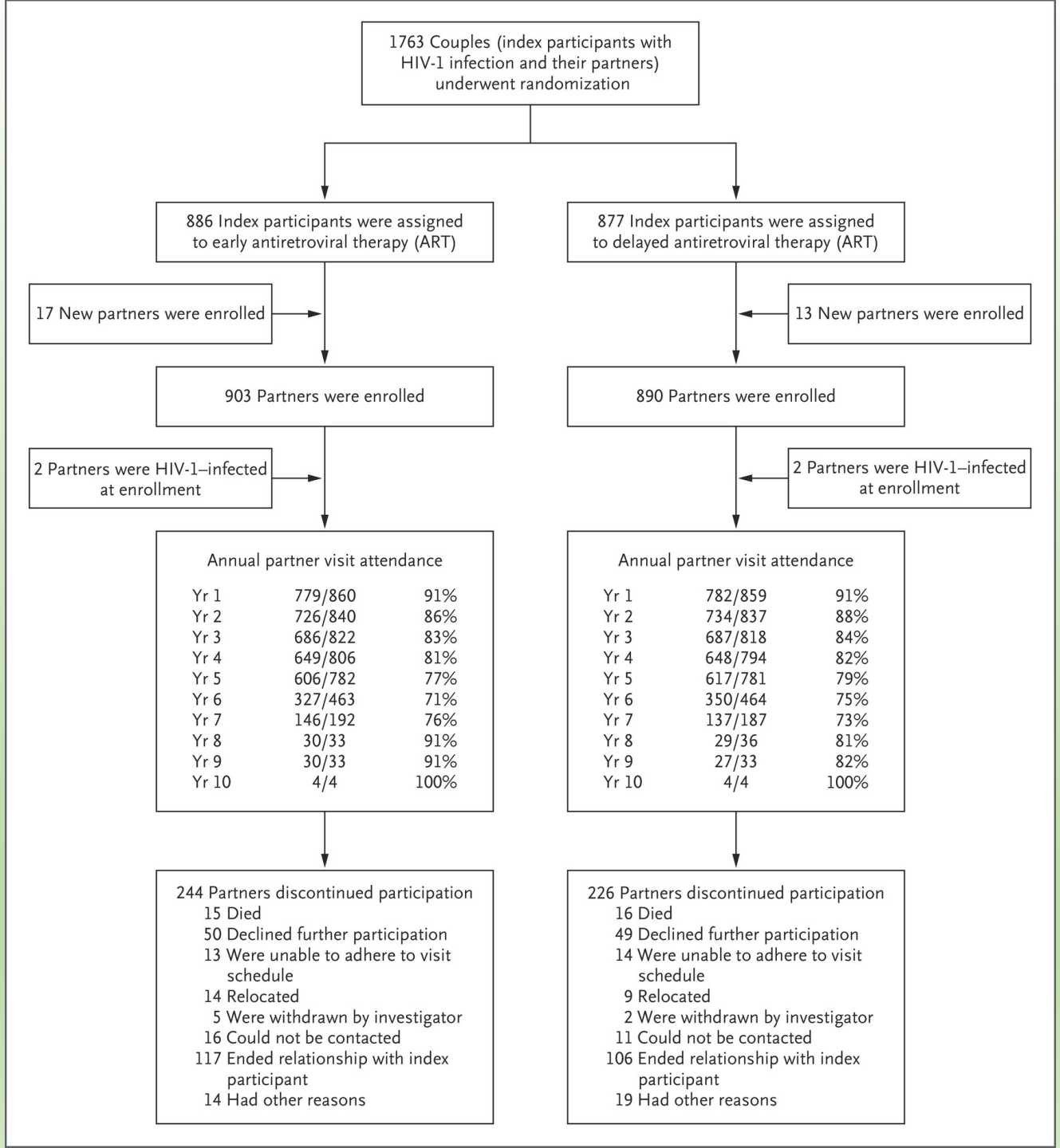
* The CD4+ count was measured in cells per cubic millimeter. Results were calculated with the use of Cox regression analyses with inverse probability-of-censoring weights. HIV denotes human immunodeficiency virus.

Kitahata M. NEJM 2009

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

Lundgren JD. NEJM 2015



Cohen MS. NEJM 2011

Table 1. Incidence of All Partner Infections and Linked Partner Infections, before and after the Interim Analysis.*

Type of Infection and Trial Period	Early ART			Delayed ART			Hazard or Rate Ratio (95% CI)†	Relative Reduction with Early ART vs. Delayed ART
	no. of infections	*person-yr of follow-up‡*	*event rate per 100 person-yr (95% CI)*	*no. of infections*	*person-yr of follow-up‡*	*event rate per 100 person-yr (95% CI)*		%
All partner infections	19	4324.6	0.44 (0.26–0.69)	59	4184.7	1.41 (1.07–1.82)	0.31 (0.19–0.53)	69
Before interim analysis	4	1751.4	0.23 (0.06–0.58)	42	1731.1	2.43 (1.75–3.28)	0.10 (0.03–0.27)	90
After interim analysis	15	2573.2	0.58 (0.33–0.96)	17	2453.6	0.69 (0.4–1.11)	0.84 (0.39–1.79)	16
Linked partner infections	3	4324.6	0.07 (0.01–0.2)	43	4184.7	1.03 (0.74–1.38)	0.07 (0.02–0.22)	93
Before interim analysis	1	1751.4	0.06 (0–0.32)	36	1731.1	2.08 (1.46- 2.88)	0.03 (0.00–0.20)	97
After interim analysis	2	2573.2	0.08 (0.01–0.28)	7	2453.6	0.29 (0.11–0.59)	0.27 (0.03–1.43)	73

Cohen MS. NEJM 2011

Viral suppression and HIV transmission in serodiscordant male couples: an international, prospective, observational, cohort study

*Benjamin R Bavinton, Angie N Pinto, Nittaya Phanuphak, Beatriz Grinsztejn, Garrett P Prestage, Iryna B Zablotska-Manos, Fengyi Jin, Christopher K Fairley, Richard Moore, Norman Roth, Mark Bloch, Catherine Pell, Anna M McNulty, David Baker, Jennifer Hoy, Ban Kiem Tee, David J Templeton, David A Cooper†, Sean Emery, Anthony Kelleher, Andrew E Grulich, for the Opposites Attract Study Group**

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This online publication has been corrected. The corrected version first appeared at thelancet.com/hiv on October 8, 2018

See Comment page e408

*Members of the study group are listed at the end of this paper

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Summary

Background Evidence on viral load and HIV transmission risk in HIV-serodiscordant male homosexual couples is limited to one published study. We calculated transmission rates in couples reporting condomless anal intercourse (CLAI), when HIV-positive partners were virally suppressed, and daily pre-exposure prophylaxis (PrEP) was not used by HIV-negative partners.

Methods In the Opposites Attract observational cohort study, serodiscordant male homosexual couples were recruited from 13 clinics in Australia, one in Brazil, and one in Thailand. At study visits, HIV-negative partners provided information on sexual behaviour and were tested for HIV and sexually transmitted infections; HIV-positive partners had HIV viral load tests, CD4 cell count, and sexually transmitted infection tests done. Viral suppression was defined as less than 200 copies per mL. Linked within-couple HIV transmissions were identified with phylogenetic analysis. Incidence was calculated per couple-year of follow-up, focusing on periods with CLAI, no use of daily PrEP, and viral suppression. One-sided upper 95% CI limits for HIV transmission rates were calculated with exact Poisson methods.

Findings From May 8, 2012, to March 31, 2016, in Australia, and May 7, 2014, to March 31, 2016, in Brazil and Thailand, 358 couples were enrolled. 343 couples had at least one follow-up visit and were followed up for 588·4 couple-years. 258 (75%) of 343 HIV-positive partners had viral loads consistently less than 200 copies per mL and 115 (34%) of 343 HIV-negative partners used daily PrEP during follow-up. 253 (74%) of 343 couples reported within-couple CLAI during follow-up, with a total of 16 800 CLAI acts. Three new HIV infections occurred but none were phylogenetically linked. There were 232·2 couple-years of follow-up and 12 447 CLAI acts in periods when CLAI was reported, HIV-positive partners were virally suppressed, and HIV-negative partners did not use daily PrEP, resulting in an upper CI limit of 1·59 per 100 couple-years of follow-up for transmission rate.

Interpretation HIV treatment as prevention is effective in men who have sex with men. Increasing HIV testing and linking to immediate treatment is an important strategy in HIV prevention in homosexual men.

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Initiation of Antiretroviral Therapy (Last updated December 18, 2019; last reviewed December 18, 2019)

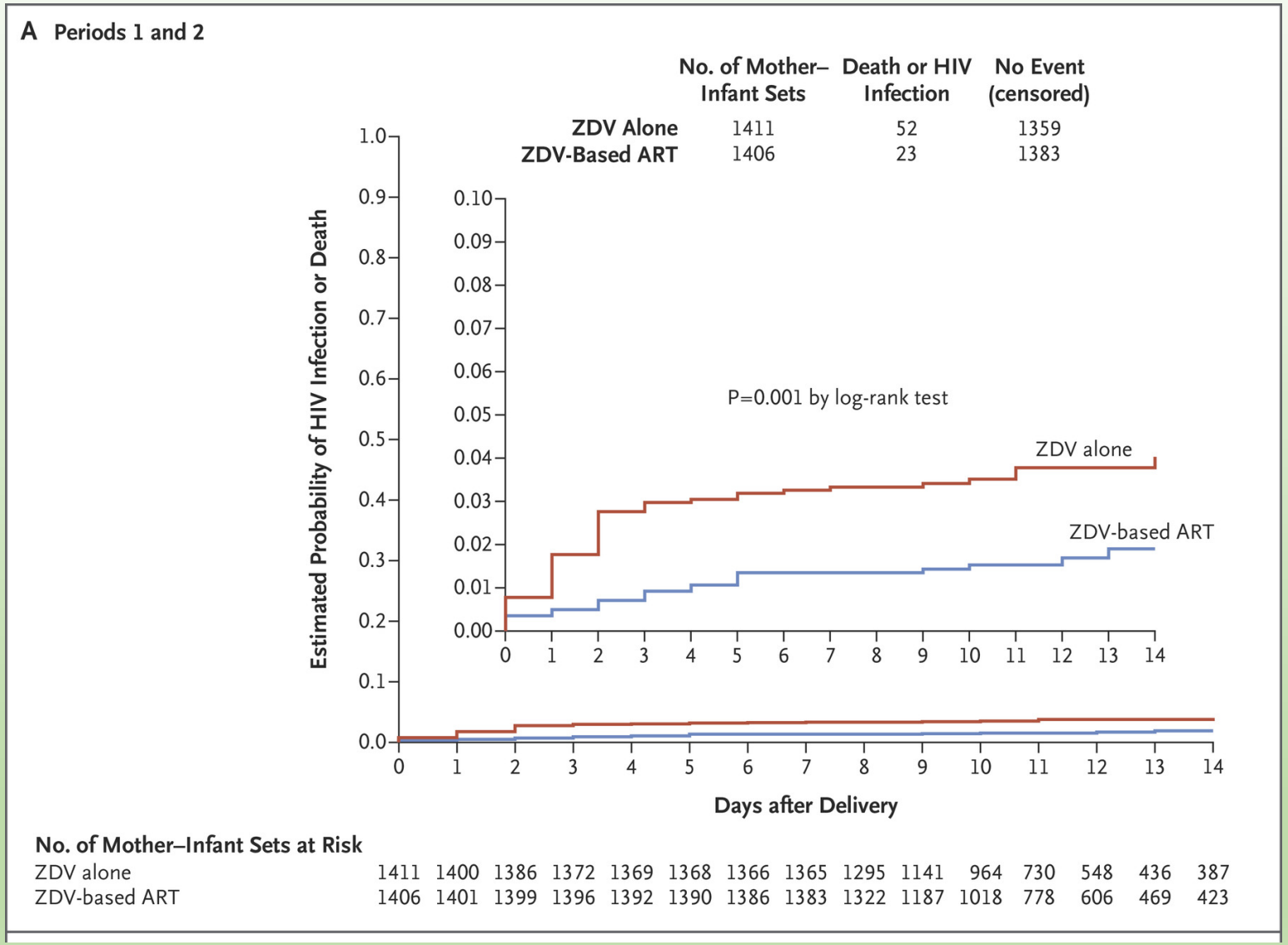
Panel's Recommendations
• Antiretroviral therapy (ART) is recommended for all persons with HIV to reduce morbidity and mortality **(AI)** and to prevent the transmission of HIV to others **(AI)**.
• The Panel on Antiretroviral Guidelines for Adults and Adolescents recommends initiating ART immediately (or as soon as possible) after HIV diagnosis in order to increase the uptake of ART and linkage to care, decrease the time to viral suppression for individual patients, and improve the rate of virologic suppression among persons with HIV **(AII)**.
• When initiating ART, it is important to educate patients regarding the benefits of ART and to deploy strategies to optimize care engagement and treatment adherence **(AIII)**.
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*

DHHS Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV 2019

Table 3. Mother-to-child transmission rates in 2007–2011 by treatment and, for women on combination antiretroviral therapy, by mode of delivery and viral load.

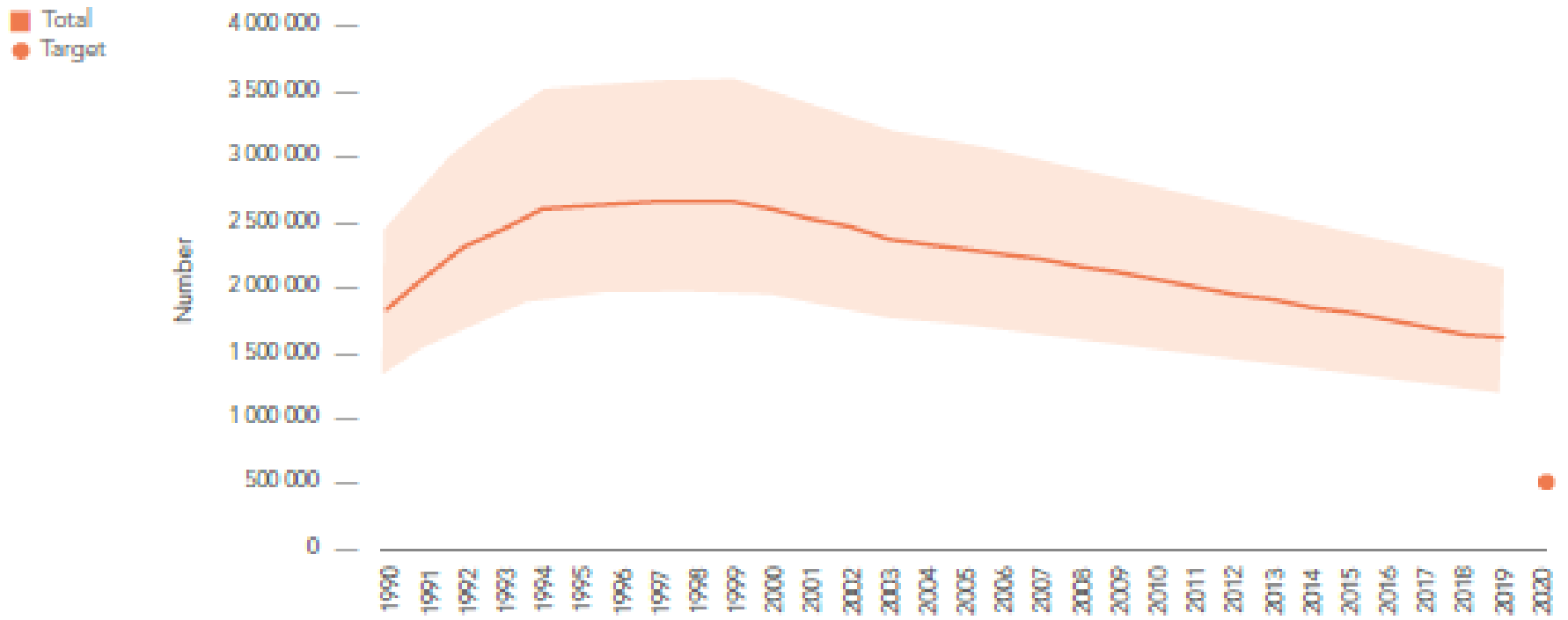
	Total	Infected	
	N	*n*	%
All births			
Antiretroviral therapy ($n=5652$)			
Untreated	54	4	7.4
Zidovudine alone	134	0	0
Two antiretroviral drugs	23	0	0
cART	5442	25	0.46
Births to women on cART ($n=5442$)			
Mode of delivery ($n=5413$)			
Elective cesarean section	2050	12	0.59
Emergency cesarean section	1360	7	0.51
Vaginal delivery	2003	6	0.30
Planned	1720	3	0.17
Unplanned	97	2	2.1
Unspecified	186	1	0.54
cART drug class ($n=5442$)			
NRTI only	73	1	1.4
NNRTI-based	1230	2	0.16
PI-based	3900	21	0.54
PI and NNRTI	239	1	0.42
HIV RNA viral load ($n=4783$)			
<50	3859	2	0.05
50–399	655	7	1.1
400–999	104	2	1.9
1000–9999	100	3	3.0
≥10000	65	6	9.2

Townsend CL. AIDS 2014



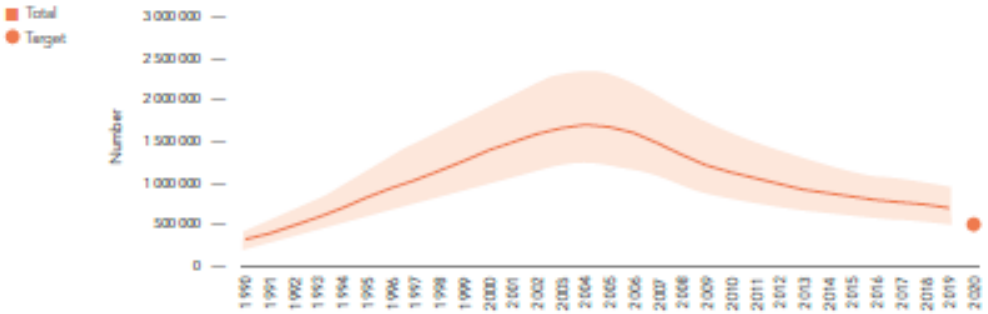
Fowler MG. NEJM 2016

Number of new HIV infections, global, 1990–2019



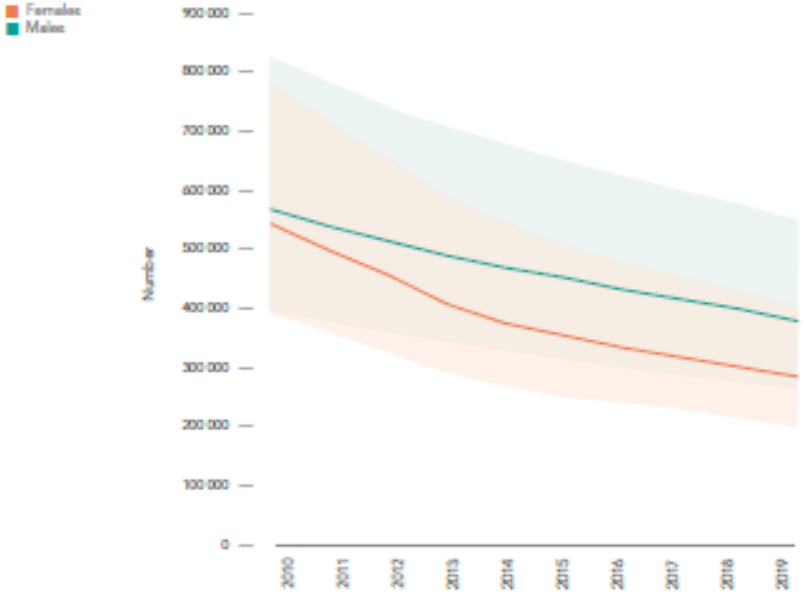
UNAIDS Data 2020

AIDS-related deaths, global, 1990–2019



Source: UNAIDS epidemiological estimates, 2020 (see https://aidsinfo.unaids.org/).

AIDS-related deaths by sex, global, 2010–2019



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UNAIDS Data 2020

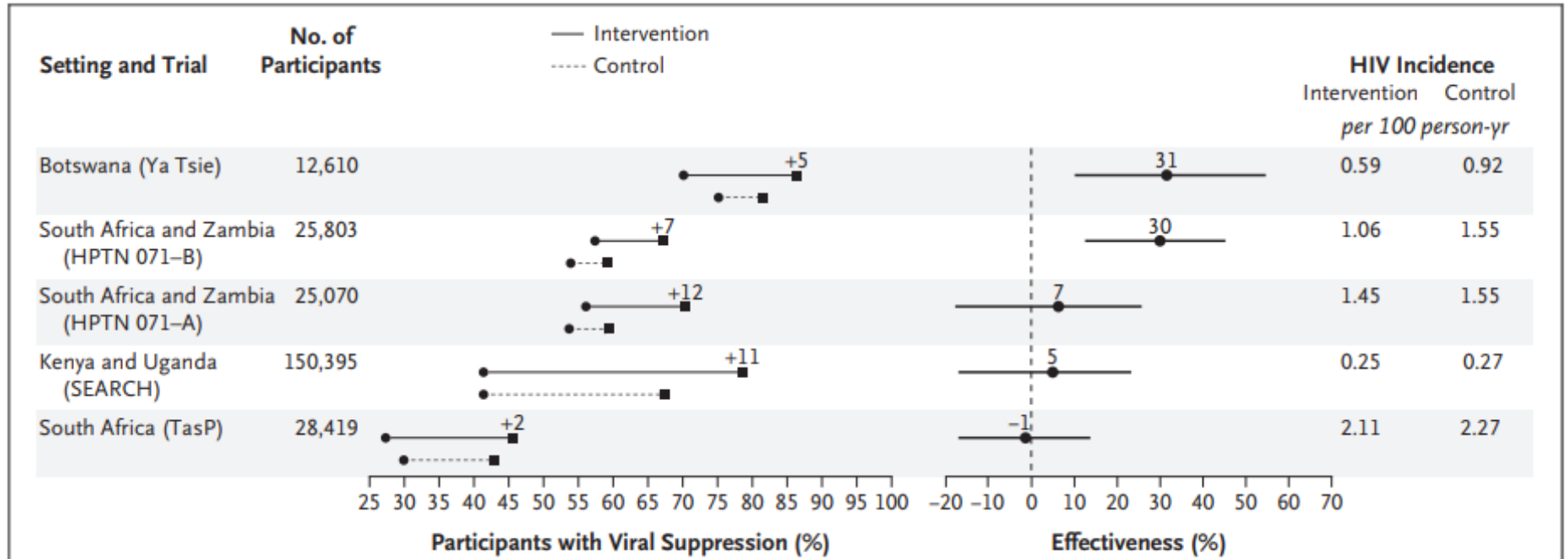
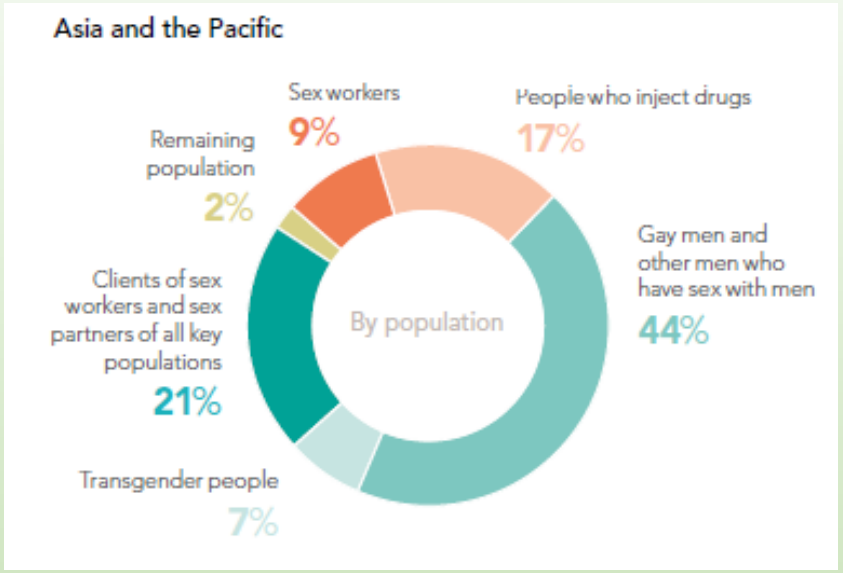
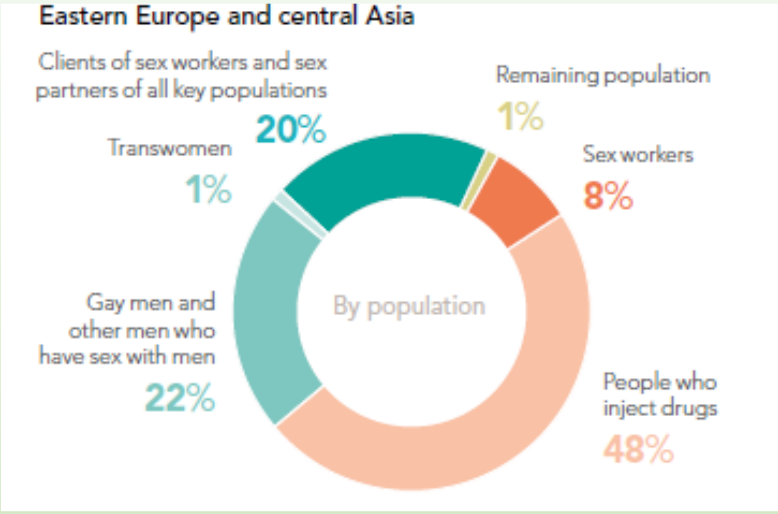


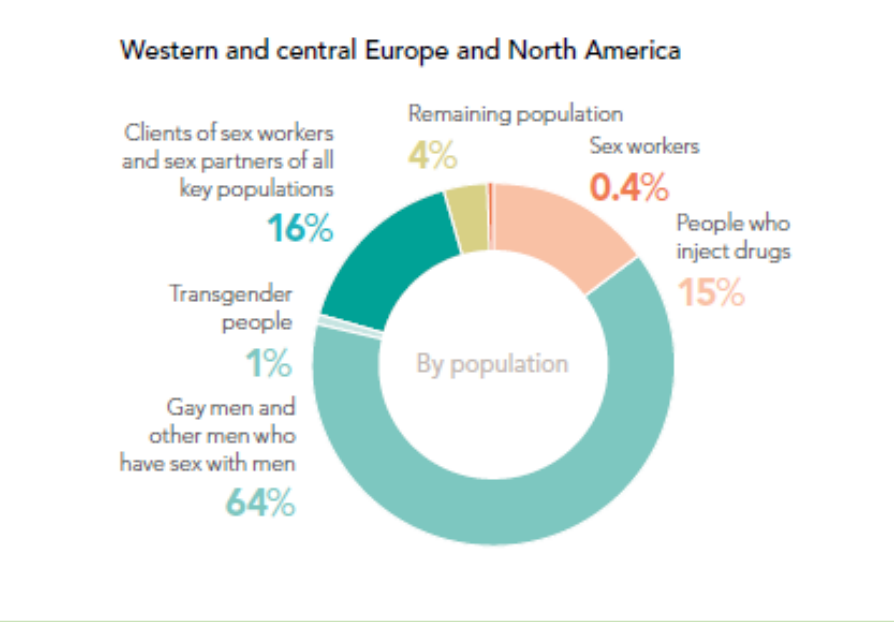
Figure 1. Effectiveness of Universal Test-and-Treat Strategies in Reducing the Incidence of Human Immunodeficiency Virus (HIV) Infection — Results from Community-Based Randomized, Controlled Trials.

Abdool-Karim S. NEJM 2019

Distribution of new HIV infections by gender and population, by region, 2019







UNAIDS Data 2020

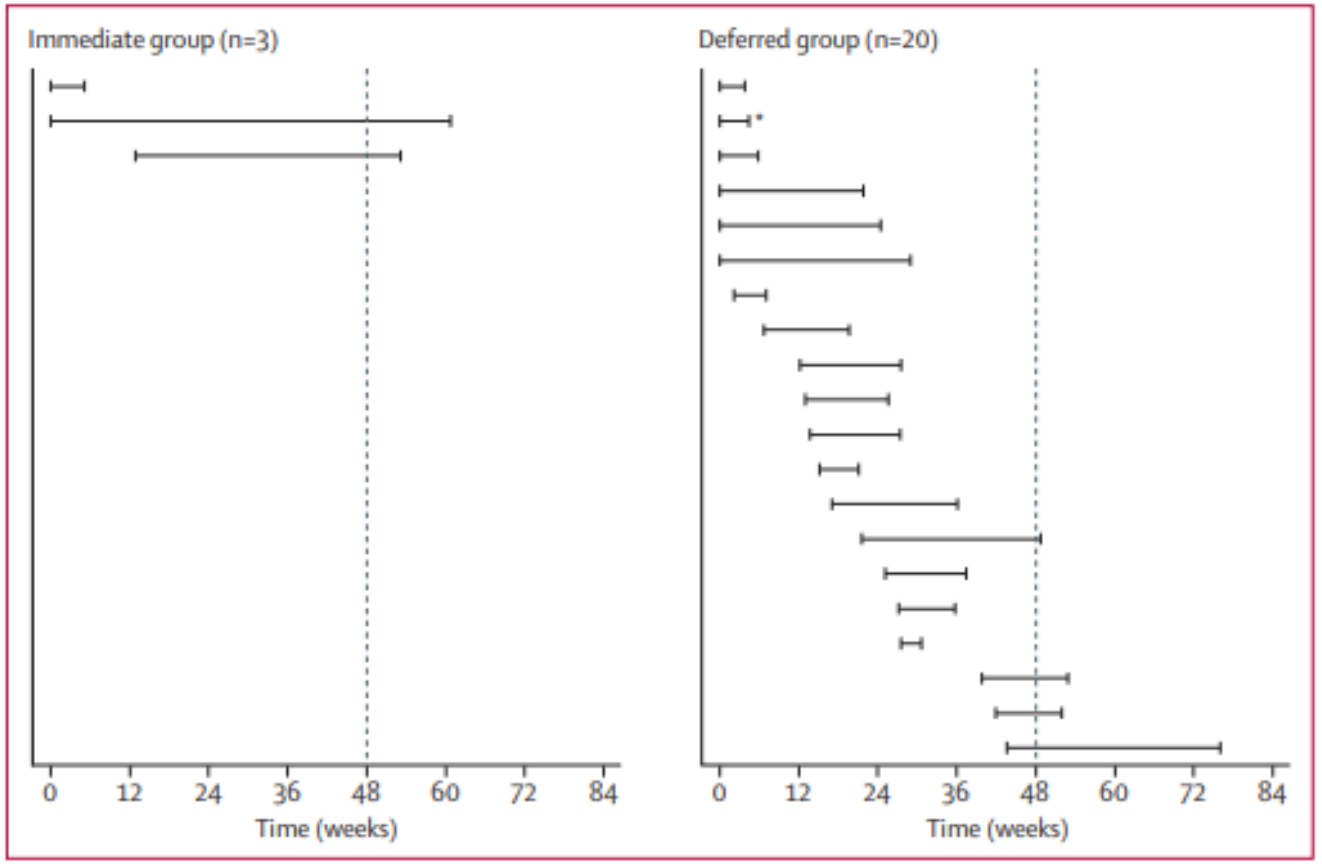


Figure 2: **Incident HIV infections**

Left bound for each HIV case represents last non-reactive HIV test; right bound represents first reactive HIV test. The dotted line represents time when participants in the deferred group became eligible for pre-exposure prophylaxis under the original protocol. *Had a stored enrolment sample that tested positive for HIV RNA but was retained in the analysis.

McCormack. Lancet 2016

Annual Review of Medicine

Long-Acting HIV Drugs for Treatment and Prevention

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Annu. Rev. Med. 2019. 70:137–50

HIV treatment as prevention

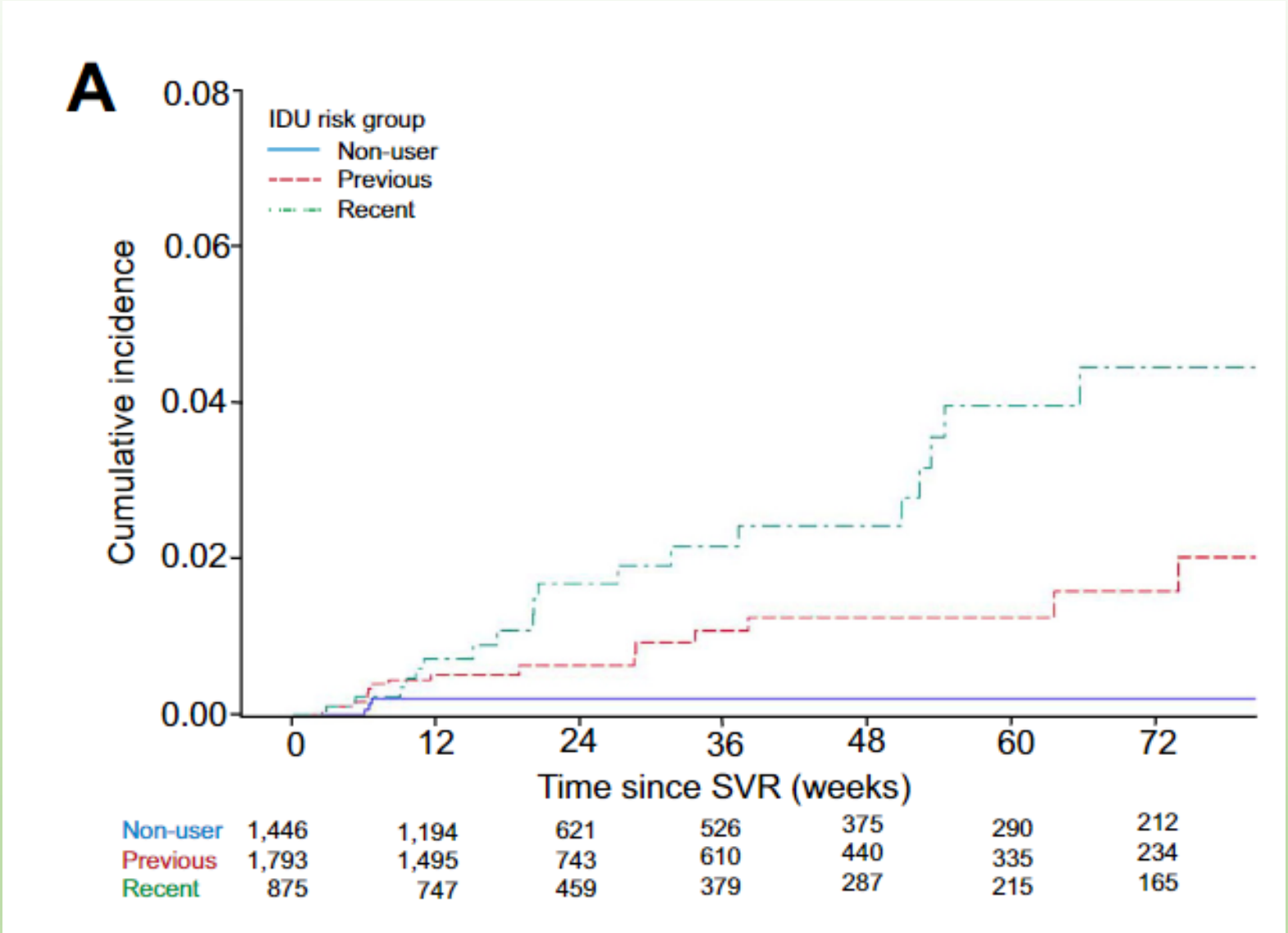
- Improvement in ART
  - Newer drugs
  - Low pill burden
  - Higher genetic barrier
  - Better side effect profile
  - Increased access
- Cost-efficient
- Lifelong treatment
  - Ensures long-term prevention

HIV treatment as prevention

- Other synergic tools
  - UTT
  - PrEP
  - New treatment options
- Solid evidence supporting early ART initiation

What can be learnt for HCV therapy?

- Awareness
- Increased testing
  - High risk groups
- Access to treatments/Costs
- Efficacious, safe therapies
- Behavioural/Harm reduction measures



Rossi C. J Hepatol 2018

Table 2. Comparison of Patients With Reinfection to the Overall Cohort

Risk factor for reinfection	Reinfection, n = 48	No Reinfection, n = 2298	*P* Value
Age, years, mean (± standard deviation)	46.1 (±8.2)	51.5 (±12.0)	<.001
Male sex, n (%)	48 (100%)	1447 (63.0%)	<.001
Cirrhosis, n (%)	5 (10.4%)	555 (24.2%)	.026
HIV coinfection, n (%)	38 (79.2%)	471 (20.5%)	<.001
Transmission, n (%)			
IVDU	9 (18.8%)	803 (34.9%)	.021
MSM	38 (79.2%)	221 (9.6%)	<.001
Needlestick injury	0	27 (1.2%)	1
Transfusion/surgery, etc.	0	352 (15.3%)	.001
Sexually, heterosexually	0	61 (2.7%)	.635
Vertical	0	11 (0.5%)	1
Tattoo	0	11 (0.5%)	1
Other/unknown	1 (2.1%)	812 (35.3%)	<.001
Treatment naive, n (%)	18 (37.5%)	1376 (59.9%)	.003
Opioid substitution, n (%)	14 (29.2%)	426 (18.5%)	.090
History of HCV cure before inclusion in GECCO, n (%)	15 (31.3%)	40 (1.7%)	<.001

Abbreviations: GECCO, German hepatitis C cohort; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IVDU, intravenous drug use; MSM, men who have sex with men.

Ingiliz P. Clin Infect Dis 2020

KEY POINTS

- Sexual transmission of HCV occurs predominantly amongst HIV-positive MSM in industrialized countries.
- Increasing cases of sexually transmitted HCV have been recognized amongst HIV-negative MSM accessing PrEP.
- Behavioural factors (high-risk sexual behaviours and sexualized drug use) appear to be driving this epidemic.
- In addition to the scale-up of DAA therapy, effective behavioural interventions and early identification of reinfections are essential to control the HCV epidemic amongst HIV-positive and HIV-negative MSM.

Lockart I. Curr Opin Infect Dis 2019