HIV Treatment as Prevention: Beyond 052 and 071

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HPTN Regional Meeting

Today's Agenda

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- What is Antiretroviral Therapy (ART) and Treatment as Prevention (TasP)?
- Landmark Studies of TasP
- Challenges to Achieve Population Levels of Prevention Intervention Efficacy
- Considerations
- Discussion

Current HIV Cascade Metrics

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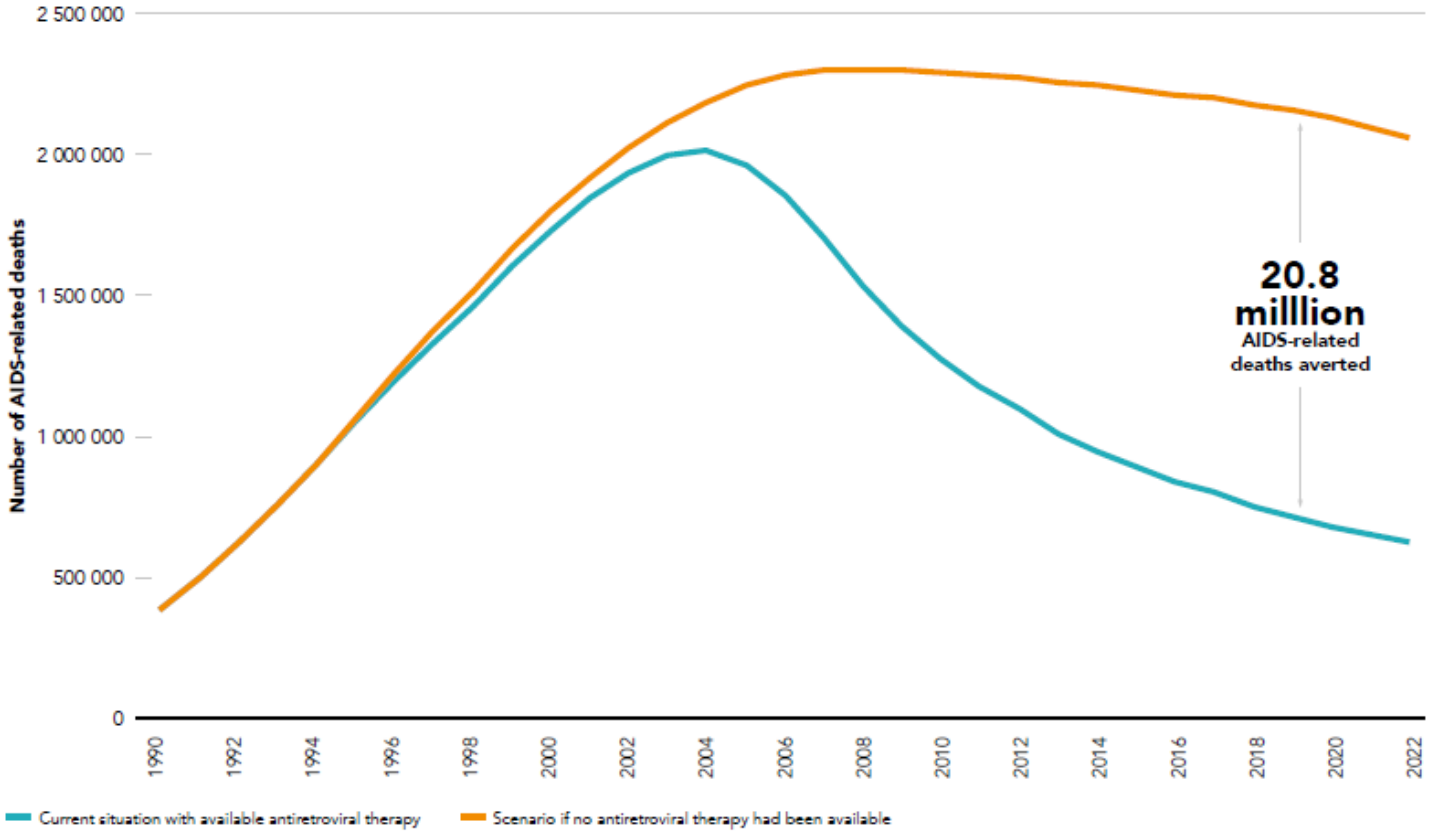
Figure 0.1 Number of AIDS-related deaths: current situation versus scenario without available antiretroviral therapy, 1990–2022



Source: UNAIDS special analysis of epidemiological estimates, 2023.

UNAIDS – 2023 UNAIDS Global AIDS Update. 2023.

HIV Treatment as Prevention - HPTN 052

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- **HIV Prevention Trials Network (HPTN) 052 (2005 – 2015):**
  Study randomly assigned 1,763 HIV-1 positive participants to receive early or delayed ART to then determine if any genetically linked HIV-1 infections occurred within couples

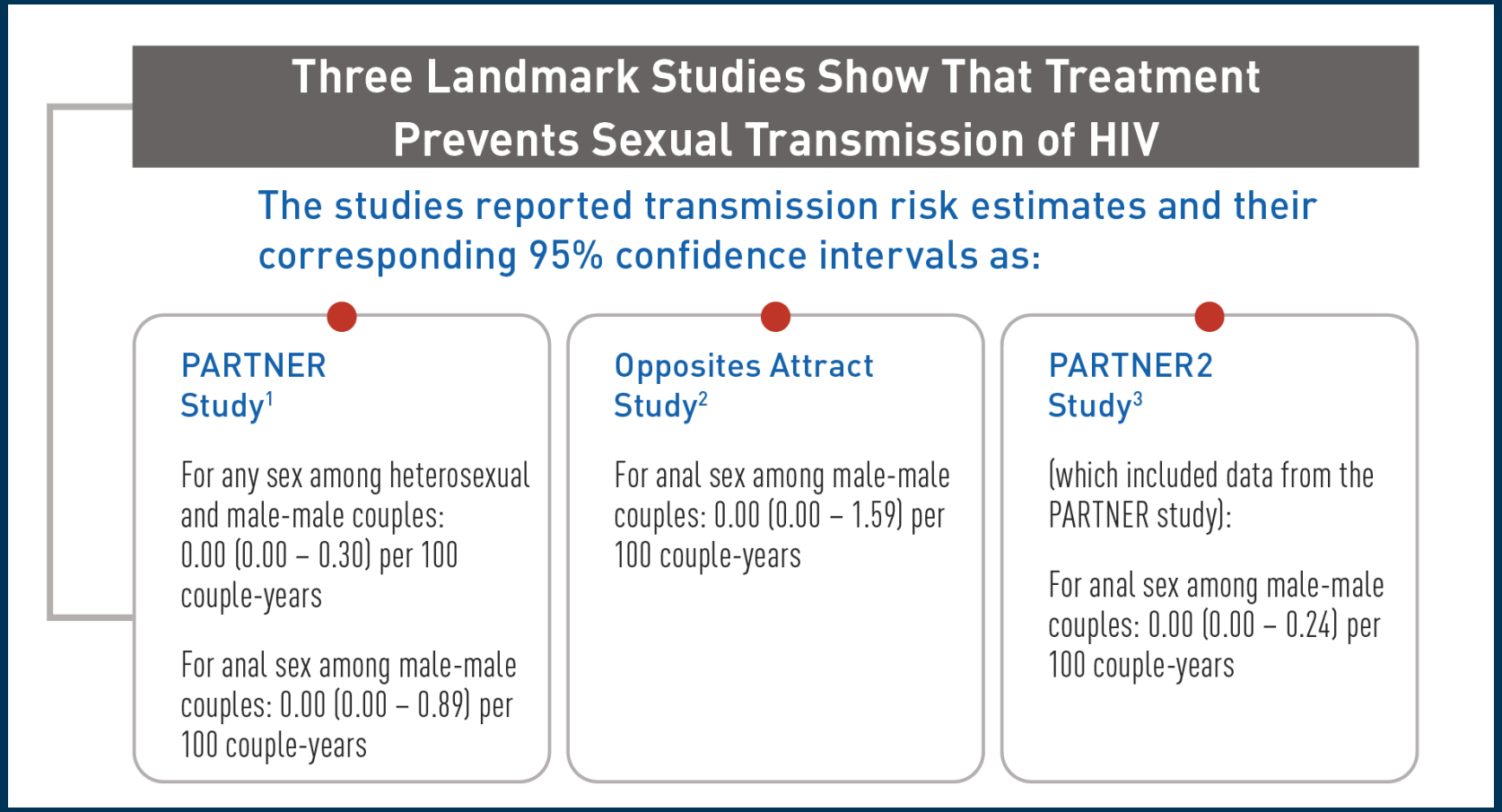
Table 1. Incidence of All Partner Infections and Linked Partner Infections, before and after the Interim Analysis.*

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

* Shown are data with respect to infections that were diagnosed among the partners of index participants during the HPTN 052 trial. Data are shown separately for linked partner infections and all partner infections (linked, unlinked, and linkage status not determined). On May 12, 2011, the investigators released interim study results showing that early antiretroviral therapy (ART) reduced genetically linked HIV-1 transmission by more than 96% and provided health benefits to the index participants. At that time, all index participants were offered ART, regardless of the CD4+ count. Follow-up then continued through May 3, 2015. CI denotes confidence interval.
† Hazard ratios for partner infections during the entire study period and the period before the interim analysis were calculated by means of unstratified univariate Cox regression analysis on an intention-to-treat basis. Rate ratios for partner infections during the period after the interim analysis were calculated according to the person-year analysis.
‡ Follow-up was determined according to the year after randomization.

Cohen MS, et al. N Engl J Med. 2016. DOI: 10.1056/NEJMoa1600693

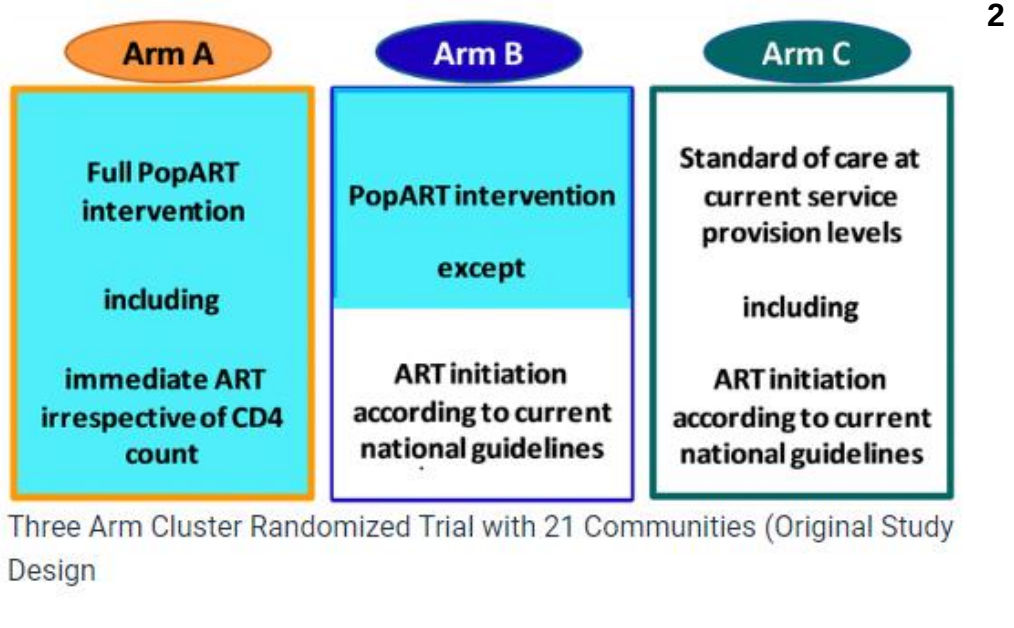
Landmark Observational Studies



Division of HIV Prevention, National Center for HIV, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention. How Does Treatment as Prevention Benefit My Patients with HIV?. Three Landmark Studies Show That Treatment Prevents Sexual Transmission of HIV. 2023. https://www.cdc.gov/hiv/clinicians/treatment-care/treatment-as-prevention.html

Landmark Studies

- **HPTN 071 - Population Effects of Antiretroviral Therapy to Reduce HIV Transmission (PopART Study) (2013 - 2018)[1]**



Three Arm Cluster Randomized Trial with 21 Communities (Original Study Design

2

	Arm A	Arm B	Arm C
HIV Incidence (geometric mean of community incidence rates)	198/12,990 (1.45%)	157/14,149 (1.06%)	198/12,563 (1.55%)
Adjusted Rate Ratio (95% CI)	0.93 (0.74, 1.18)	0.70 (0.55, 0.88)	1
Incidence compared to Arm C	7% reduction	30% reduction	
P value	0.51	0.006	

Adjusted for age category, sex and baseline community HIV prevalence.

3

[1]Hayes RJ, *et al*. N Engl J Med. 2019. DOI: 10.1056/NEJMoa1814556
[2]HIV Prevention Trials Network. PopART HPTN 071: Study Summary. https://www.hptn.org/research/studies/hptn071
[3]HPTN 071 (PopART) – Key Outcomes Web Conference. https://www.hptn.org/sites/default/files/inline-files/HPTN%20071%20Key%20Outcomes%20Web%20Conference%20%2827March2019%29.pdf

Landmark Studies

- **SEARCH Study (2013 – 2017):** Participants from 32 rural communities in Uganda and Kenya randomly assigned to control or intervention group for HIV testing/treatment

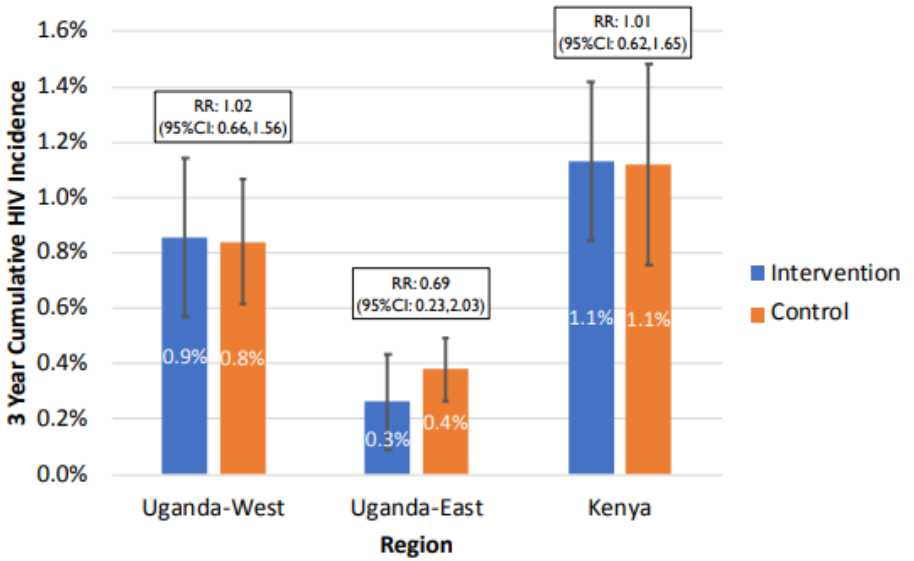
Table 2. Change in the Annual Incidence of HIV Infection over Time in the Intervention Group.*

Region	Incidence Rate per 100 Person-Yr			Relative Rate (95% CI)†
	Year 1	Year 2	Year 3	
All regions	0.43	0.38	0.31	0.68 (0.56–0.84)
Kenya	0.69	0.62	0.39	0.54 (0.39–0.75)
Western Uganda	0.35	0.35	0.38	1.03 (0.73–1.44)
Eastern Uganda	0.29	0.19	0.18	0.61 (0.39–0.95)

* The annual incidence rate of HIV infection per 100 person-years was calculated in three annual incidence cohorts of HIV-negative adults 15 years of age or older (including nonstable residents, persons who migrated into the community, and persons who migrated out) who had repeat annual HIV testing. At year 1, the analysis included 52,474 persons, representing 51,975 person-years of follow-up; at year 2, the analysis included 55,531 persons, representing 53,371 person-years of follow-up; at year 3, the analysis included 58,145 persons, representing 52,567 person-years of follow-up. For incident infections, the date of infection was imputed as the midpoint of the time between repeat HIV tests.

† The relative rate (year 3 vs. year 1) was based on Poisson generalized estimating equations with an exchangeable covariance matrix, with adjustment for age, sex, and mobility (i.e., at least 1 month of the previous year spent outside the community).

Figure S14: Three-year HIV Cumulative Incidence in Intervention vs. Control Arm by Region. Among incidence cohort of baseline HIV-uninfected stable residents who were alive, not out-migrated and had HIV serostatus measured at Year 3. Uganda-West: N= 31,633; Uganda-East: N= 33,916; Kenya: N= 29,534. Comparison between arms based on community-level TMLE.



Havlir DV, et al. N Engl J Med. 2019. DOI: 10.1056/NEJMoa1809866

What Does the Totality of the Data Tell Us?

- **Key Challenges to Effective HIV Prevention with ART in High-Burden Settings**

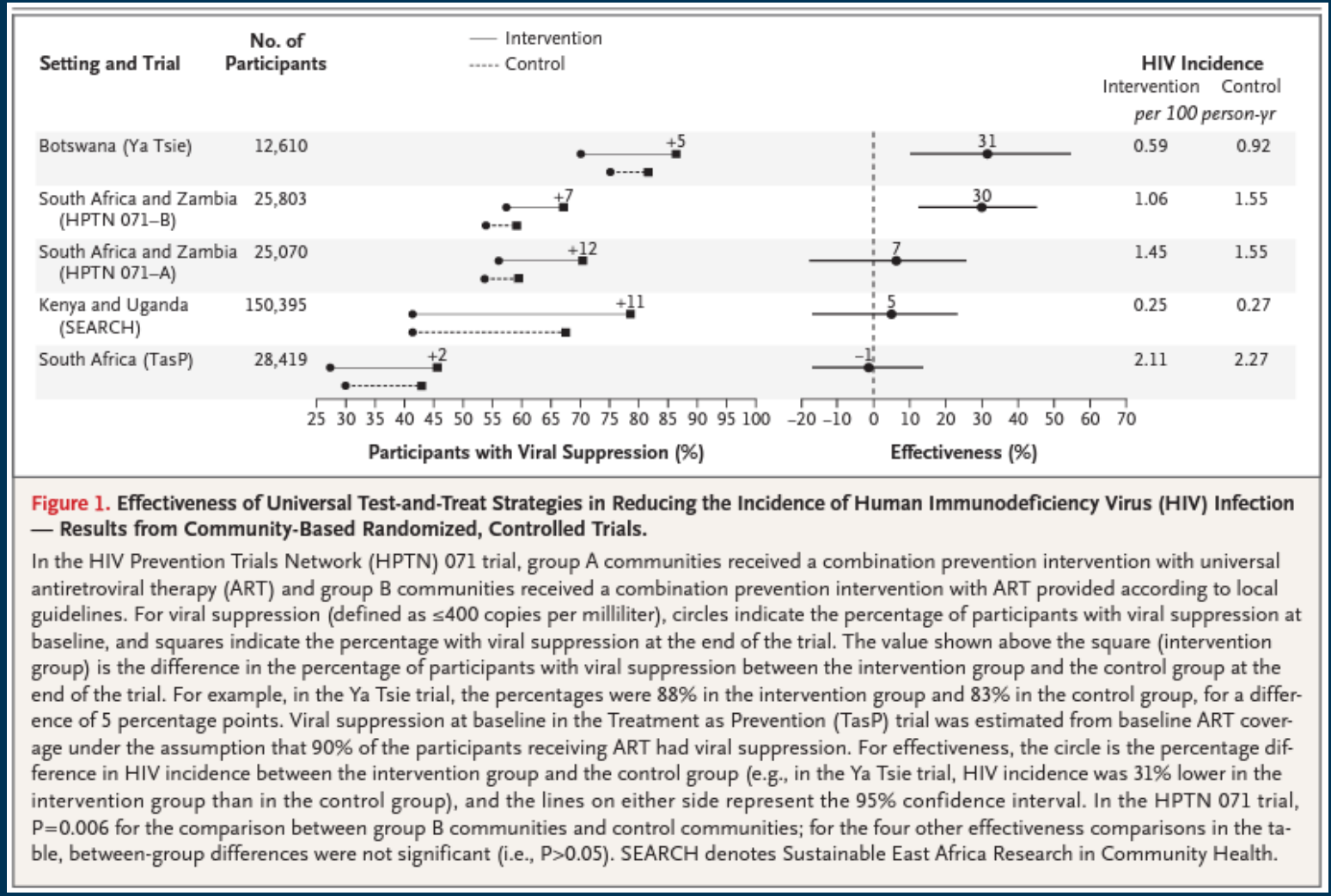
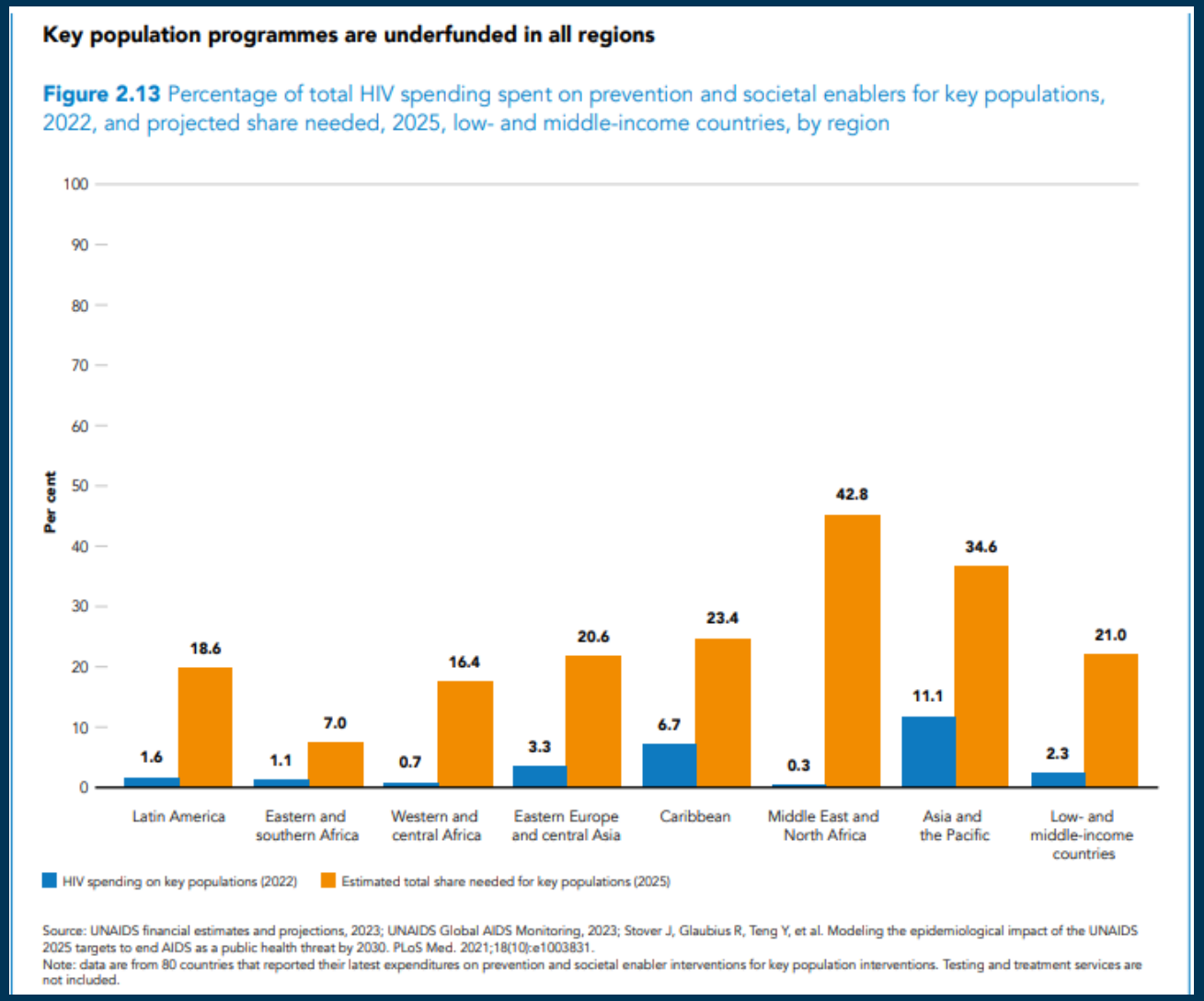


Figure 1. Effectiveness of Universal Test-and-Treat Strategies in Reducing the Incidence of Human Immunodeficiency Virus (HIV) Infection — Results from Community-Based Randomized, Controlled Trials.

In the HIV Prevention Trials Network (HPTN) 071 trial, group A communities received a combination prevention intervention with universal antiretroviral therapy (ART) and group B communities received a combination prevention intervention with ART provided according to local guidelines. For viral suppression (defined as ≤400 copies per milliliter), circles indicate the percentage of participants with viral suppression at baseline, and squares indicate the percentage with viral suppression at the end of the trial. The value shown above the square (intervention group) is the difference in the percentage of participants with viral suppression between the intervention group and the control group at the end of the trial. For example, in the Ya Tsie trial, the percentages were 88% in the intervention group and 83% in the control group, for a difference of 5 percentage points. Viral suppression at baseline in the Treatment as Prevention (TasP) trial was estimated from baseline ART coverage under the assumption that 90% of the participants receiving ART had viral suppression. For effectiveness, the circle is the percentage difference in HIV incidence between the intervention group and the control group (e.g., in the Ya Tsie trial, HIV incidence was 31% lower in the intervention group than in the control group), and the lines on either side represent the 95% confidence interval. In the HPTN 071 trial, P=0.006 for the comparison between group B communities and control communities; for the four other effectiveness comparisons in the table, between-group differences were not significant (i.e., P>0.05). SEARCH denotes Sustainable East Africa Research in Community Health.

Abdool Karim SS. N Engl J Med. 2019. DOI: 10.1056/NEJMe1907279

Barriers to Treatment for PLWH



- Stigma and Discrimination
- Gender and other inequalities
- Discriminatory criminal laws
- Lack of funding for key populations

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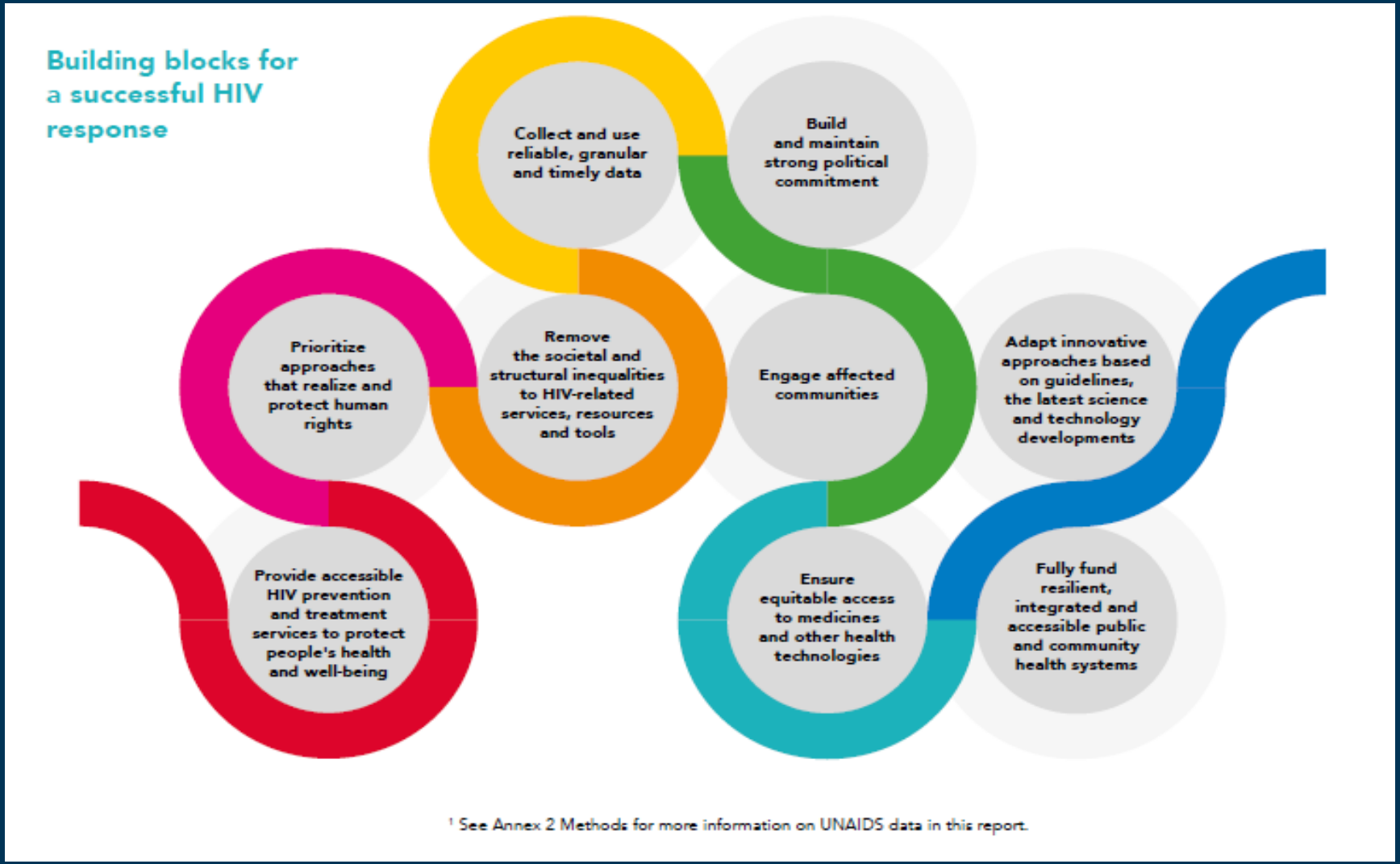
Addressing Barriers



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Research Questions

- Would providing HIV treatment (ART) to at-risk populations regardless of HIV status help reduce costs on testing and diagnosis?
- Treatment: Injections vs. Pills
  - Would this improve viral suppression?
  - Would acceptance levels improve?
- How can we expand the reach of prevention interventions? How to improve care/prevention cascade?
- What other social/structural factors affect viral suppression?

Potential Solutions/Study Ideas

- **Would providing HIV treatment (ART) to at-risk populations regardless of HIV status help reduce costs on testing and diagnosis?**
  - Universal testing could be too costly and instead use a targeted approach[1]
  - However, limiting HIV testing to high-risk groups can miss individuals with unknown HIV status[1]
  - Andrew Phillips has proposed a “universal” TLD community randomized study
    - Modeling (*Phillips Lancet HIV 2023*)
    - Numerous potential advantages
  - Could an “injectable” version of this be ready for “prime time”?

[1] Havlir D, *et al*. JIAS. 2020. https://doi.org/10.1002/jia2.25455

Potential Solutions/Study Ideas
Integrated Strategies

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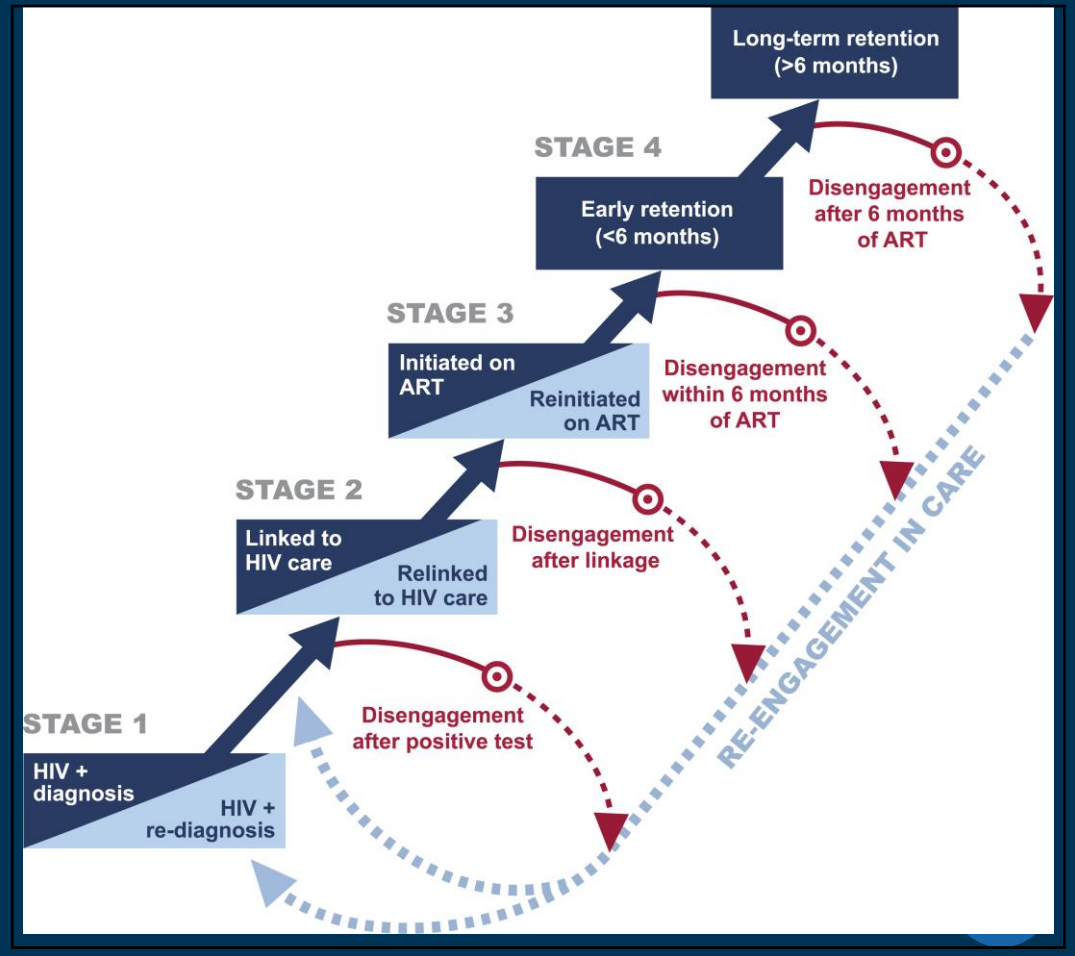
- **Streamlining Prevention/Care Cascade & Expanding Reach**
  - Cyclical cascade of HIV care (Revolving door of HIV care)[1]
  - Patient-centered Care/Programs[2]
  - Implement "warm handoffs" for care coordination instead of just referrals[3]
  - Rapid and Same-day ART Initiation[2]
  - Client-managed community adherence and support groups[2]
  - Tailored interventions[4]

1



[1] Ehrenkranz P, *et al*. PLoS Med. 2021. https://doi.org/10.1371/journal.pmed.1003651
[2] Levitt D, Lillie T. Long-Term HIV Treatment Adherence for Key Populations: Program Considerations. FHI 360; Durham (NC): 2020.
[3] Bacon OML, *et al*. Am J Prev Med. 2021. https://doi.org/10.1016/j.amepre.2021.06.001
[4] Havlir D, *et al*. JIAS. 2020. https://doi.org/10.1002/jia2.25455

Potential Solutions/Study Ideas

- **What about PWID?**
  - Is it possible (is it needed) to do an 052-likes study for PWID vis a vis parenteral transmission?
  - Is this better approached from a TREATMENT perspective, PREVENTION perspective, or BOTH?
  - How does Substance Abuse treatment (if applicable) get co-administered?
  - Are SA treatment strategies in-and-of themselves HIV prevention strategies?

Thank you

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