What the Science is Saying: making the case for Treat All

CARICOM SECRETARIAT
Georgetown, Guyana
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PANCAP- Knowledge for Health Project

Outline

- History of HIV and Fundamentals of Antiretorvirals (ARVS)
- Antiretroviral therapy's role in Prevention

✓Making the case for **Treat All**

✓PreP

✓Post exposure prophylaxis

✓Voluntary Male Medical Circumcision

✓Condom use

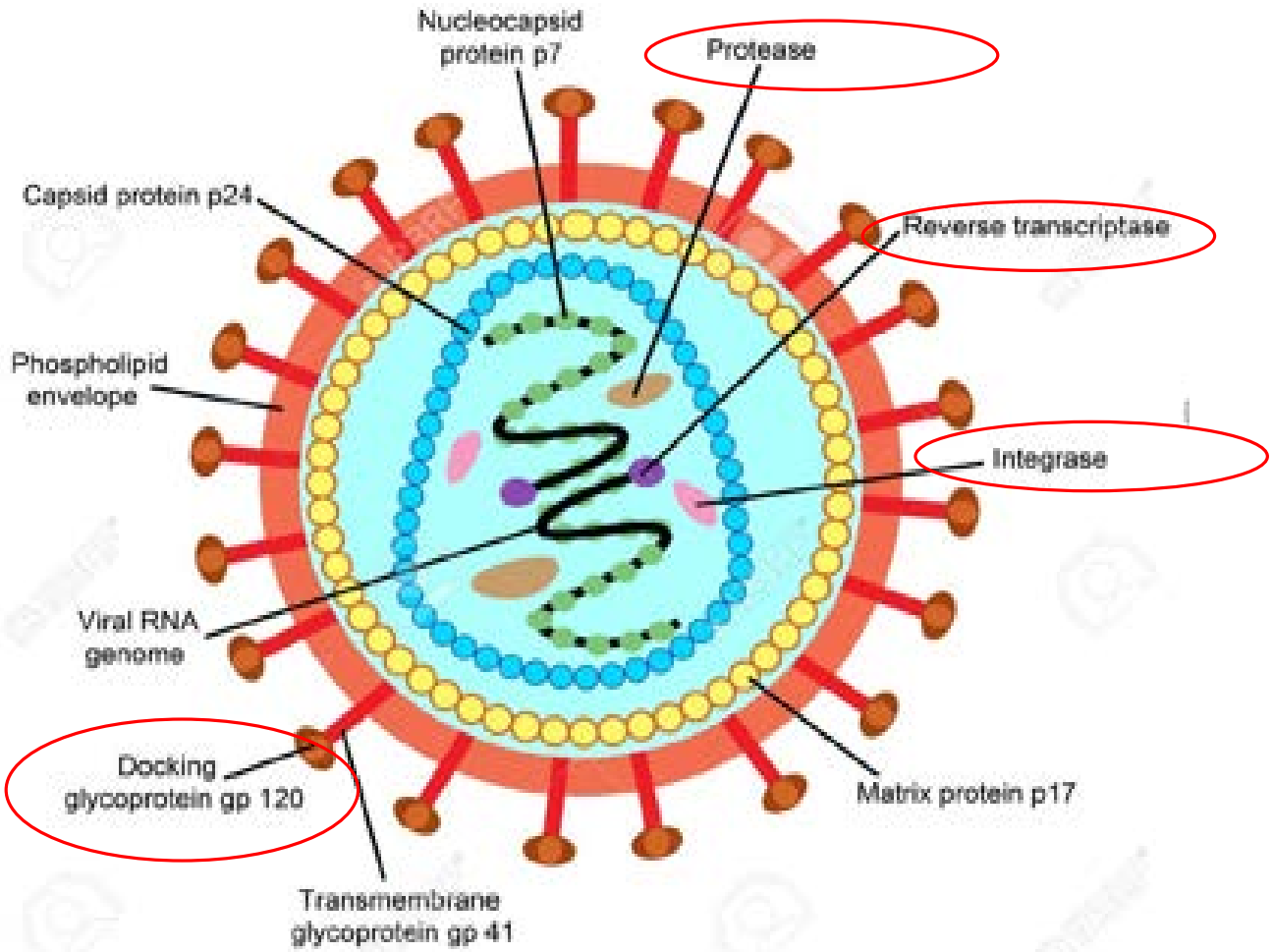
✓90-90-90 and Ending AIDS

History of HIV and Antiretroviral Therapy (ART)

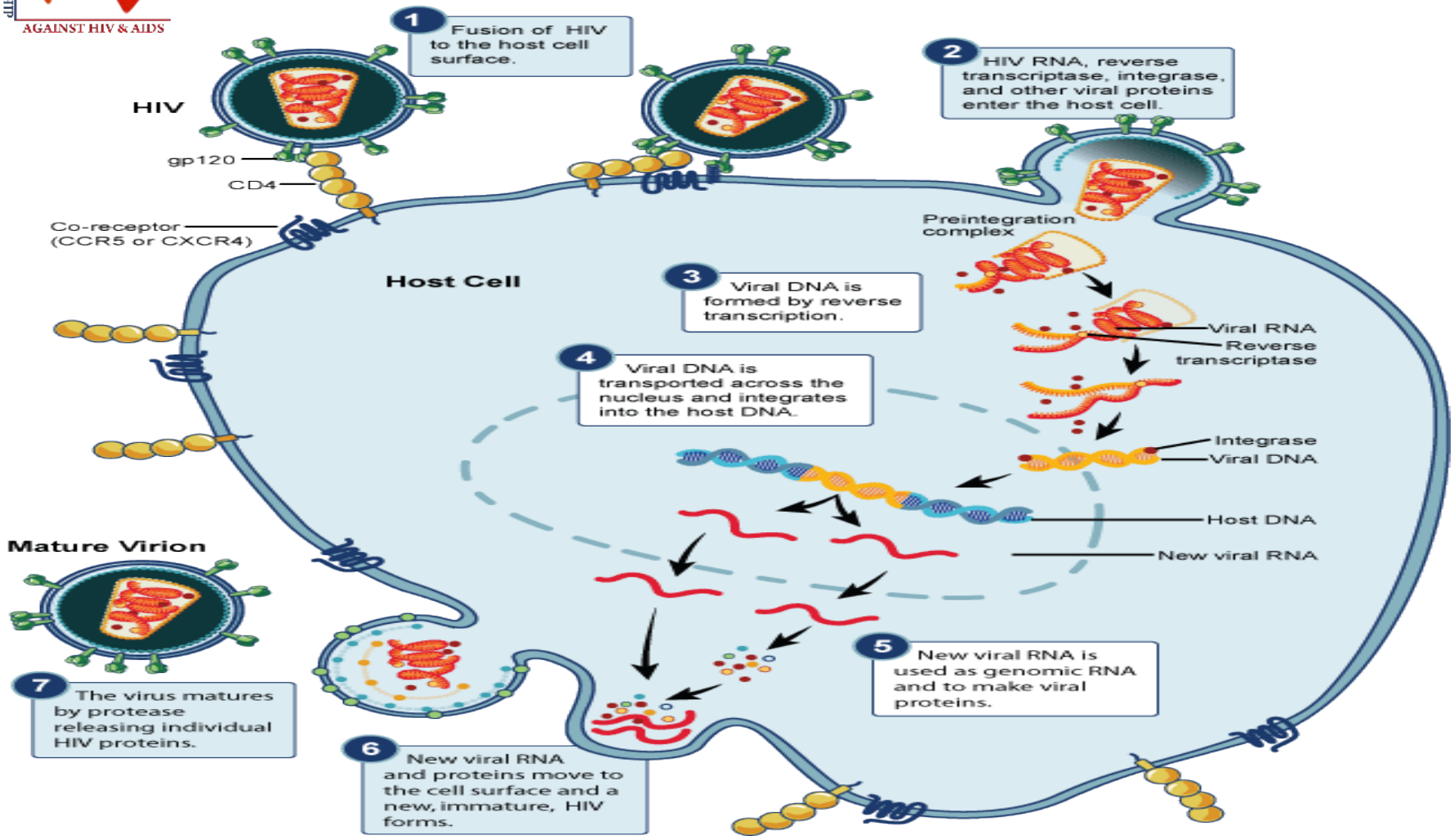
- **1981**: 5 cases of PCP in gay men from UCLA (MMWR)
- By the end of 1981, there was a cumulative total of 270 reported cases of severe immune deficiency among gay men, and 121 of those individuals had died.
- **1983**: Luc Montagnier and Françoise Barré-Sinoussi reported the discovery of a new virus (later called HIV) that is the cause of AIDS.
- **1985**: The first commercial blood test for HIV was licensed, allowing screening of the U.S. blood supply.
- **1987**:the first anti-HIV drug (AZT) was approved by the U.S. Food and Drug Administration.
- **1995**: The first potent combination of anti-HIV drugs became available.

Gottlieb MS NEJM 2001;344:1788-91

HIV Structure



Life Cycle of HIV; Drug targets



Four Prevention Opportunities

Status	Prevention Measure	Timing
Uninfected, unexposed	Behavioral, structural interventions (**eg, condoms, circumcision**)	Years
Uninfected, exposed (precoital/coital)	PrEP	Hours
Uninfected, exposed (postcoital)	PEP	72 hours
Infected	Treatment of HIV to reduce infectivity	Years

Cohen MS, et al. J Clin Invest. 2008;118:1244-1254.
Cohen MS, et al. J Int AIDS Soc. 2008;11:4.

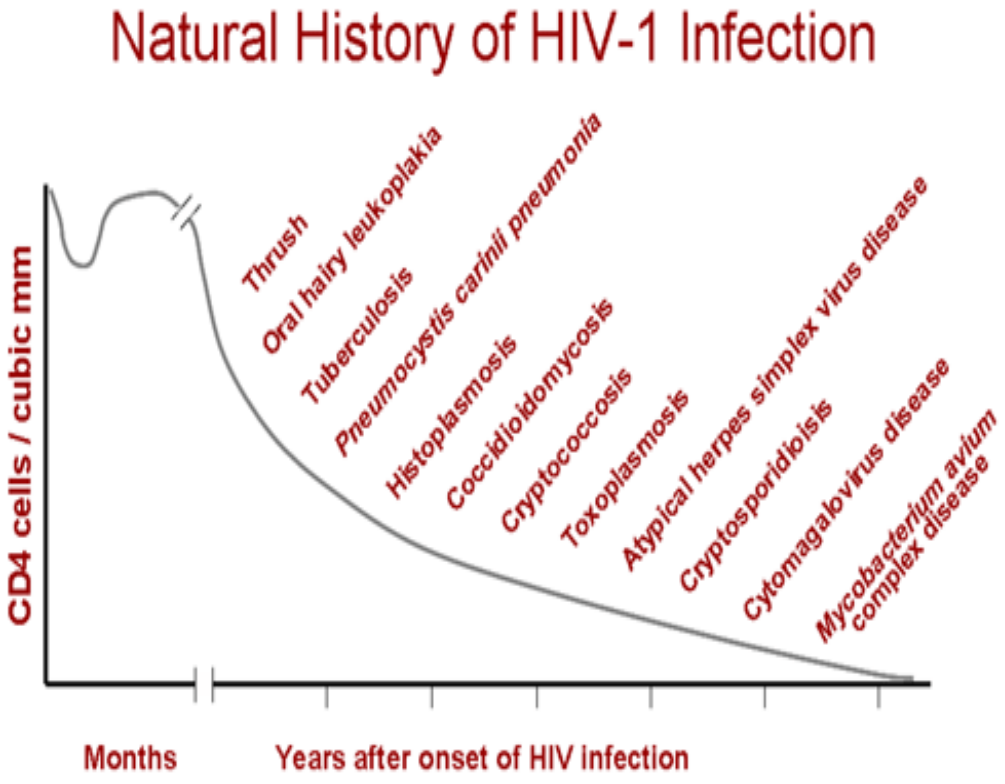
Slide credit: clinicaloptions.com

WHAT IS TREAT ALL?

Making the case for Treat All

Treat All- *Initiating ART among all adults living with HIV regardless of WHO clinical stage or at any CD4 cell count.*

No treatment-AIDS (CD4 <200)-Advanced disease (CD4<350)-CD4 <500- Treat All



Treat All:

- ✓Reduces mortality, improves survivability.
- ✓Reduces morbidity and
- ✓Reduces HIV transmission.

How do we know this?

START trial

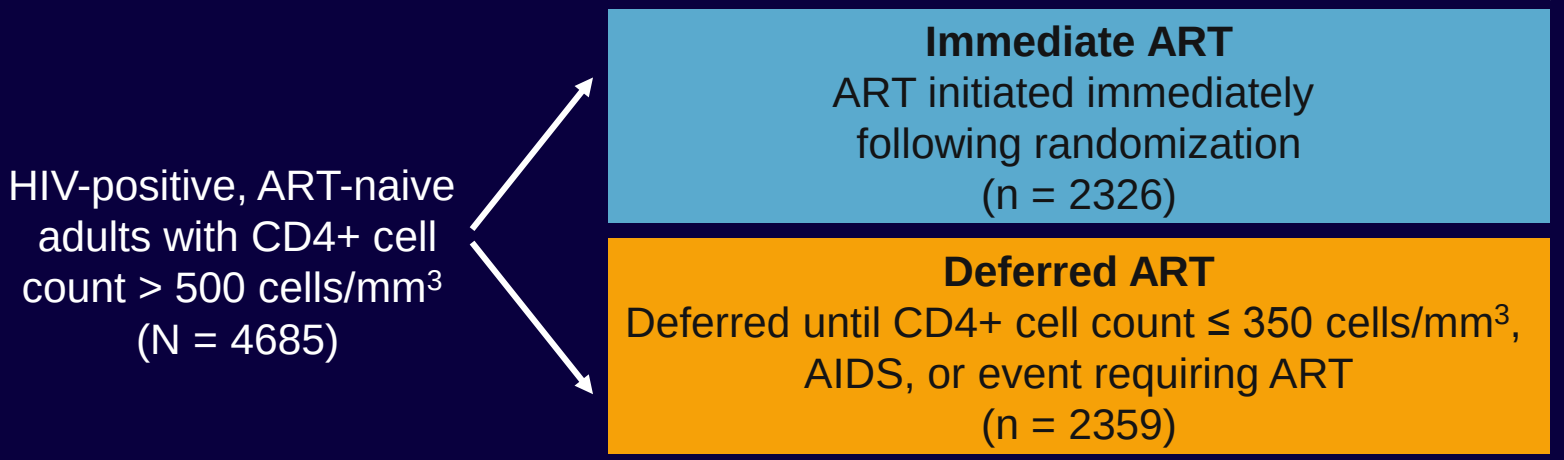
Temprano Study

HPTN 052

START: Immediate vs Deferred Therapy for Asymptomatic, ART-Naive Pts

- International, randomized trial

Study closed by DSMB following interim analysis

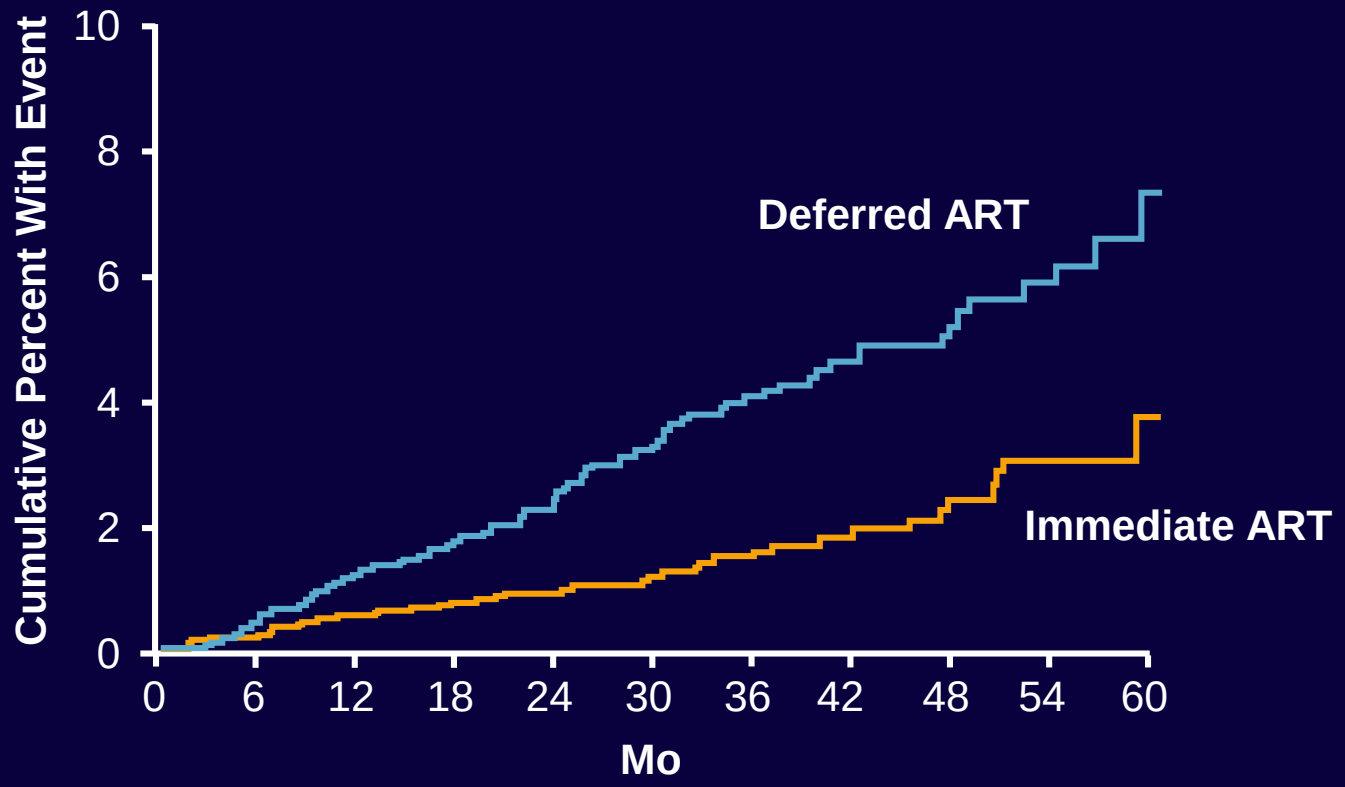


- Composite primary endpoint: any serious AIDS-related (AIDS-related death or AIDS-defining event) or non-AIDS–related event (non-AIDS–related death, CVD, end-stage renal disease, decompensated liver disease, non-AIDS–defining cancer)
- Mean follow-up: 3 yrs; median baseline CD4+ cell count: 651 cells/mm^3; median baseline HIV-1 RNA: 12,759 copies/mL
- Median CD4+ cell count at initiation of ART for deferred group: 408 cells/mm^3

INSIGHT START Study Group. N Engl J Med. 2015;373:795-807. Lundgren J, et al. IAS 2015. Abstract MOSY0302.

START: 57% Reduced Risk of Serious Events or Death With Immediate ART

- 4.1% vs 1.8% in deferred vs immediate arms experienced serious AIDS or non-AIDS–related event or death (HR: 0.43; 95% CI: 0.30-0.62; *P* < .001)



INSIGHT START Group. N Engl J Med. 2015;373:795-807. Lundgren J, et al. IAS 2015. Abstract MOSY0302. Reproduced with permission.

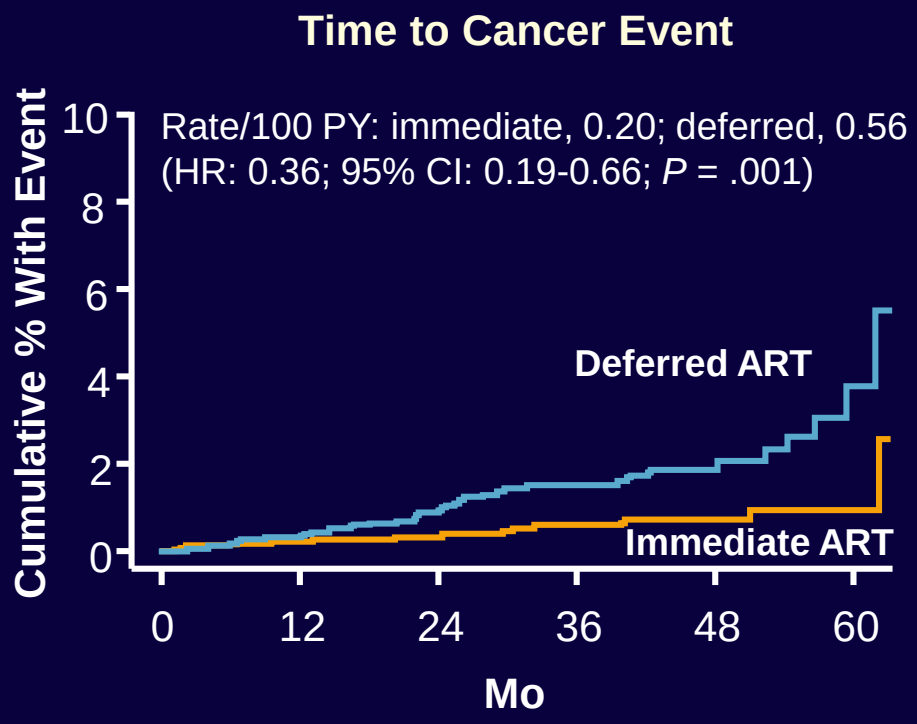
START: Primary Endpoint Components With Immediate vs Deferred ART

Endpoint	Immediate ART (n = 2326)		Deferred ART (n = 2359)		HR (95% CI)	*P* Value
	N	Rate/100 PY	N	Rate/100 PY		
Serious AIDS-related event	14	0.20	50	0.72	0.28 (0.15-0.50)	< .001
Serious non-AIDS–related event	29	0.42	47	0.67	0.61 (0.38-0.97)	.04
All-cause death	12	0.17	21	0.30	0.58 (0.28-1.17)	.13
Tuberculosis	6	0.09	20	0.28	0.29 (0.12-0.73)	.008
Kaposi's sarcoma	1	0.01	11	0.16	0.09 (0.01-0.71)	.02
Malignant lymphoma	3	0.04	10	0.14	0.30 (0.08-1.10)	.07
Non-AIDS–defining cancer	9	0.13	18	0.26	0.50 (0.22-1.11)	.09
CVD	12	0.17	14	0.20	0.84 (0.39-1.81)	.65

INSIGHT START Group. N Engl J Med. 2015;373:795-807. Lundgren J, et al. IAS 2015. Abstract MOSY0302.

START: Cancer Events With Immediate vs Deferred ART

Cancer Event, n	Immediate ART (n = 2326)	Deferred ART (n = 2359)
Total	**14**	**39**
Kaposi's sarcoma	1	11
Lymphoma, NHL + HL	3	10
Prostate cancer	2	3
Lung cancer	2	2
Anal cancer	1	2
Cervical or testis cancer	1	2
Other types*	4	9



*Immediate ART: squamous cell carcinoma, plasma cell myeloma, bladder cancer, fibrosarcoma. Deferred ART: gastric adenocarcinoma, breast cancer, ureteric cancer, malignant melanoma, myeloid leukemia, thyroid cancer, leiomyosarcoma, liver cancer, squamous cell carcinoma of head and neck.

INSIGHT START Group. N Engl J Med. 2015;373:795-807. Lundgren J, et al. IAS 2015. Abstract MOSY0302. Reproduced with permission.

TEMPRANO: Immediate or Deferred ART Initiation ± IPT for African Pts

- Randomized, controlled, unblinded, multicenter (Ivory Coast), 2 x 2 factorial

Pts with HIV infection and CD4+ cell count < 800 cells/mm^3 who did not meet WHO criteria for initiating ART* (N = 2056)

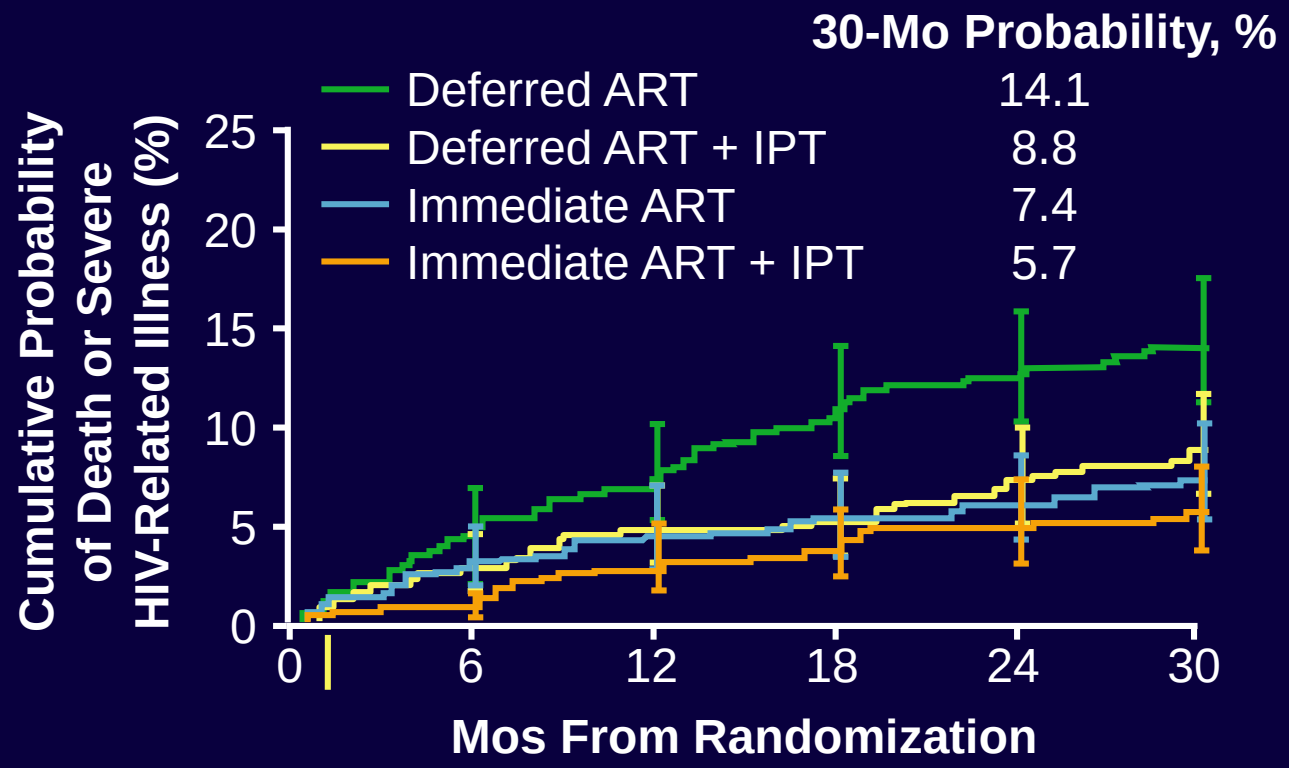
- **Immediate ART†** (n = 515)
- **Immediate ART† + IPT‡** (n = 518)
- **Deferred ART§** (n = 511)
- **Deferred ART§ + IPT‡** (n = 512)

*WHO criteria evolved during the study (updates 2006, 2010, 2013). †ART initiated immediately following randomization. ‡IPT = 300 mg daily isoniazid initiated 1 mo after enrollment and terminated 7 mos after enrollment. §Deferred until meeting WHO criteria for initiating ART.

- Pts in the treatment arms well matched at baseline
  - First-line ART primarily EFV + TDF/FTC (68% to 71%) or LPV/RTV + TDF/FTC (22% to 24%)
- Median duration of follow-up: 29.9 mos

TEMPRANO ANRS 12136 Study Group. N Engl J Med. 2015;373:808-822.

TEMPRANO: Immediate vs Deferred ART Initiation and IPT Delivery for African Pts

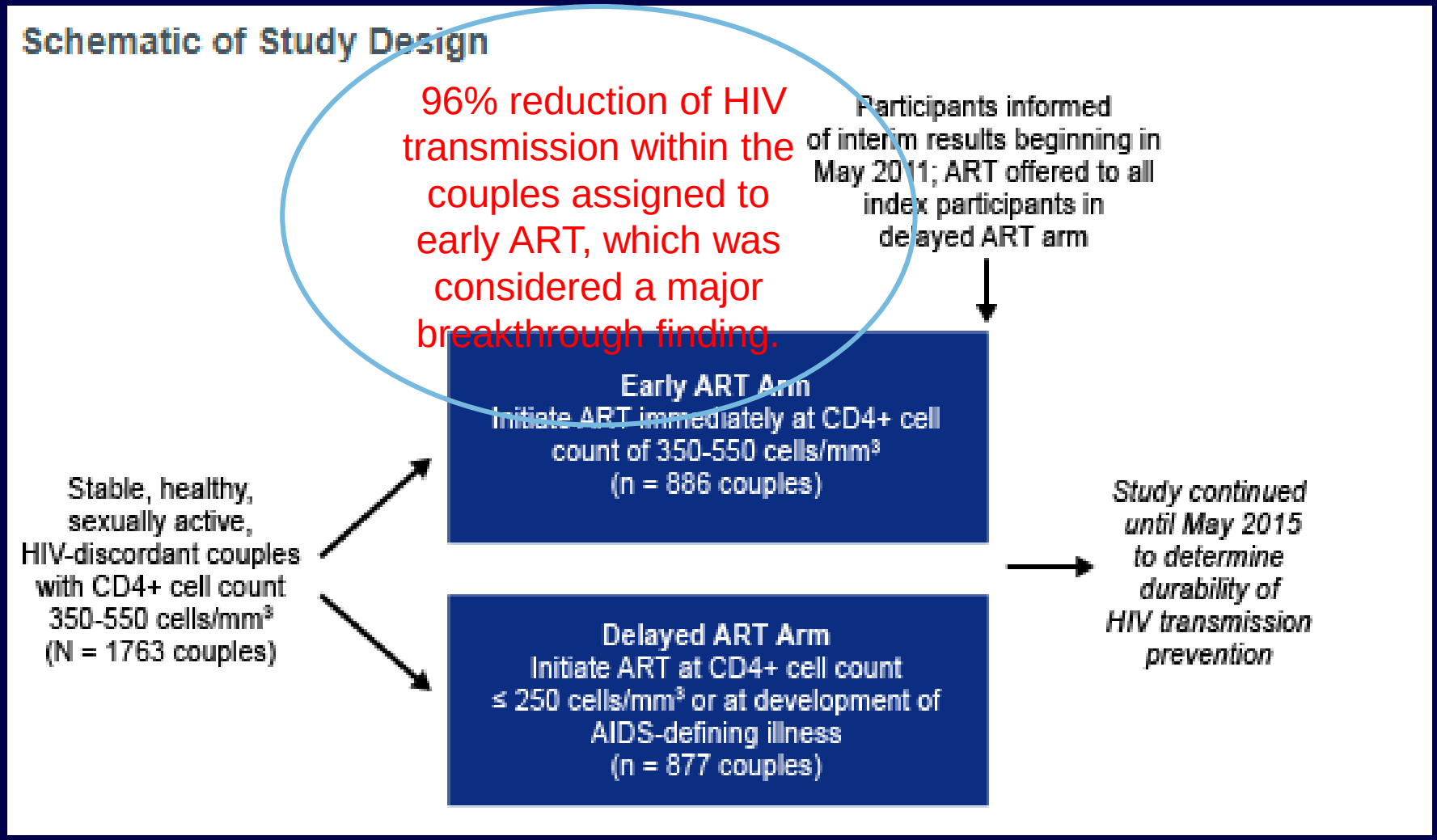


TEMPRANO ANRS 12136 Study Group. N Engl J Med. 2015;373:808-822.

13 sites in 9 countries - 2005

HPTN 052

Primary endpoint - Virologically linked partner infections



HPTN 052: Partner Infections With Early vs Delayed ART

- No linked HIV transmissions observed when index participant stably suppressed on ART

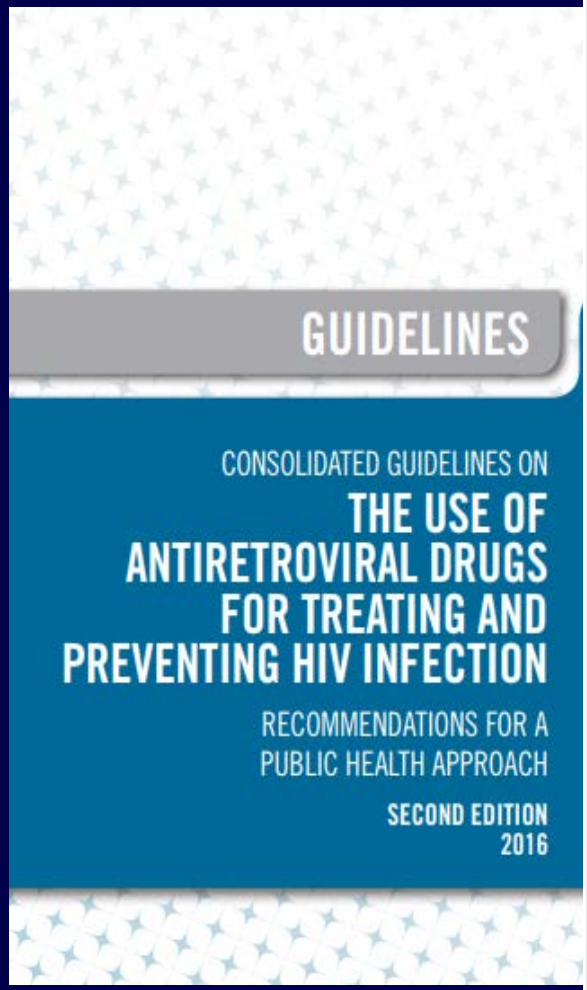
Partner Infections, n (rate/100 PY)	April 2005 - May 2011		May 2011 - May 2015		Overall (April 2005 - May 2015)	
	Early (1751 PY F/U)	Delayed (1731 PY F/U)	Early (2563 PY F/U)	Delayed (2449 PY F/U)	Early (4314 PY F/U)	Delayed (4180 PY F/U)
All	4 (0.23)	42 (2.43)	15 (0.59)	17 (0.69)	19 (0.44)	59 (1.41)
Linked	1 (0.06)	36 (2.08)	2 (0.08)	7 (0.29)	3 (0.07)	43 (1.03)
Risk Reduction With Early ART, %						
All infections	91	--	14	--	69	--
Linked infections	97	--	72	--	93	--

- 8 linked HIV infections diagnosed after seropositive pt started ART
  - 4 infections likely occurred before, or soon after, ART initiation, and 4 infections occurred after ART failure in seropositive pt
- Unlinked partner infection rates similar between study arms

Cohen MS, et al. IAS 2015. Abstract MOAC0101LB.

Early ART associated with 93% reduction in risk of linked HIV transmission

Offer ART to persons with CD4>350 in serodiscordant relationships



4. CLINICAL GUIDELINES: ANTIRETROVIRAL THERAPY

4.3 When to start ART

NEW 4.3.1 When to start ART in adults (>19 years old)	ART should be initiated in all adults living with HIV, regardless of WHO clinical stage and at any CD4 cell count (strong recommendation, moderate-quality evidence).
	As a priority, ART should be initiated in all adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adults with a CD4 count ≤350 cells/mm³ (strong recommendation, moderate-quality evidence).
NEW 4.3.2 When to start ART in pregnant and breastfeeding women	ART should be initiated in all pregnant and breastfeeding women living with HIV, regardless of WHO clinical stage and at any CD4 cell count and continued lifelong (strong recommendation, moderate-quality evidence).
NEW 4.3.3 When to start ART in adolescents (10–19 years of age)	ART should be initiated in all adolescents living with HIV, regardless of WHO clinical stage and at any CD4 cell count (conditional recommendation, low-quality evidence). As a priority, ART should be initiated in all adolescents with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adolescents with a CD4 count ≤350 cells/mm³ (strong recommendation, moderate-quality evidence).
4.3.4 When to start ART in children younger than 10 years of age	NEW ART should be initiated in all children living with HIV, regardless of WHO clinical stage or at any CD4 cell count:
	• Infants diagnosed in the first year of life (strong recommendation, moderate-quality evidence).
	NEW • Children living with HIV 1 year old to less than 10 years old (conditional recommendation, low-quality evidence).
	As a priority, ART should be initiated in all children <2 years of age or children younger than 5 years of age with WHO clinical stage 3 or 4 or CD4 count ≤750 cells/mm³ or CD4 percentage <25% and children 5 years of age and older with WHO clinical stage 3 or 4 or CD4 count ≤350 cells/mm³ (strong recommendation, moderate-quality evidence).

ART should be initiated in all adults living with HIV, regardless of WHO clinical stage and at any CD4 cell count

Making the case for Treat All

Treat All- Initiating ART among all adults living with HIV regardless of WHO clinical stage or at any CD4 cell count.

Treat All:

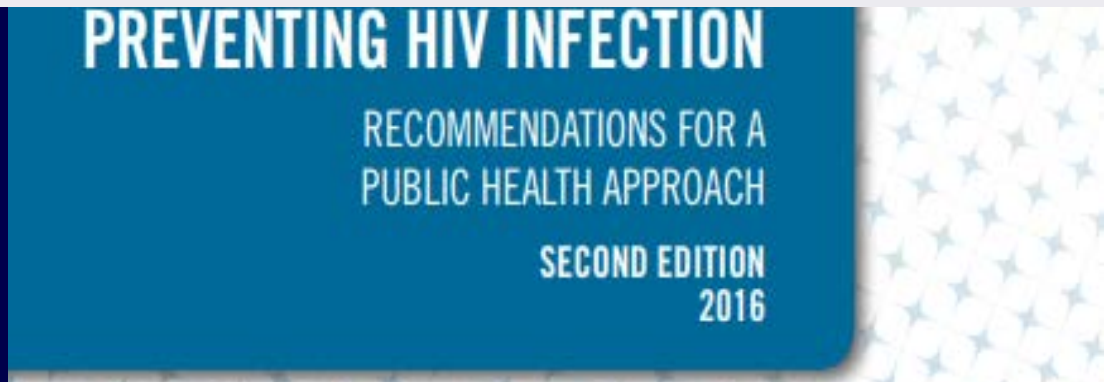
- ✓Reduces mortality, improves survivability.
- ✓Reduces morbidity and
- ✓Reduces HIV transmission.

NEW

Recommendation

Oral pre-exposure prophylaxis (PrEP) containing TDF should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination HIV prevention approaches (strong recommendation, high-quality evidence).

Source: Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva: World Health Organization; 2015 (http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en).



12 Prep Studies

Four Prevention Opportunities

Status	Prevention Measure	Timing
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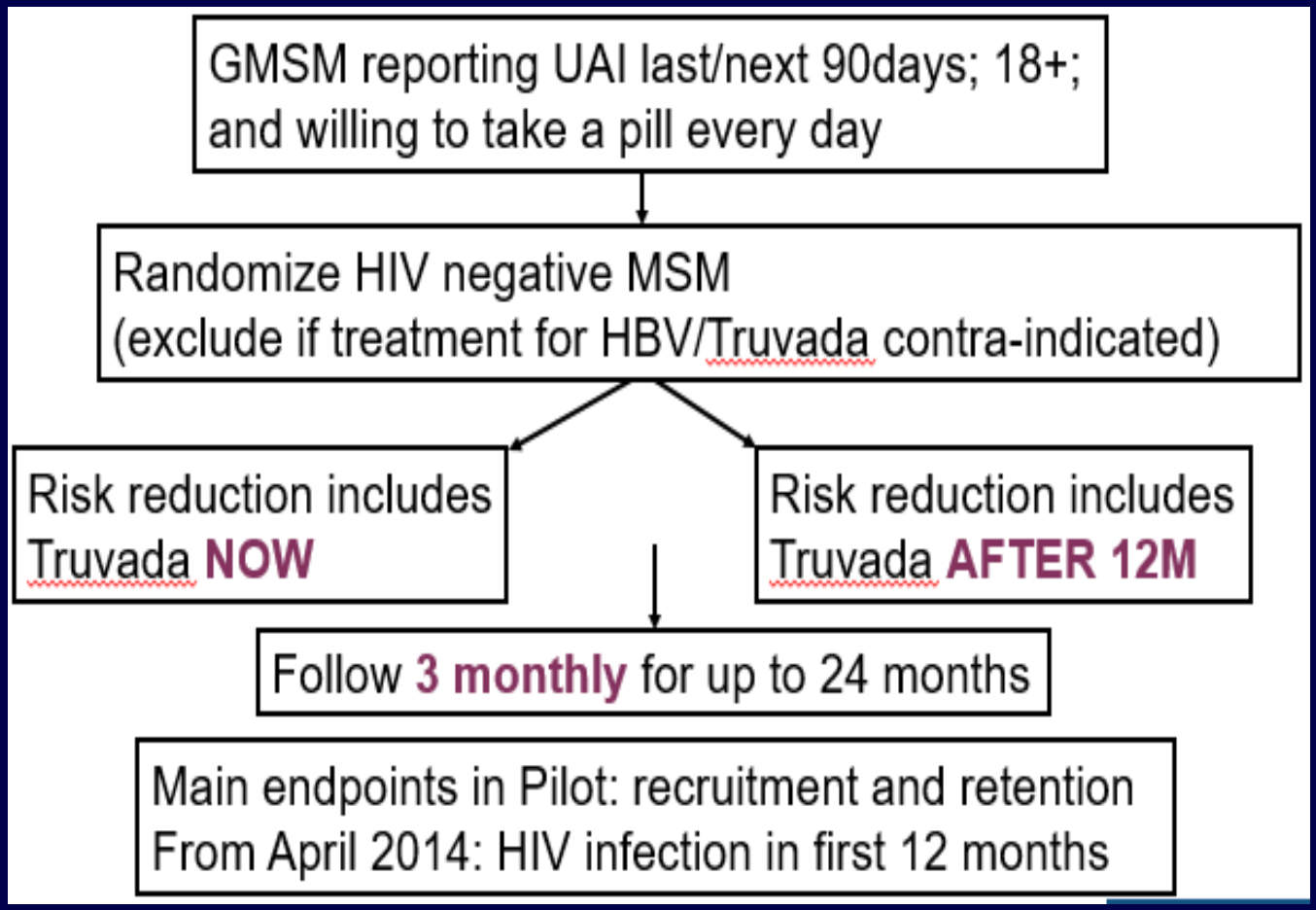
Infected	Treatment of HIV to reduce infectivity	Years

Cohen MS, et al. J Clin Invest. 2008;118:1244-1254.
Cohen MS, et al. J Int AIDS Soc. 2008;11:4.

Slide credit: clinicaloptions.com

WHAT IS PrEP?

PROUD



554 persons enrolled
276 in the immediate arm and 269 in the deferred arm

PROUD Study

Group	No. of infections	Follow-up (PY)	Incidence (per 100 PY)	90% CI
Overall	22	453	4.9	3.4–6.8
Immediate	3	239	1.3	0.4–3.0
Deferred	19	214	8.9	6.0–12.7

Efficacy =86% (90% CI: 58 – 96%)
P value =0.0002

Rate Difference =7.6 (90% CI: 4.1 – 11.2)
Number Needed to Treat =13 (90% CI: 9 – 25)

IPERGAY Study- ON DEMAND PrEP

Double-Blinded Randomized Placebo-Controlled Trial

- **HIV negative high risk MSM**
- **Condomless anal sex with ≥ 2 partners within 6 m**
- **eGFR > 60 mL/mn**

Full prevention services* TDF/FTC before and after sex

Full prevention services* Placebo before and after sex

* Counseling, condoms and gels, setting and treatment for STIs, vaccination for HBV and HAV, PEP

- Follow-up visits: month 1, 2 and every two months thereafter

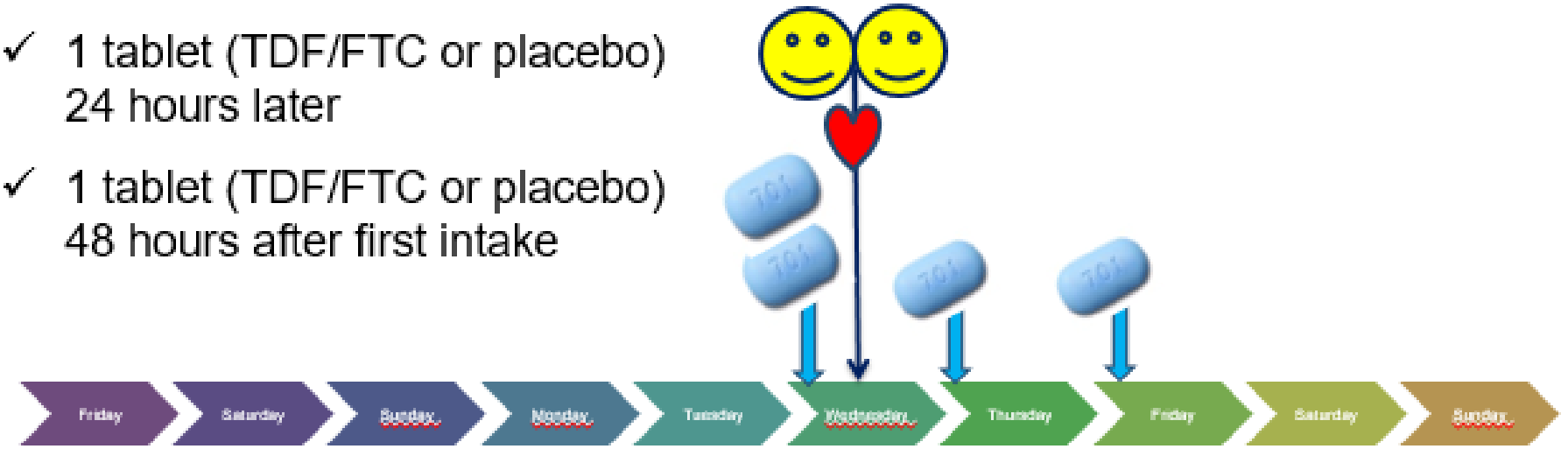
414 study participants

206 person in intervention

201 in the placebo arm

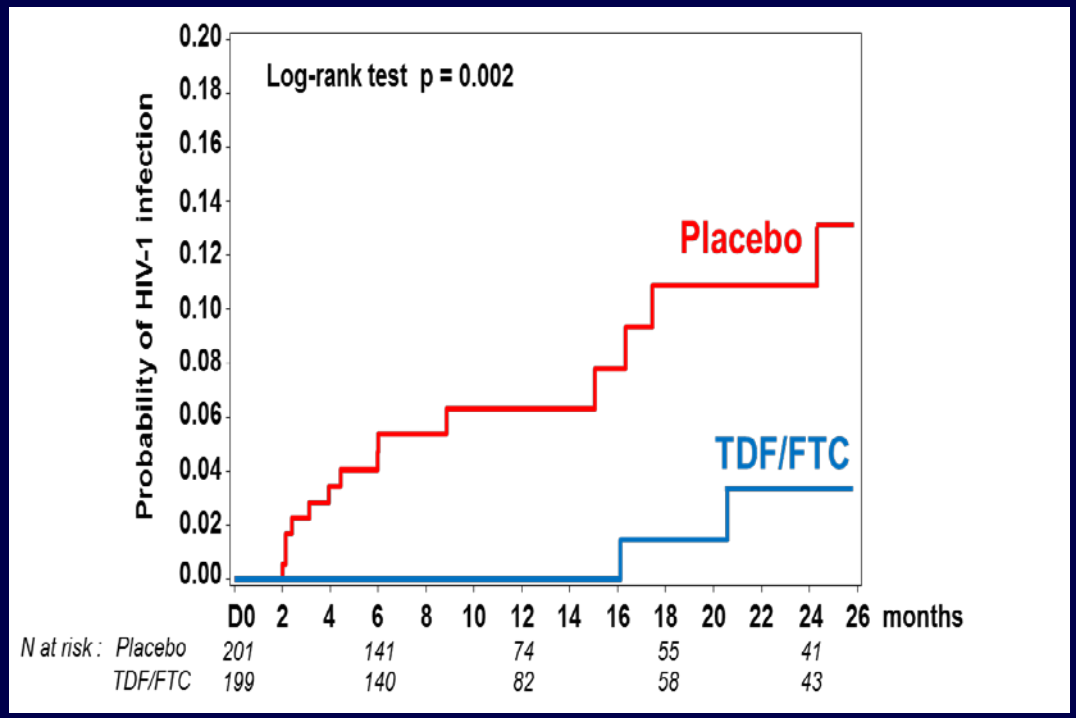
ON DEMAND PreP

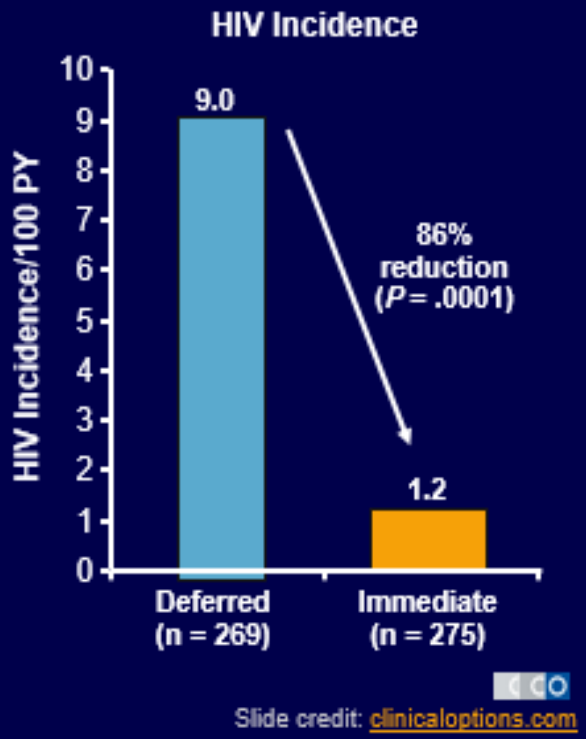
- ✓ 2 tablets (TDF/FTC or placebo)
  2-24 hours before sex
- ✓ 1 tablet (TDF/FTC or placebo)
  24 hours later
- ✓ 1 tablet (TDF/FTC or placebo)
  48 hours after first intake



RESULTS

3 intervention arm and 20 in placebo arm





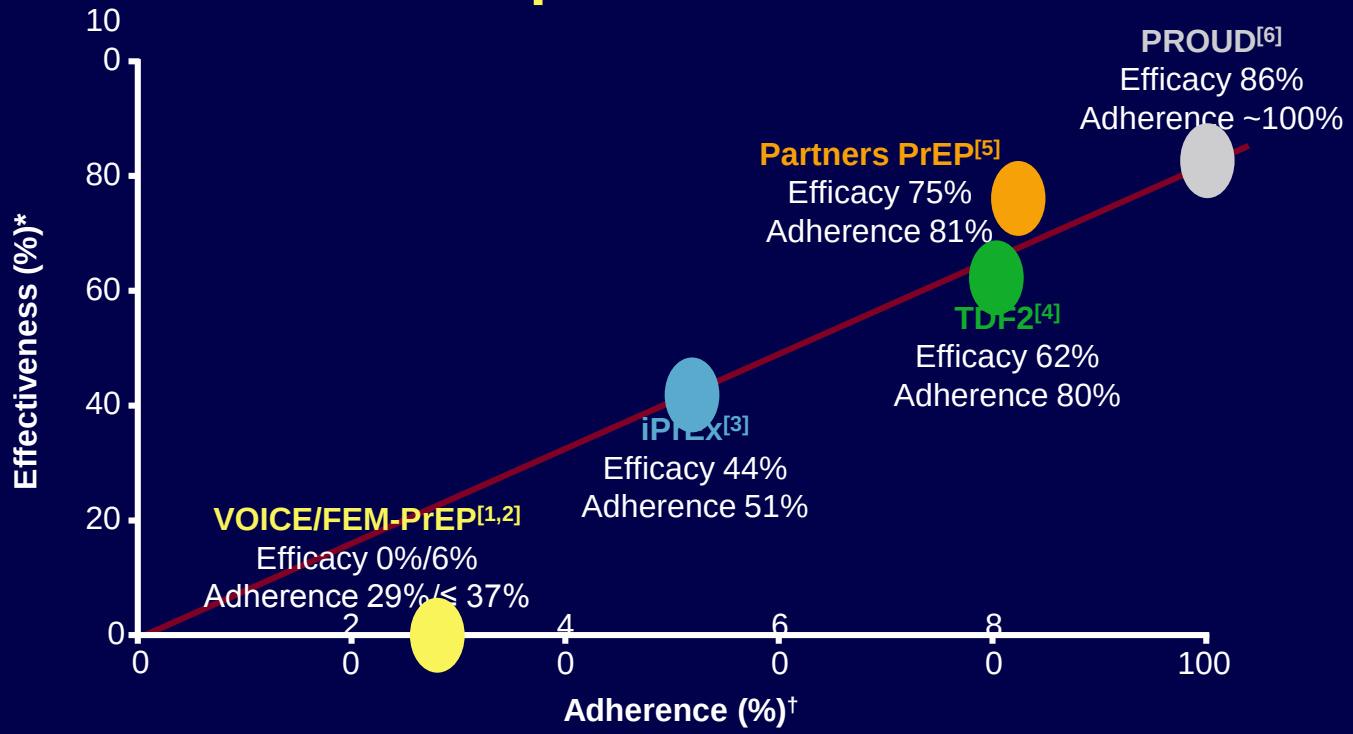
Mean follow-up of 13 months: 16 subjects infected
14 in placebo arm (incidence: 6.6 per 100 PY), **2 in TDF/FTC arm** (incidence: 0.94 per 100 PY)

86% relative reduction in the incidence of HIV-1 (95% CI: 40-99, p=0.002)

Who is eligible for PreP

- **Indications for PrEP (by history over the past 6 months):**
- HIV negative **AND**
- Sexual partner with HIV who has not been on effective therapy for the preceding 6 months, OR
- Sexually active in a high HIV prevalence population AND any of the following:
- Vaginal or anal intercourse without condoms with more than one partner, OR
- A sexual partner with one or more HIV risk factors, OR
- A history of an STI by lab testing or self-report or syndromic STI treatment, OR
- Any use of post-exposure prophylaxis (PEP), OR
- Requesting PrEP.

Select Daily Oral TDF/FTC PrEP Trials: Effectiveness Improves With Adherence

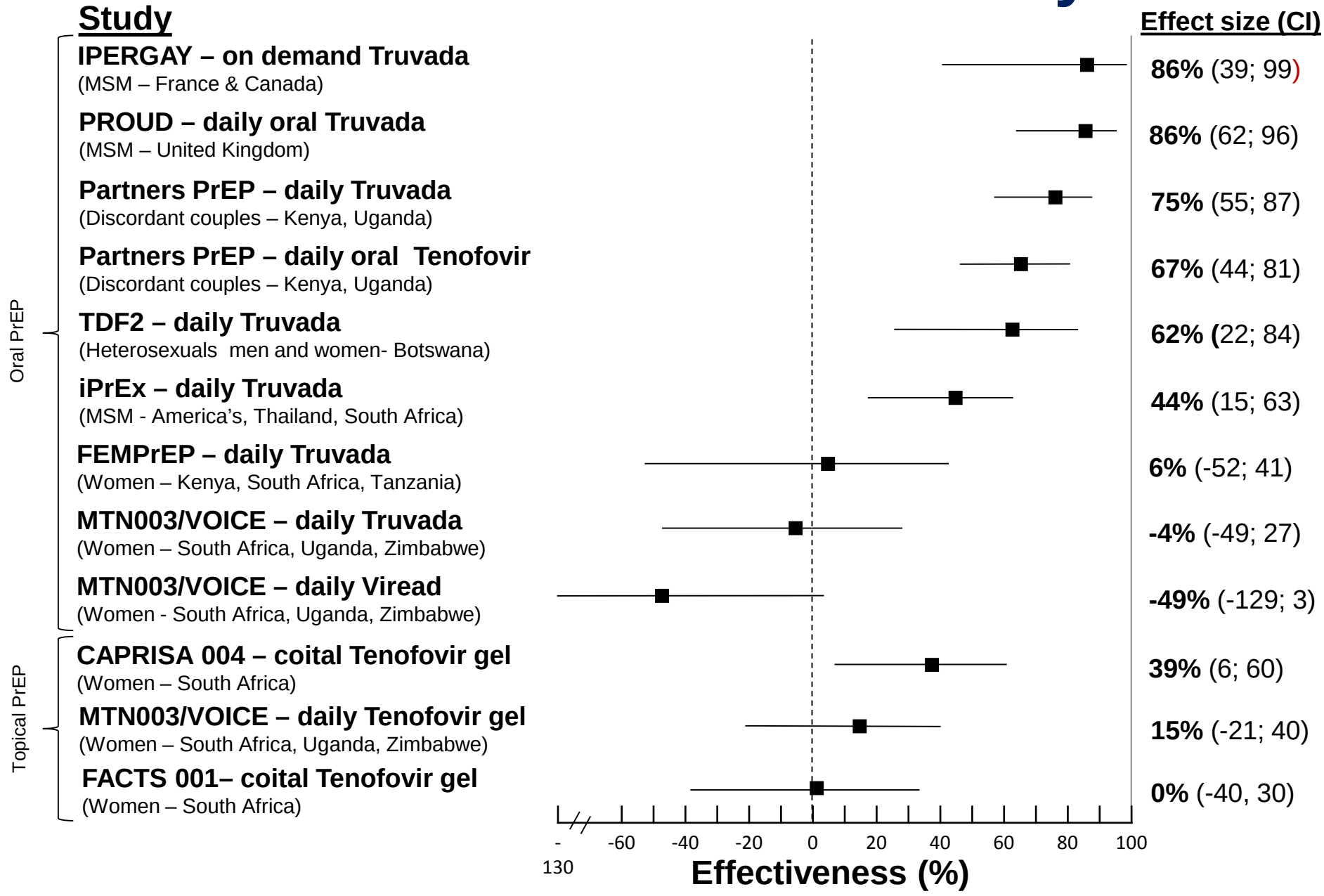


*Reduction in HIV incidence vs control. †Based on pill counts or the detection of study drug in plasma.

References in slidenotes.

Slide credit: clinicaloptions.com

Overall evidence for PrEP: July 2015



Four Prevention Opportunities

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Infected	Treatment of HIV to reduce infectivity	Years

Cohen MS, et al. J Clin Invest. 2008;118:1244-1254.
Cohen MS, et al. J Int AIDS Soc. 2008;11:4.

Slide credit: clinicaloptions.com

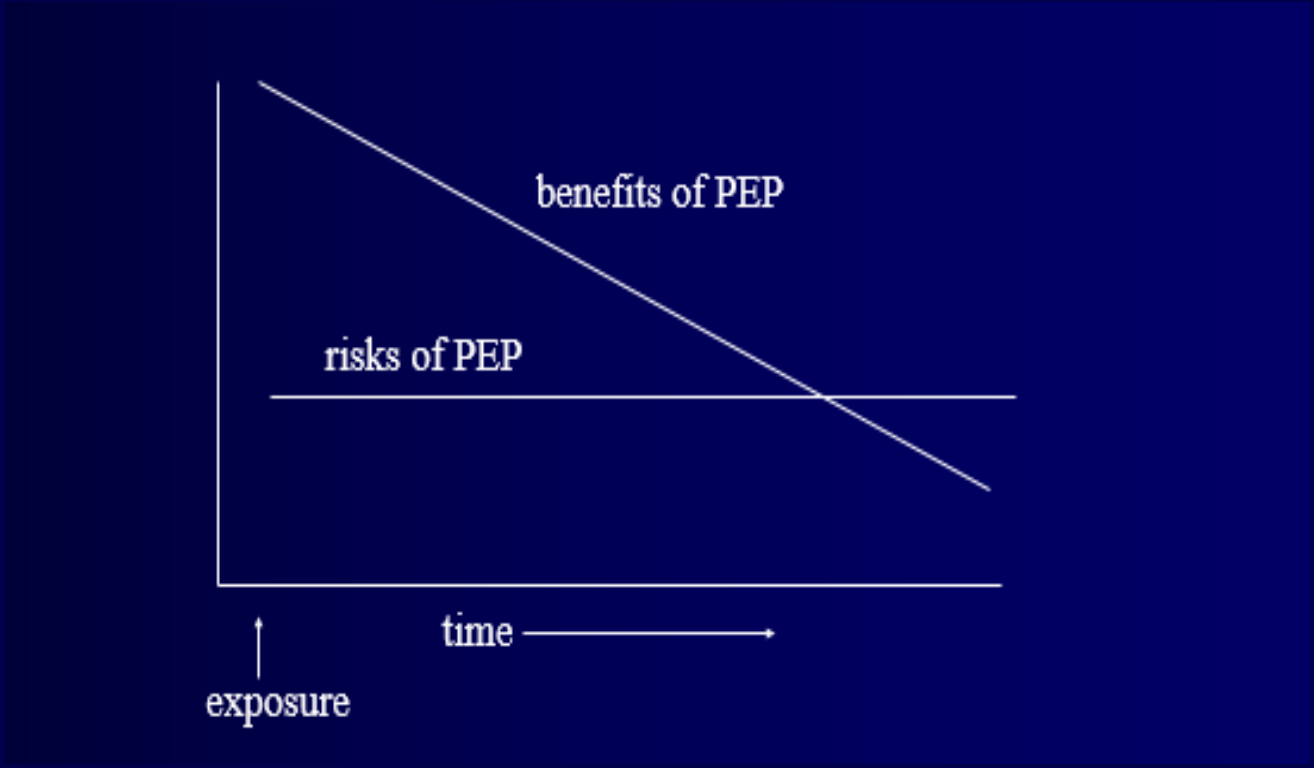
PEP AND RISK OF SEROCONVERSION

PEP-The use of therapeutic agents to prevent infection following exposure to a pathogen

Risk Factor	Odds Ratio*	95% CI
Deep injury	15	6.0 – 41
Visibly bloody device	6.2	2.2 – 21
Device in artery/vein	4.3	1.7 – 12
Terminally ill SP	5.6	2.0 – 16
AZT PEP	0.19	0.06 – 0.52

What and when?

- Three ARVs drugs – started as soon as possible.
- Efficacy of PEP thought to wane with time
- At what point is PEP “no longer worth it”?



Voluntary Male Medical Circumcisions

Four Prevention Opportunities

Status	Prevention Measure	Timing
Uninfected, unexposed	Behavioral, structural interventions (**eg, condoms, circumcision, HIV testing**)	Years
Uninfected, exposed (precoital/coital)	PrEP	Hours
Uninfected, exposed (postcoital)	PEP	72 hours
Infected	Treatment of HIV to reduce infectivity	Years

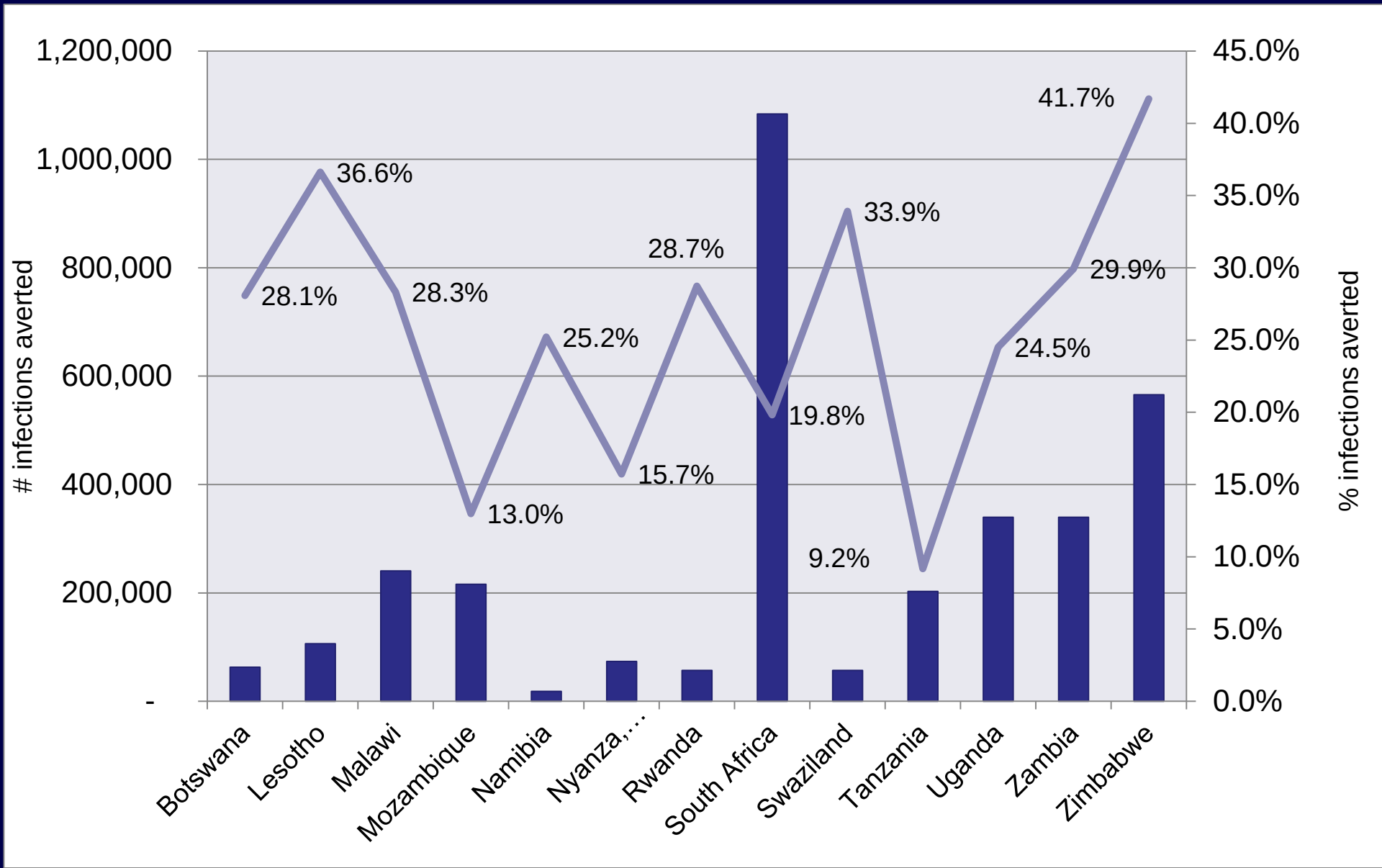
Cohen MS, et al. J Int AIDS Soc. 2008;11:4.

Slide credit: clinicaloptions.com

Voluntary male medical circumcision- Scientific Evidence

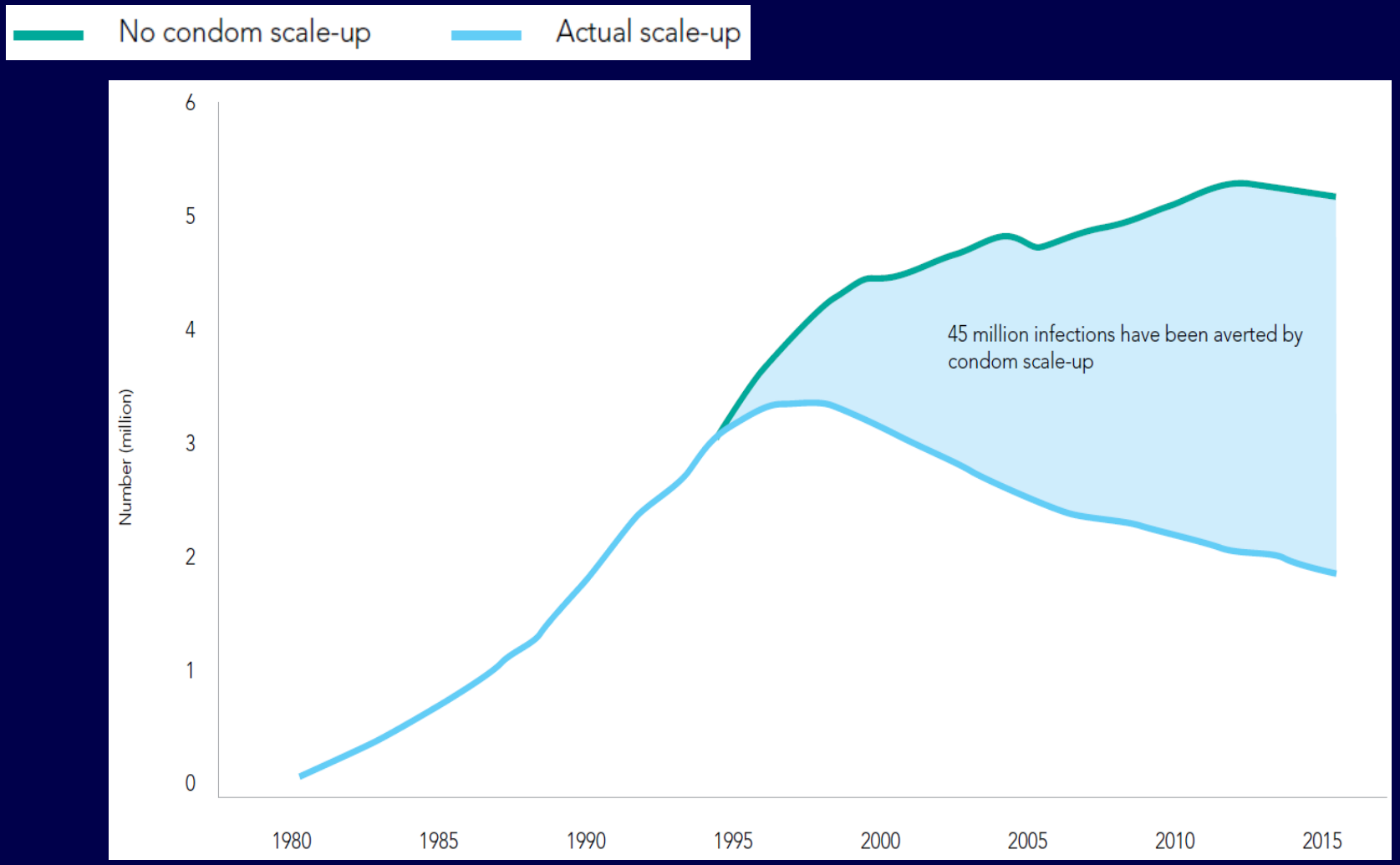
- Biological plausibility
  - Inner surface of the foreskin highly vulnerable to HIV infection
  - Up to nine times more vulnerable than cervical tissue
- Over 50 ecological and observational studies: lack of male circumcision associated with higher HIV in men
- Three RCTs in Kenya, Uganda, and South Africa: **60% protection**
- Longer-term (4-5 yrs) follow up of the Kenya and Uganda RCT participants: protective effect sustained/increased
- Community level impact evaluation in South Africa (Orange Farm) demonstrate 76% incidence reduction

Cumulative Number and Percentage of HIV Infections Averted between 2011 to 2025 by scaling up VMMC



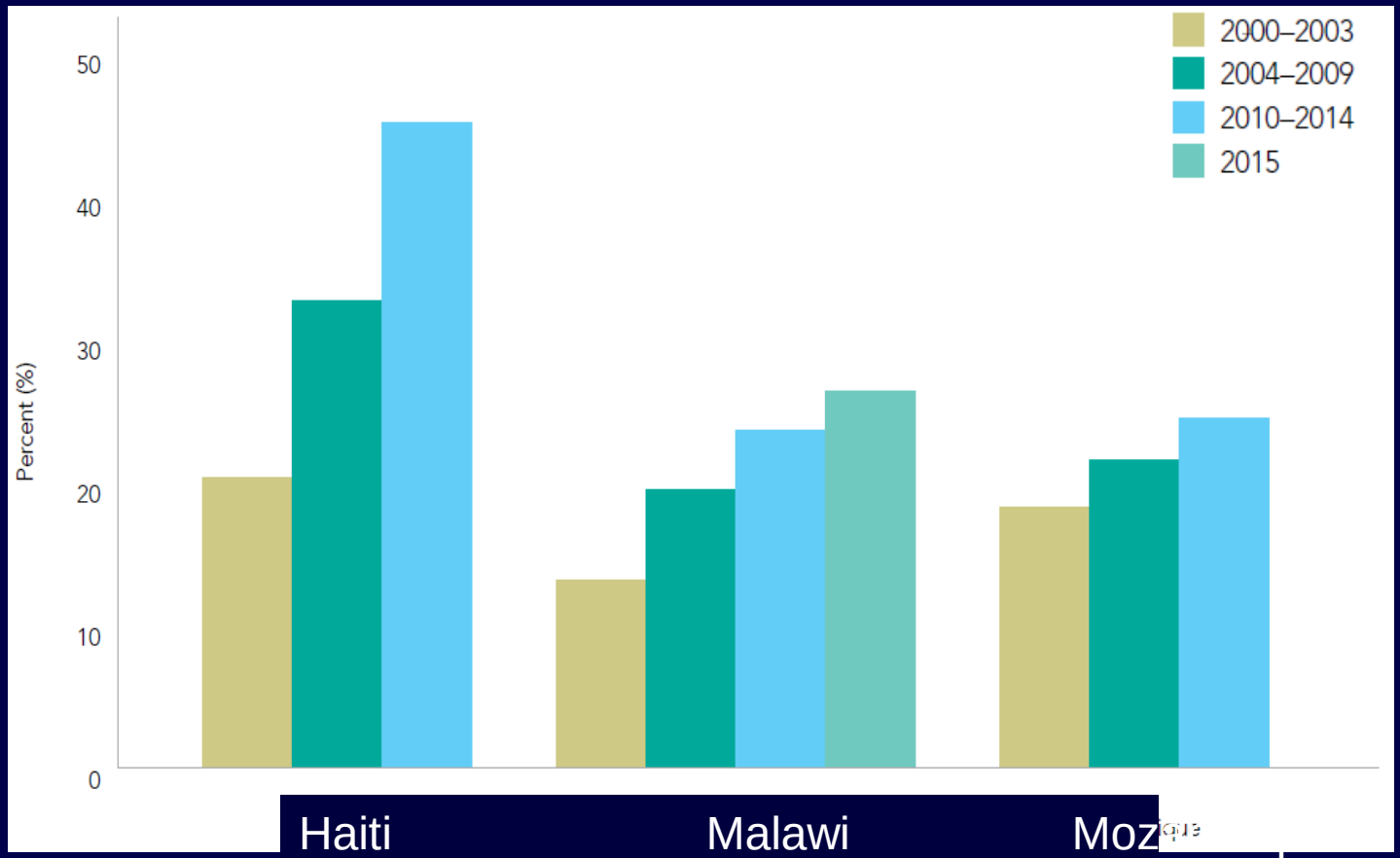
CONDOMS

Number of HIV infections averted through condom use, global, 1990–2015



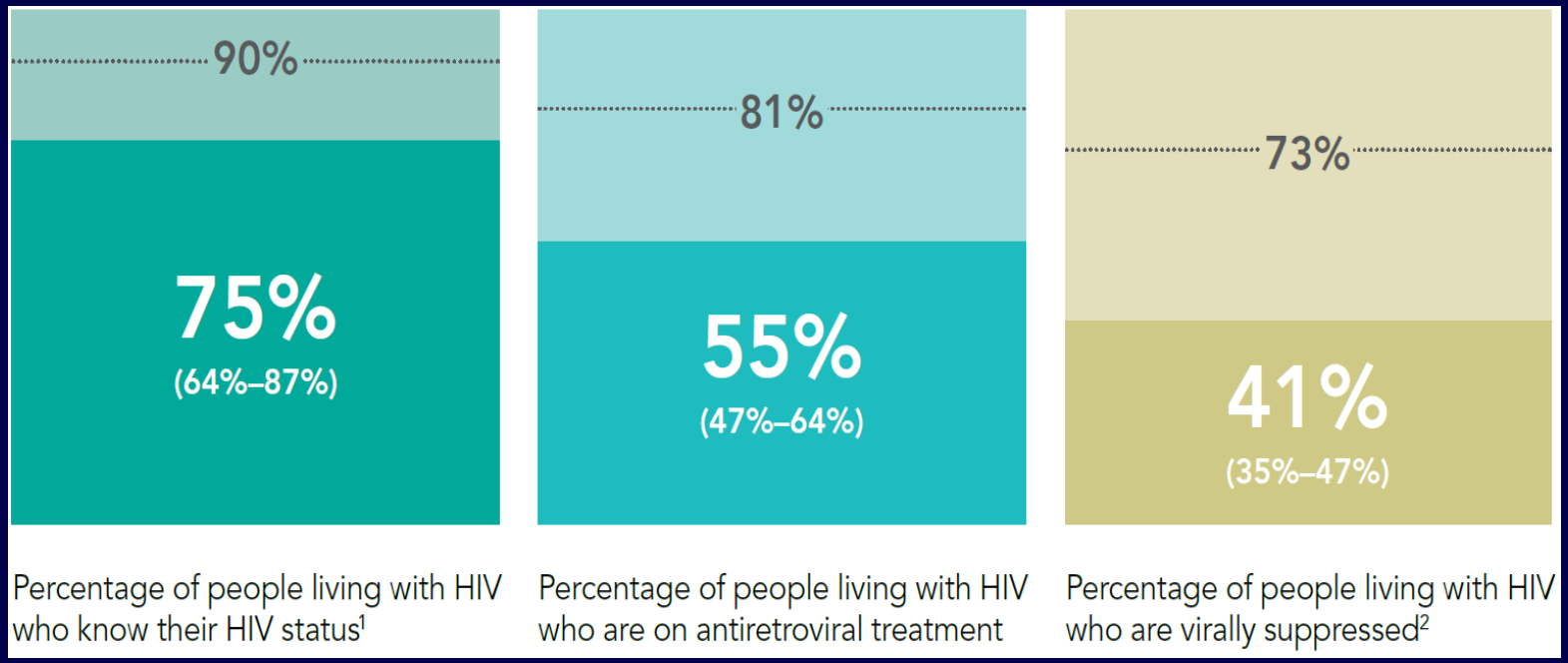
Source: John Stover, Avenir Health, 2016. The Contribution of Condoms to HIV Prevention. Data for Fast-Tracking Condom Programmes. Presented at of the Global Condom Steering Group
21-23 March 2016, Geneva.

Number of HIV infections averted through condom use, global, 1990–2015



Source: Demographic and Health Surveys, 2000-2015.

Progress towards the 90–90–90 target, Latin America and the Caribbean, 2015



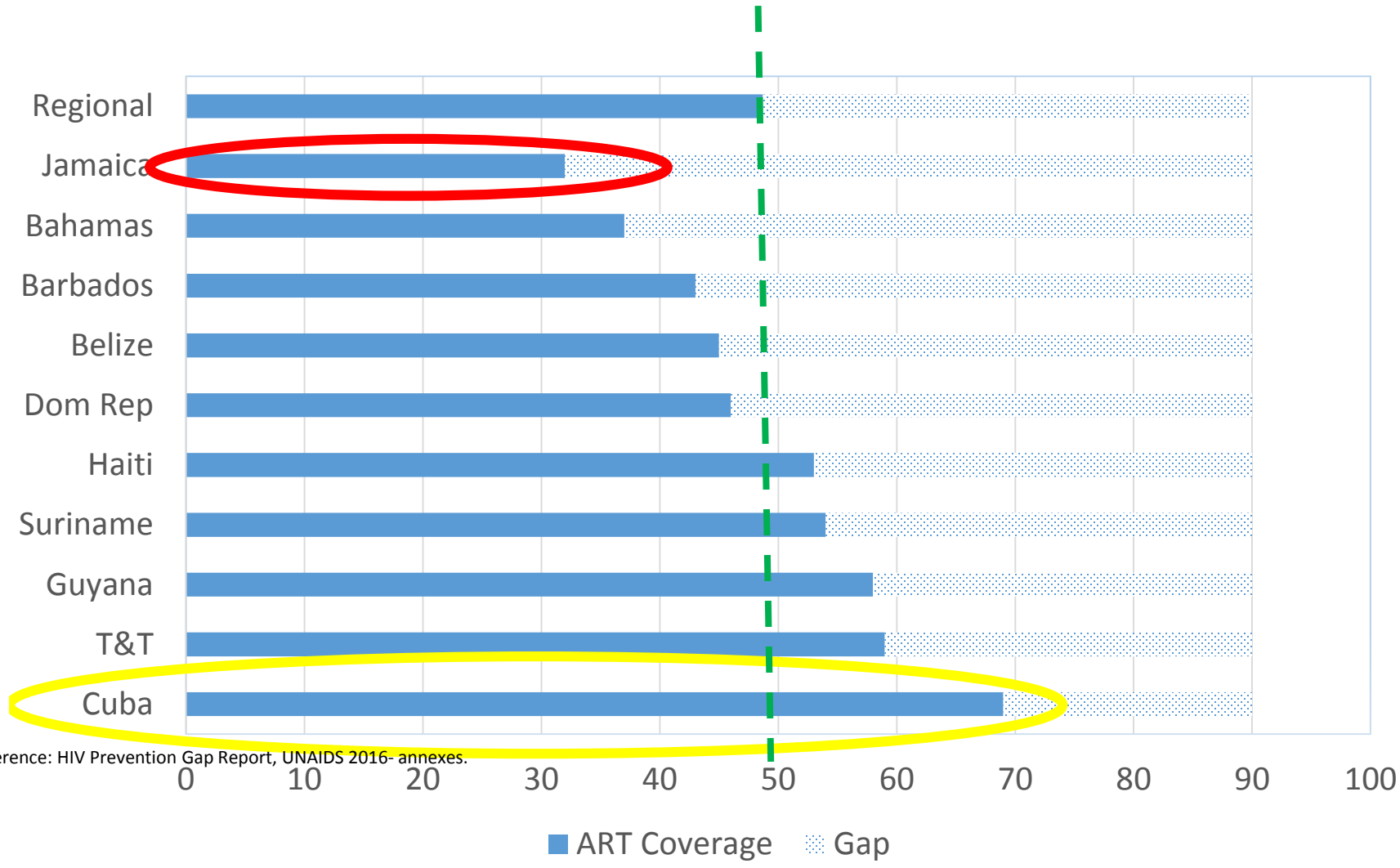
[1] 2015 measure derived from data reported by 15 countries, which accounted for 76% of people living with HIV in the region.
[2] 2015 measure derived from data reported by 21 countries. Regionally, 77% of all people on antiretroviral therapy were reported to have received a viral load test during the reporting period.

Source: UNAIDS special analysis, 2016; for more details, see annex on methods.

HIV Testing

- Dominican Republic – 67%
- Jamaica – 85%
- Haiti – 70%
- Guyana – 71%
- Barbados – 83%
- Trinidad and Tobago – 82%

ART Coverage in the Caribbean in 2015: Towards the second 90



Reference: HIV Prevention Gap Report, UNAIDS 2016- annexes.

What Are Potential Future Strategies in HIV Prevention?

Vaginal Rings for HIV Prevention

- Potential for better adherence vs oral PrEP; sustained and controlled drug release
- Dapivirine ring: silicone elastomer vaginal matrix ring containing NNRTI dapivirine

Trials	Design and Findings
MTN-020/ASPIRE[1] and IPM-027/Ring[2] studies ▪ Phase III ▪ N = 4588	▪ **Dapivirine vaginal ring Q4W** + HIV prevention services for sexually active HIV-uninfected African women ▪ Dapivirine ring associated with significant reductions in the risk of HIV infection vs PBO ring (27% to 31%; *P* ≤ .05) ▪ No clinically relevant safety differences between dapivirine and PBO ring groups

1. Baeten JM, et al. N Engl J Med. 2016;[Epub ahead of print].
2. Nel A, et al. CROI 2016. Abstract 110LB.

Additional Emerging HIV Prevention Strategies

Strategy	Findings
Vaccines	▪ HVTN100 vaccine met immunogenic criteria required to move into phase IIb/III efficacy study (HVTN702)[1,2] ▪ Other vaccine concepts in earlier phases of study
Implants	▪ Several approaches using subdermal implant models in preclinical development[3,4]

1. Bekker LG, et al. IAC 2016. Abstract TUAX0102LB.
2. ClinicalTrials.gov. NCT02968849.
3. Gunawardana M, et al. Antimicrob Agents Chemother. 2015;59:3913-3919.
4. Schlesinger E, et al. Pharm Res. 2016;33:1649-1656.

ENDING AIDS:

TREAT ALL
PrEP
PEP
Condoms
VMMC

What will it take to end AIDS?

"There is absolutely no scientific reason at all that we cannot end the epidemic".

"HIV is not going to outflank the science. If HIV outflanks anything, it would be our inability to properly implement."

Anthony S. Fauci, Director of the National Institute of Allergy and Infectious Diseases with the National Institutes of Health.

http://fpc.state.gov/258213.htm

"A community issue is whether all clients feel like they can access treatment, whether they want to know their status, or whether there is so much stigma and discrimination at the community level … that they feel like they can't access and know their status".

Ambassador Deborah L. Birx, U.S. Global AIDS Coordinator & U.S. Special Representative for Global Health Diplomacy.

http://fpc.state.gov/258213.htm

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Thank you!

Questions