IAS-AIDS 2018

22. Uluslararası AIDS konferansı
Amsterdam, Hollanda
23-27 Temmuz 2018

AIDS 2018

Panel VI- Kongrelerde Öne Çıkan Araştırmalar

HIV/AIDS KONGRESİ2018

DOÇ. DR. ULULHAN SILI

MARMARA ÜNIVERSITESI TIP FAKÜLTESI

ENFEKSIYON HASTALIKLARI VE KLINIK MIKROBIYOLOJI AD

17 KASIM 2018

17:30 – 18:00

MARMARA ÜNİVERSİTESİ 1883

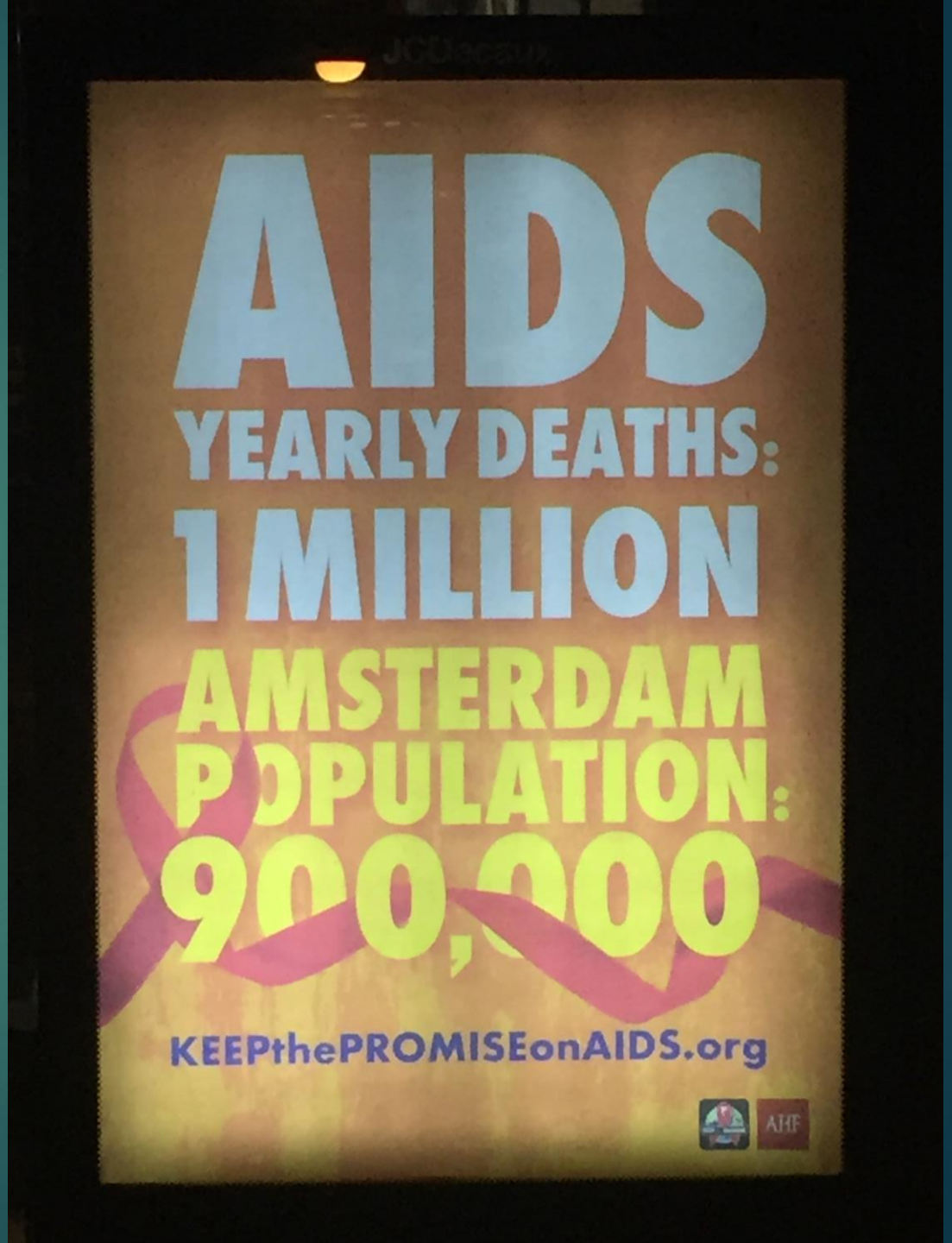
Tıp Fakültesi

IAS- AIDS 2018

- HIV'in tüm yönlerinin tartışıldığı bir kongre
  - Sosyal konular
    - Stigma ile mücadele
    - «HIV decriminalization»
    - «harm reduction»
  - Kür
  - Yeni ilaçlar
- Community perspective
  - Kamuouyu görüşü

- Program
  - 7:00 – 20:30
- 21 Cumartesi- Pre-conference
- 22 Pazar- Pre-conference
- 23 Pazartesi
- 24 Salı
- 25 Çarşamba
- 26 Perşembe
- 27 Cuma


I amsterdam.
Amsterdam welcomes you
to AIDS 2018
AIDS 2018
22nd INTERNATIONAL AIDS CONFERENCE
AMSTERDAM, NETHERLANDS
23-27 JULY 2018
BREAKING BARRIERS • BUILDING BRIDGES


AIDS
YEARLY DEATHS:
1 MILLION
AMSTERDAM
POPULATION:
900,000
KEEPthePROMISEonAIDS.org
AHF


UMBOOT
C3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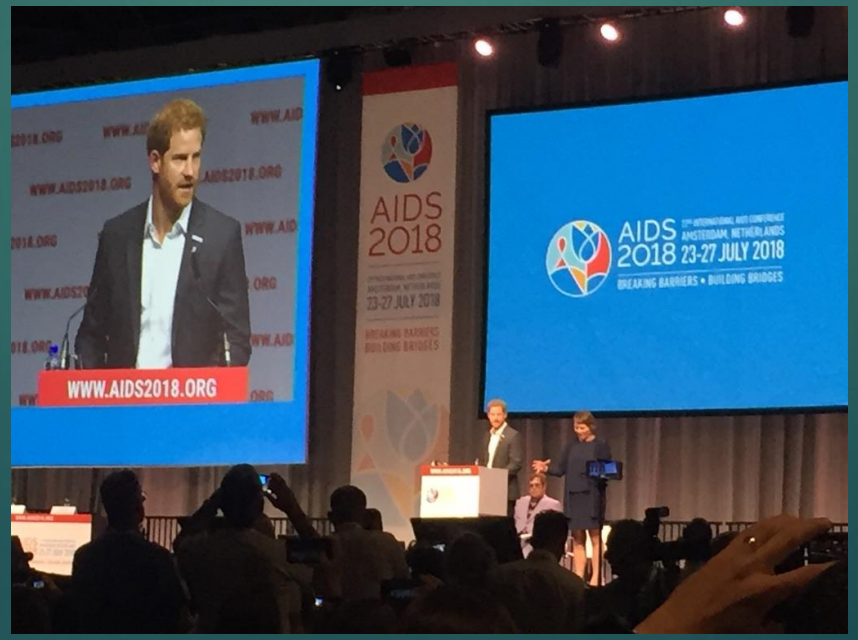
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Fred Verdult

Positive Flame

This inspired us to introduce the Positive Flame at AIDS 2018. This Positive Flame will burn in the evening of Wednesday

Positive Flame Tour

The Positive Flame Tour will take place on Wednesday July 25 2018 from 4:00 to 7:30 p.m.: thirty-seven torchbearers will


OUTREACH
HARM
REDUCTION
ARV
AWARENESS
DRUGS CONSUMPTION
ROOM
GOOD PRISON
HEALTH
=
GOOD PUBLIC
HEALTH
EQUAL ACCESS
TO
SERVICES


BREAKING
BARRIERS
18
BUILDING
BRIDGES

HIV cure
-community prespective-

- Tek tablet rejimleri ile virolojik baskılama başarılıyor.
- Kür'e ihtiyaç var mı?
  - ART ile virolojik baskılama ve CD4 toparlanması yeterli midir?
  - Kronik immün aktivasyon ve zararları
- Kamuoyunun kür ile ilgili görüşü nedir?
- Hastalar kür istiyorlar mı?
  - Kür denemelerine katılmaya istekliler mi?
  - Kür denemelerinin riskleri nelerdir?
  - «shock-and-kill»

HIV cure
-community prespective-

- Hastaların beklentisi ne?
  - ART'yi kesebilmek yeter mi?
  - Anti-HIV negatifliği?
- Kür çalışması demek eninde sonunda ART'yi kesip nüks var mı diye beklemek demek?
  - Nüksün hastaya zararı var mı?
  - Nüks ettiğinde bulaş olur mu?
    - Eşlerin durumu
- Araştırmacı hekimler kür denemeleri ile ilgilenmeli mi?
  - Kür için geliştirilecek stratejinin ART ile baskılı hastaya getireceği riskler kabul edilebilir mi?
    - Aydınlatılmış onam

An Ideal HIV Cure

- SAFE
- AFFORDABLE
- PERMANENT
- CONVENIENT
- SCALABLE/ ACCESSIBLE/ UNIVERSAL
- BIOMARKER (Can show you are cured or not)
- EASY/ ONE TIME

Joseph Klibansky
«Self-portrait of a Dreamer»

Technological advances: Viral Reservoir; Autopsy study

- Development of ultra-sensitive techniques (all HIV-1 subtypes)
- (Full-length) single genome sequencing of HIV RNA or DNA

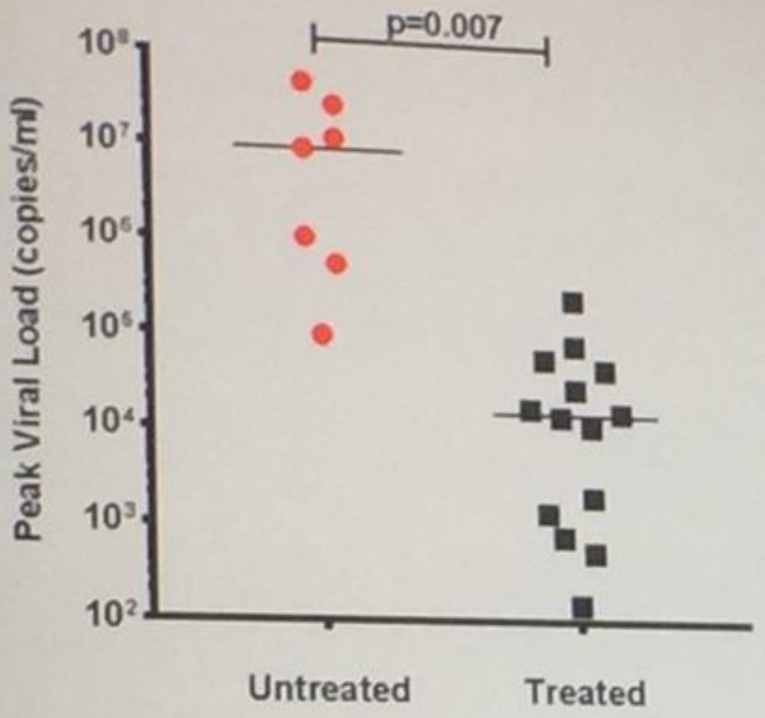
Lymph node, blood, lung, and colon sequences were interspersed

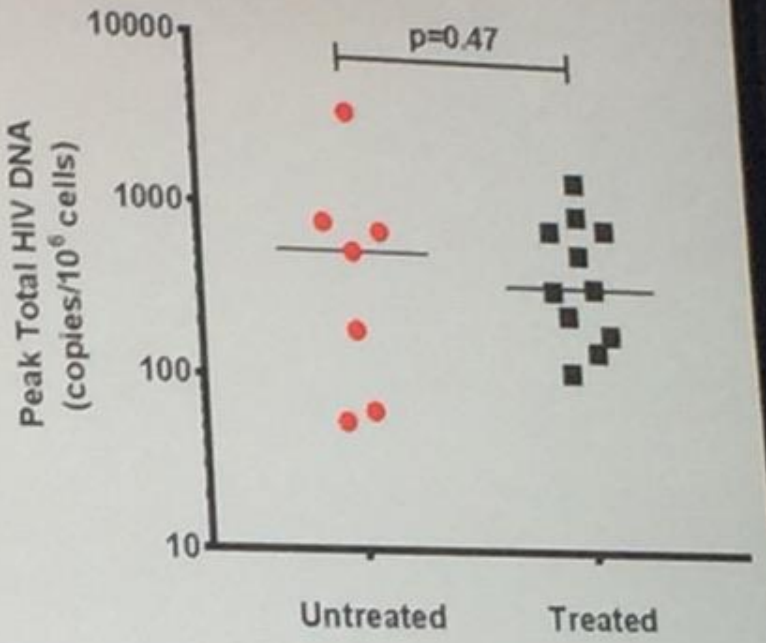
- More autopsy studies: T cells versus long lived macrophages, microglia
- Model systems (animal and laboratory)

Brese et al, J of Neurovir, 2018

www.iasociety.org

Total DNA reservoir is similar in early treated versus untreated participants at hyperacute infection phase





HIV'den korunma

- Partner 2: Serodiscordant MSM çiftlerde HIV riski
  - Partner 1'in devamı niteliğinde
    - Partner 1: MSM (340 çift) + heterosekseül (548 çift)
    - Partner 2: MSM
    - Toplamda 783 MSM çift- 1596 couple-year-follow-up
  - Ana hedef
    - HIV-1 RNA <200 kopya/mL olan eş ile kondom kullanmadan cinsel ilişkiye girildiğinde eşler arası HIV bulaşının saptanması
    - HIV negatif eş PEP veya PrEP kullanmıyor
    - Eğer bulaş olursa, HIV-1 *pol* ve *env* dizi analizi yapılarak filogenetik ilişki araştırılıyor

PARTNER2: HIV Transmission

- No linked transmissions documented in ~ 77,000 condomless sex acts when HIV-positive MSM partner suppressed to HIV-1 RNA < 200 copies/mL

Sexual Behavior Reported by HIV-Negative Partner	Linked Transmissions, n	Upper 95% CL*	Condomless Sex Acts, n	CYFU
Any sex	0	0.23†	76991	1596
Anal sex	0	0.24	70743	1546
Insertive anal sex	0	0.27	52572	1345
Receptive anal sex without ejaculation	0	0.43	23153	867
Receptive anal sex with ejaculation	0	0.57	20770	652
Any sex with an STI	0	2.74	6301	135

*For rate of within-couple HIV transmission per 100 CYFU. †Compared with 0.84 for MSM and 0.46 for heterosexuals in PARTNER1.

- Unlinked transmissions occurred in 15 initially HIV-negative MSM partners

Rodger A, et al. AIDS 2018. Abstract WEAX0104LB.

Slide credit: clinicaloptions.com

HIV bulaşı

- 2008 Swiss statement
- **U**ndetectable = **U**ntransmissable
  - Saptanamıyorsa bulaşmaz
    - heteroseksüellerde olduğu kadar MSM'lerde de böyle
  - U = U, if U is you.
  - HIV^+ eş baskılı ise HIV^- eş için PrEP'e gerek yok.
- HIV bulaşı olmuyor ama ya diğer CYBH?

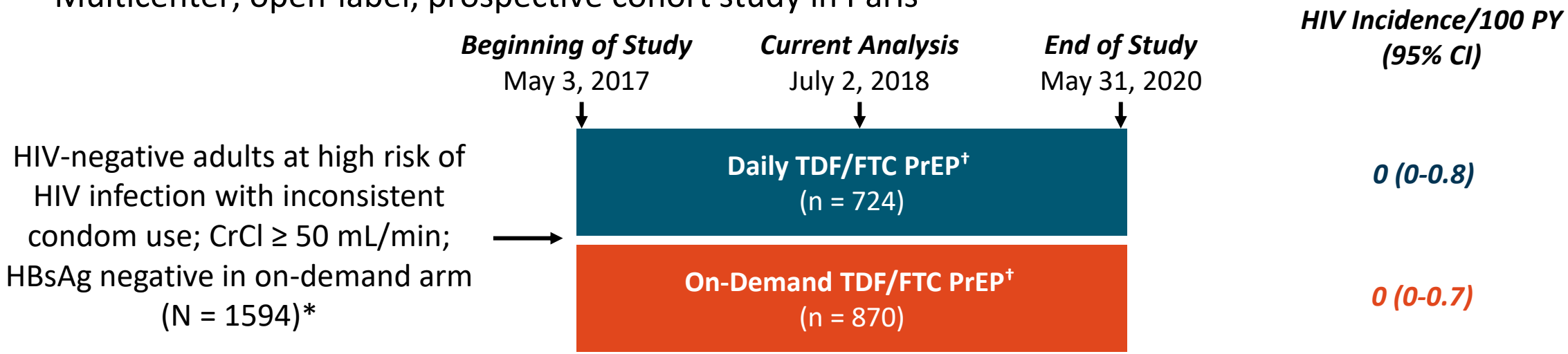
«Gerektiğinde TDF/FTC» ile PrEP

- ANRS IPERGAY: «gerektiğinde PrEP» ile plasebo, yüksek riskli MSM'lerde
  - «On-demand TDF/FTC oral PrEP»
    - 2tb (öncesindeki 24 saat içerisinde) → 24 s → 1 tb → 24 s → 1tb
  - «Gerektiğinde PrEP» ile risk azalması %86 - %100
    - HIV insidansı/ 100 PY: 0.91 (TDF/FTC) ile 6.6 (plasebo)
  - Gerektiğinde PrEP alan grupta ortanca TDF/FTC dozu/ ay >15: günlük ile gerektiğinde alma karşılaştırması sınırlı

- ANRS Prevenir: günlük ile gerektiğinde PrEP karşılaştırması
  - 5-2017'den 5-2020'ye kadar devam edecek
  - Hedef sayı 3000; MSM'lerde test ediliyor; yüksek riskli kadınlarda geçerliliği ?

ANRS Prevenir: Daily vs On-Demand TDF/FTC Oral PrEP

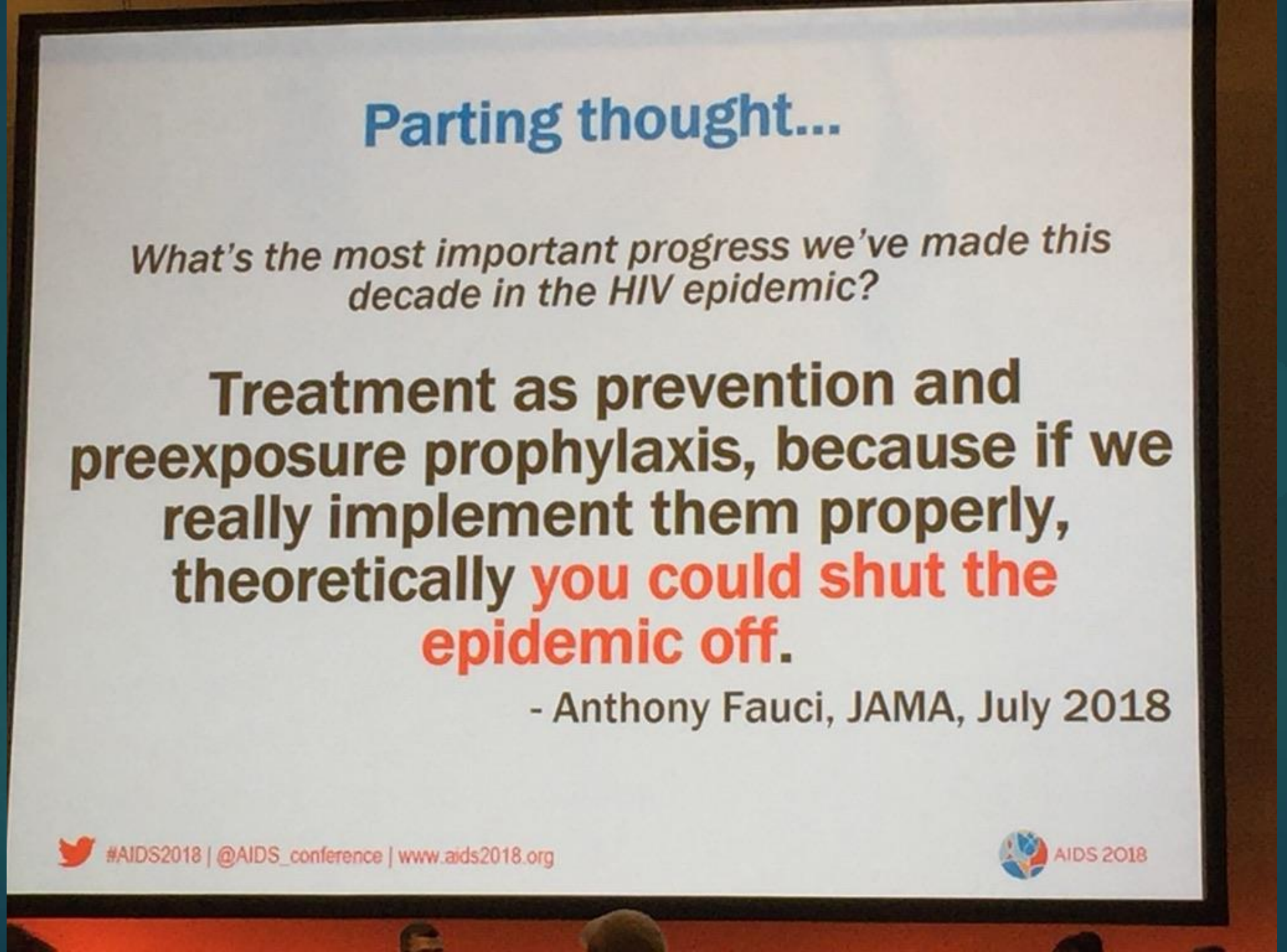
- Multicenter, open-label, prospective cohort study in Paris

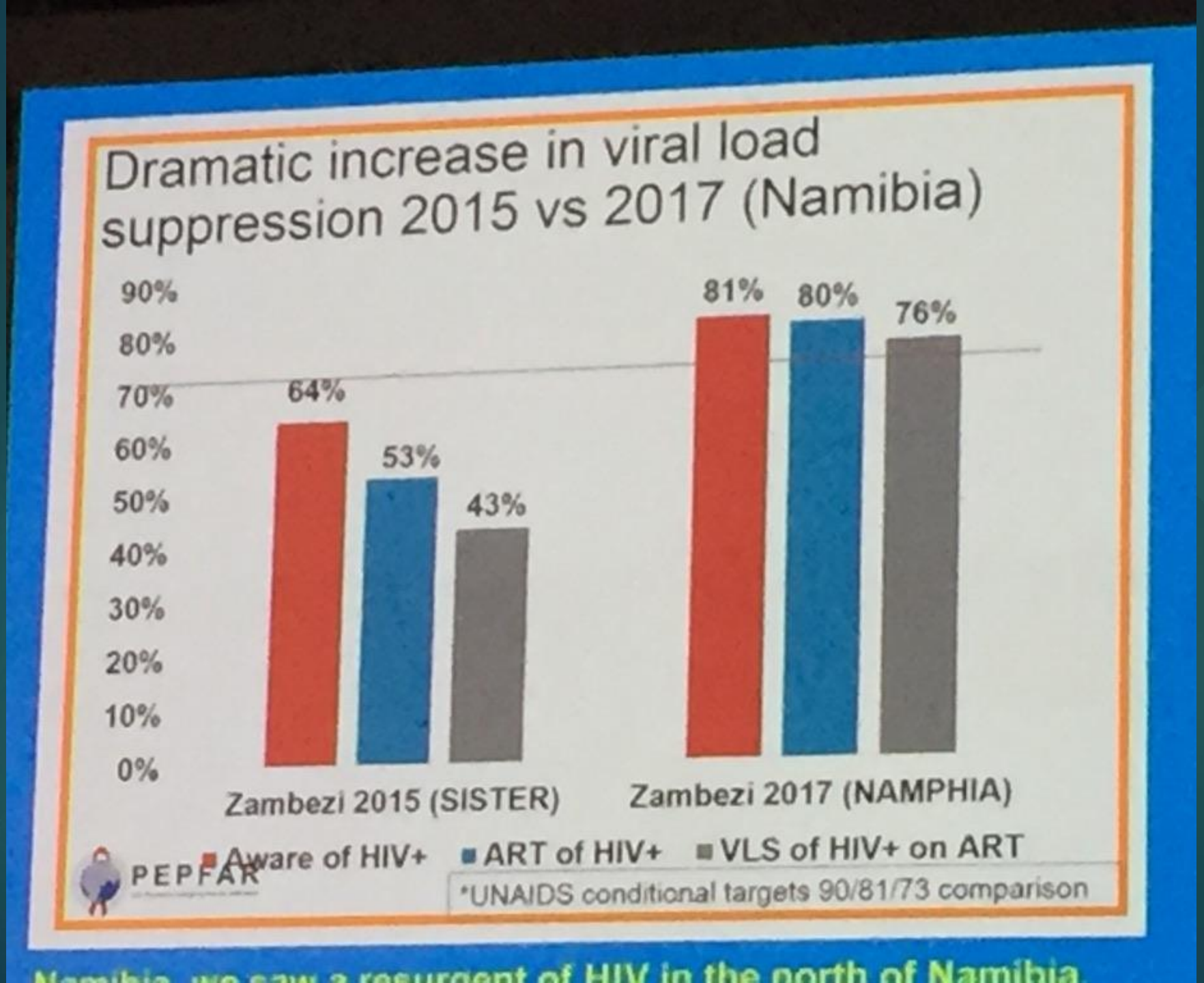


*Participants enrolled in arm of their choice with ability to switch; target enrollment, N = 3000 (85% MSM).
†Plus condoms, gels, risk reduction and adherence counseling, questionnaire on sexual behavior. Follow-up every 3 mos with STI and/or HIV testing, plasma creatinine measurement.

- Predominantly MSM (98.8%), white (85.2%); median age: 36 yrs; mean follow-up: 7 mos
- Overall HIV infections averted, n = 85
  - Assuming incidence of 9.17/100 PY as reported for ANRS IPERGAY study among participants in Paris

Molina J-M, et al. AIDS 2018. Abstract WEAE0406LB.

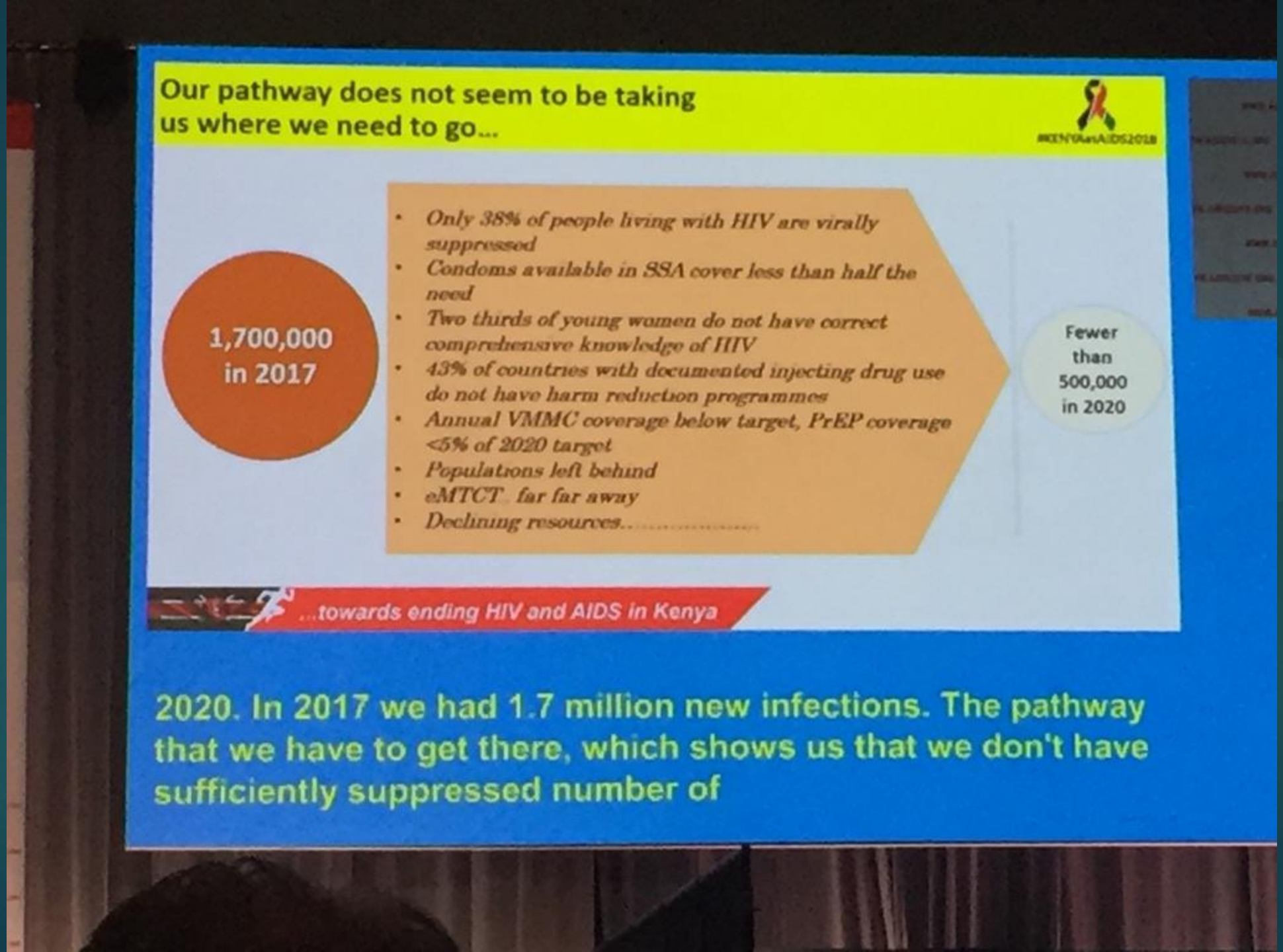

Parting thought...
What's the most important progress we've made this decade in the HIV epidemic?
Treatment as prevention and preexposure prophylaxis, because if we really implement them properly, theoretically you could shut the epidemic off.
- Anthony Fauci, JAMA, July 2018
#AIDS2018 | @AIDS_conference | www.aids2018.org
AIDS 2018


Dramatic increase in viral load suppression 2015 vs 2017 (Namibia)
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
64%
53%
43%
81%
80%
76%
Zambezi 2015 (SISTER)
Zambezi 2017 (NAMPHIA)
Aware of HIV+
ART of HIV+
VLS of HIV+ on ART
PEPFAR
*UNAIDS conditional targets 90/81/73 comparison

PHIA - West Africa Stalled Progress

PEPFAR

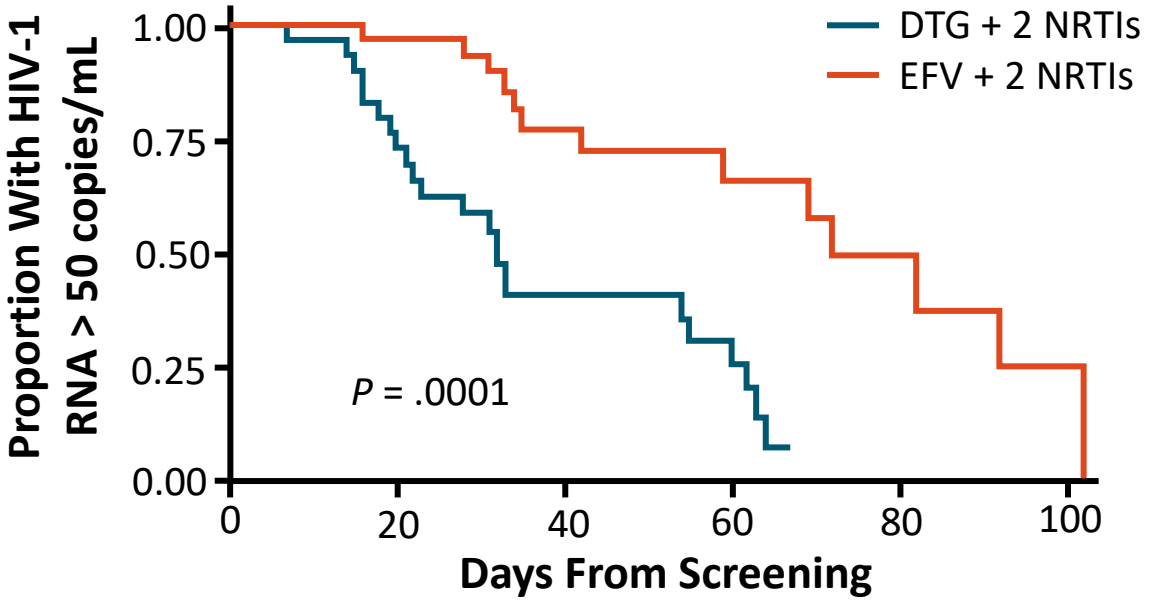
These are their surveys. Less than half of the adults are aware of their status. In Cote d'Ivoire only a third. It is less than any other


Our pathway does not seem to be taking us where we need to go...
1,700,000 in 2017
Only 38% of people living with HIV are virally suppressed
Condoms available in SSA cover less than half the need
Two thirds of young women do not have correct comprehensave knowledge of HIV
43% of countries with documented injecting drug use do not have harm reduction programmes
Annual VMMC coverage below target, PrEP coverage <5% of 2020 target
Populations left behind
eMTCT far far away
Declining resources.....
Fewer than 500,000 in 2020
...towards ending HIV and AIDS in Kenya
2020. In 2017 we had 1.7 million new infections. The pathway that we have to get there, which shows us that we don't have sufficiently suppressed number of

ART ve Gebelik

- DolPHIN-1
  - 3. TM'de başlanan DTG + 2 NRTI ile EFV + 2 NRTI karşılaştırması
  - 28. – 36. hafta arası; ART naif
  - Birincil sonlanım: DTG'nin maternal farmakokinetiği (50 mg/gün)
    - Tepe düzeyi bir miktar düşse de kandaki konsantrasyonu yeterli
  - İkincil sonlanım: post-partum 2. haftada HIV-1 RNA <50 kopya/mL olması

DolPHIN-1: Virologic Response



HIV-1 RNA < 50 copies/mL, n (%)	DTG + 2 NRTIs (n = 29)	EFV + 2 NRTIs (n = 31)	*P* Value
2 wks postpartum	20 (69.0)	12 (38.7)	.02

- Median time to virologic suppression approximately halved with DTG vs EFV

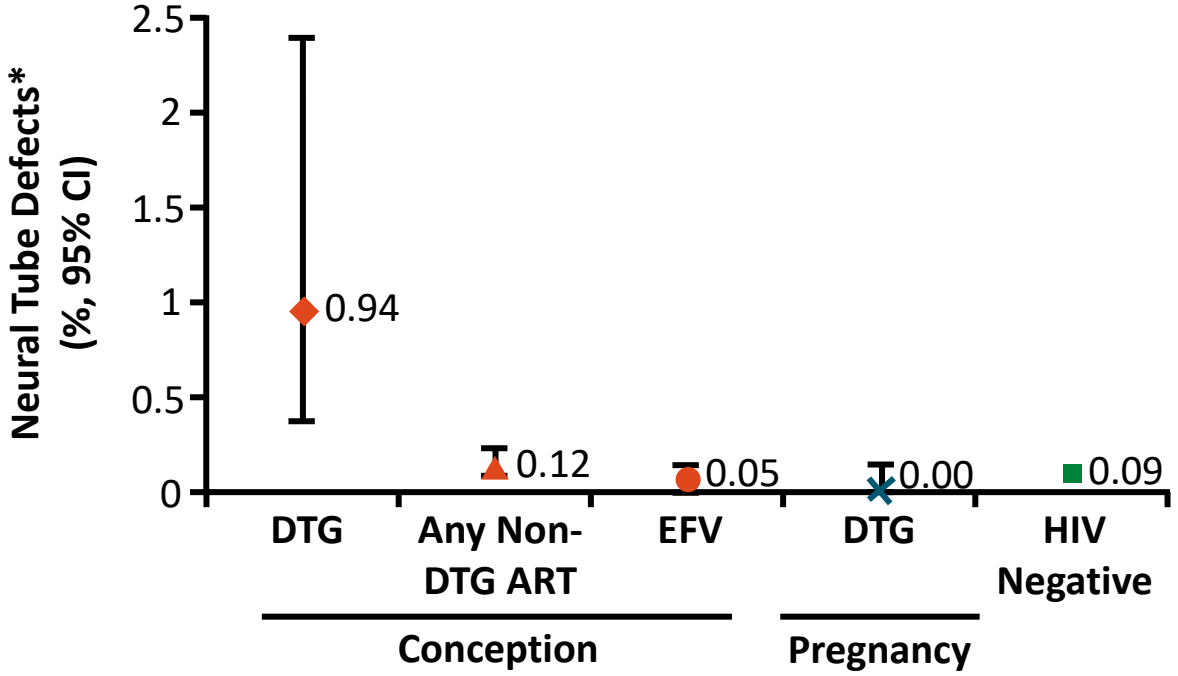
Orrell C, et al. AIDS 2018. Abstract THAB0307LB.

Slide credit: clinicaloptions.com

Gebelik Sırasında ARV Sürveyansı

Tsepamo: Neural Tube Defects and DTG Exposure

- Unplanned analysis of ongoing birth outcomes surveillance study among Botswanan women ± HIV infection[1,2]



*In 89,064 births as of **May 1, 2018.**

- At latest analysis on **July 15, 2018**[2]
  - NTD prevalence with DTG exposure **at conception**: 4/596 (0.67%; 95% CI: 0.26% to 1.7%)
  - NTD prevalence with DTG started **during pregnancy**: 1/3104 (0.03%; 95% CI: 0.01% to 0.18%)
- Next formal analysis to occur after **March 31, 2019,** which will include 72% of national births

1. Zash R, et al. N Engl J Med. 2018;[Epub ahead of print]. 2. Zash R, et al. AIDS 2018. Session TUSY15.

Guidance on the Use of DTG in Women

DTG may be used | Use DTG or another option | Do not use DTG

Currently Receiving DTG?	Pregnancy Status	Recommendation on DTG		
		DHHS[1]	BHIVA[2]	WHO[3]
No	Early pregnancy*			
	Late pregnancy†			
	Childbearing potential, no contraception			
	Childbearing potential, effective contraception			
Yes	Early pregnancy*			
	Late pregnancy†			
	Childbearing potential, no contraception			
	Childbearing potential, effective contraception			

*DHHS: < 8 wks from last menstrual period; BHIVA and WHO: first trimester.

†DHHS: ≥ 8 wks from last menstrual period; BHIVA and WHO: second and third trimesters.

References in slidenotes. Adapted from Doherty M, et al. AIDS 2018. Session TUSY15.

Slide credit: clinicaloptions.com

Situation – Background

Botswana Tsepamo study interim results indicated a potential link between **neural tube defects (NTD) and dolutegravir (DTG)** use at the time of conception.

Global and national stakeholders reacted quickly to the safety signal. The messages and directives in the responses varied, but they all have one thread in common: **limited to no community consultation.**

This means that we, the global community, **did not consult the primary population affected by these findings, the women living with HIV,** in regards to their own health care decisions.

Situation – Actions Taken

WHO recommended that countries continue to follow their current guidelines until further updates are available.

Ministries have created interim plans to adapt their HIV treatment guidelines while they wait for more data and guidance.

- Some countries are introducing **TLD for all first-line patients** *(with note of caution for women of childbearing age, counseling on contraception, and option of TLE if they choose).*
- Several countries made **highly conservative choices that restrict DTG for all women of child bearing age.**
- Other countries are **still deliberating.**

Community consultations were held in some countries but without one clear message from communities the impact on influencing policy decisions was minimal.

Source: WHO Statement 18 May, 2018

Result - Community Response

AfroCAB organized a meeting of **39 women living with HIV** representing **18 countries** in Kigali, Rwanda on July 13 and 14 to **discuss** the potential NTD safety signal and **develop a joint position on behalf of women** for access to optimal HIV treatment and prevention.

Topline Message

Unanimous decision based on the data currently available that DTG's benefits – reduced side effects, improved efficacy, and a high barrier to resistance – outweigh its potential risks.

Concluded that blanket exclusions that deny women equitable access to this optimal HIV treatment are not warranted or justified.

Discussion – Benefits

The benefits of DTG have been well documented and studied. An IAS presentation by CEPHAC earlier this week provided **further analysis on the potential benefits of DTG over EFV**. The following are key findings presented:

- **Dolutegravir-based ART would avert >25,000 deaths among women of childbearing age and 5,000 pediatric HIV infections** compared to efavirenz-based ART over a five-year period in South Africa
- These benefits **may come at the expense of overall pediatric survival** if the increased risk of NTDS with DTG from Tsepamo persists with additional data.
- However, there would be **approximately 3-fold more deaths averted among women than pediatric deaths added** with use of DTG for all women of childbearing age with HIV in South Africa.

urce: CEPHAC. IAS 2018

Discussion – Patient Experience

"On TLE, I felt dizzy, tired, couldn't work, and couldn't take care of my small kids properly. It's been one month since I started using it [DTG]. It's a big change. I'm active, my kids are happy because they have an active mother, and I can do my work without depending on anybody."

– meeting participant on DTG

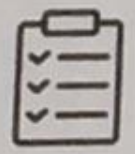
Key Takeaways – Voices of WLHIV

Potential **risk similar to the other ARV treatments** that are currently available to us.

We are diverse – **not all women seek to have children.**

We can make **decisions about our reproductive health**.

We are **disappointed at our lack of involvement** in decision making in regards to our treatment access.



We believe that, with correct information and contraceptive access, **we can make informed choices** in using DTG and planning our pregnancy.

This is an opportunity for **integrating much-needed access to contraceptives within HIV treatment** in order to achieve universal reproductive health care for all.

Act Now

We are calling for TLD to be made available urgently across Africa, with everyone having access, regardless of gender or reproductive capability, and with integration of sexual and reproductive health services.

It is critical to not just view a pregnant mother, or any woman of childbearing potential, as a vessel for a baby, but as an individual in her own right, who deserves access to the very best, evidence-based treatment available and the right to be adequately informed to make a choice that she feels is best for her.

Thank You

NOTHING FOR US WITHOUT US.

AFROCAB

ART'de İlk Tercih

DHHS, IAS-USA Guidelines: Recommended Regimens for First-line ART

Class	DHHS[1]	IAS-USA[2]
INSTI	▪ **BIC/TAF/FTC** ▪ **DTG/ABC/3TC** ▪ DTG + (TAF or TDF)/FTC ▪ **EVG/COBI/(TAF or TDF)/FTC** ▪ RAL + (TAF or TDF)/FTC	▪ **BIC/TAF/FTC** ▪ **DTG/ABC/3TC** ▪ DTG + TAF/FTC

Bold text identifies single-tablet regimens.

- Recommendations may differ based on baseline HIV-1 RNA, CD4+ cell count, CrCl, eGFR, HLA-B*5701 status, HBsAg status, osteoporosis status, and pregnancy status
- Data are lacking for women of child-bearing age not using contraception
- IAS-USA now lists EVG/COBI/TAF/FTC and RAL + TAF/FTC as alternative regimens owing to their lower resistance barriers and, respectively, more drug interactions and higher pill burden[2]

1. DHHS Guidelines. May 2018. 2. Saag MS, et al. JAMA. 2018;320:379-396.

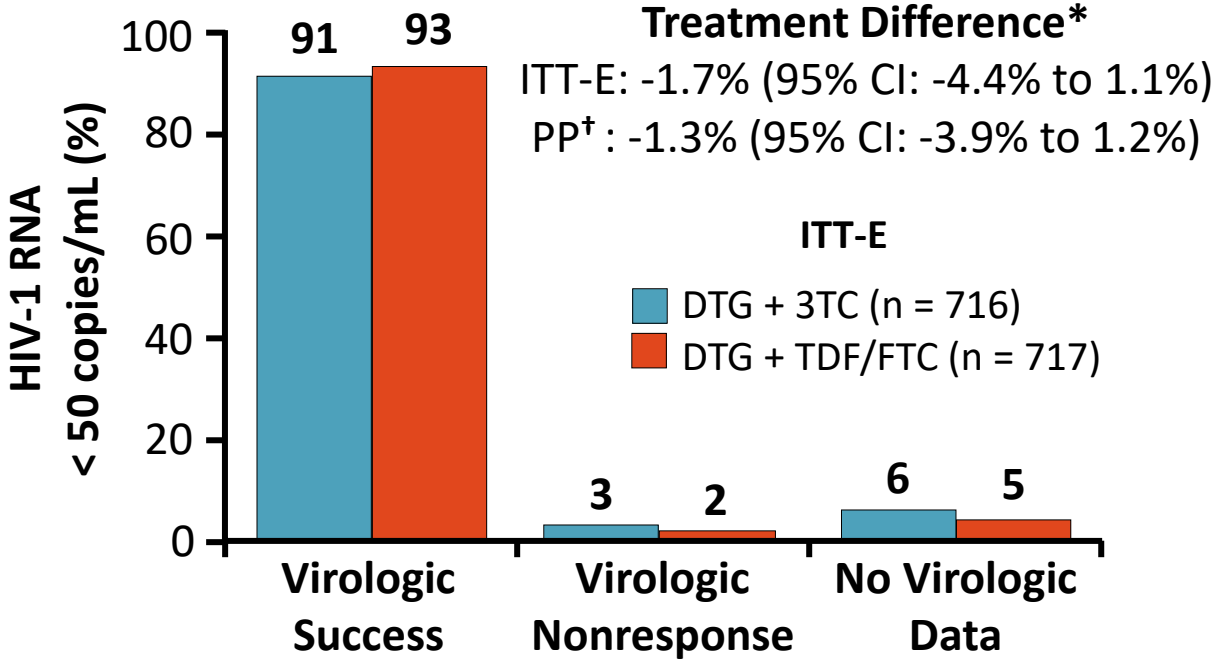
GEMINI-1 ve 2

ART naif hastalarda DTG + 3TC ile DTG + TDF/FTC karşılaştırması

- Randomize, çift kör, non-inferiority çalışması
- Birincil sonlanım noktası: 48. haftada HIV-1 RNA <50 kopya/mL
  - non-inferiority sınırı: -10%
- HIV-1 RNA: 1000 – 500.000 kopya/mL arası
- Genotipik direnç analizi yapılmış
- Kronik HBV dışlanmış

- Kümülatif ilaç maruziyetini ve toksisitesini sınırlandırmak

GEMINI-1 and -2: DTG + 3TC Noninferior to DTG + TDF/FTC in Treatment-Naive Patients at Wk 48



- No treatment-emergent INSTI or NRTI mutations in patients with VF in either arm
- Confirmed VF with DTG + 3TC: n = 6
- Confirmed VF with DTG + TDF/FTC: n = 4
- Bone and kidney safety markers more favorable with DTG + 3TC vs DTG + TDF/FTC

*Adjusted for HIV-1 RNA (≤ vs > 100,000 copies/mL), CD4+ cell count(≤ vs > 200 cells/mm^3), and study (GEMINI-1 vs GEMINI-2).
†PP = the ITT-E population excluding significant protocol violations.

DTG + 3TC was noninferior vs 3-drug therapy, no resistance in either arm

Cahn P, et al. AIDS 2018. Abstract TUAB0106LB.

Virolojik Baskılanmış Hastada ART Değiştirme

- SWORD-1 ve 2
  - DTG + RPV'ye değiştirme ile başlangıç ART'nin devamının karşılaştırması
  - ART ile stabil olan hasta
    - INSTI, NNRTI veya PI bazlı rejimde
    - ≥6 aydır <50 kopya/mL
  - Birincil sonlanım noktası
    - 48. hf'da HIV-1 RNA <50 kopya/mL
  - Sonuç olarak DTG + RPV kolunda (NRTI'sız grup)
    - Virolojik baskılama oranları benzer
    - Kemik yapım/ yıkım göstergeleri daha düşük
    - Böbrek tübül fonksiyonları daha iyi
    - Yağ düzeyleri aynı

SWORD-1 and -2: Resistance

- 10/990 (1%) confirmed virologic withdrawals through Wk 100
  - Treatment-emergent NNRTI resistance mutations documented in 3/10, all from early switch arm*

Time of Failure	Previous Regimen	Mutations at Baseline		Mutations at Confirmed Virologic Withdrawal	
		NNRTI	INSTI	NNRTI	INSTI
Wk 36	EFV/TDF/FTC	None	None	K101K/E	None
Wk 88	DTG/ABC/3TC	None	None	E138E/A	None
Wk 100	EFV/TDF/FTC	K101E, E138A	G193E	K101E, E138A, M230M/L	Assay failure

*For these 3 patients, HIV-1 RNA at last measurement: < 50 copies/mL, 55 copies/mL, 300 copies/mL, respectively.

Aboud M, et al. AIDS 2018. Abstract THPEB047.

Baskılı hastada DTG monoterapisi ile 3'lü ART'yi karşılaştırma

- MONCAY
  - randomize, açık etiketli, 158 baskılı hastada
  - DTG ile DTG/ABC/3TC karşılaştırması
  - 24. hf'da non-inferior
  - 48.hf'da inferior
    - yeni INSTI mutasyonları
- DOMONO çalışmasında da benzer sonuç

Emergence of DTG resistance in monotherapy studies

Study name	N	Efficacy	VF (N)	DRM/n DRM/VFs	Mutations
ITALY	20	95%	1	0	-
DONOMO	86	88%	8	3/86 (3.5%) 3/8 (37.5%)	263K (1) 155H (1) 230R (1)
DOLAM	31	93.5%	2	2/31 (65%) 2/2 (100%)	155H, 147G, 148R (1) 138K, 155H, 140S (1)
REDOMO	122	91%	11	9/122 (7.4%) 9/11 (82%)	(various)
DOLUFRENCH	28	89%	3	3/28 (11%) 3/3 (100%)	138K, 140A, 148R (1), 74I, 92Q (1), 155H (1)
MONOCAY	78	93.6%	7	2/78 (2.6%) 2/7 (29%)	147G, 155H (1) 263K (1)

Adapted from Blanco JL et al Curr Opin Infect Dis 2018

M184V/I'sı olan virolojik baskılı hastalarda EVG/COBI/FTC/TAF'a değişim (Study 1824)

- ≥6 aydır HIV-1 RNA <50 kopya/mL
- TDF/FTC veya ABC/3TC + 3. ilaç
  - 3. ilaç= %54 PI, %32 INSTI, %11 NNRTI
- Önceki genotipik direnç analizinde M184V ve/veya M184I
- Birincil sonlanım noktası
  - 12. haftada HIV-1 RNA <50 kopya/mL
- SONUÇ
  - 12. ve 24. hf'da %100 (37/37) hastada virolojik başarı
- ? Başlangıç rejimlerin daha ayrıntılı sunumu

Yeni ve Araştırma Aşamasındaki Yaklaşımlar

- DRIVE-FORWARD
  - Naif hastalarda 2 NRTI + doravirin ile 2 NRTI + DRV/RTV karşılaştırması
  - Randomize, çift-kör, faz III
  - Birincil sonlanım: 48. haftada HIV-1 RNA <50 kopya/mL
    - Doravirine %84; DRV/RTV %80 (non-inferior)
    - 96. hf'da doravirine %73.1 (280/383), DRV/RTV %66 (252/383) (üstün)
  - İlaç-ilaç ve ilaç-besin etkileşimleri sınırlı
  - Yan etki profili olumlu
  - Virolojik başarısızlıkta doravirin direnci görülüyor
  - Jenerik DOR/3TC/TDV tek tableti fiyatları düşürür mü?

DRIVE-FORWARD and DRIVE-AHEAD: Resistance

- Susceptibility analysis of the 7 doravirine-resistant clinical mutants from DRIVE-FORWARD and DRIVE-AHEAD phase III studies

Fold Change by Virus	NRTI							NNRTI			
	ZDV	d4T	ddI	ABC	FTC	3TC	TFV	DOR	EFV	ETR	RPV
WT	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
A98G/F227C/M184V	0.1	0.7	1.2	2.7	> 100	> 100	0.5	> 93	9.0	2.8	3.8
A98G/V106I/H221Y/F227C/ M184V	0.1	0.6	1.2	3.2	> 100	> 100	0.6	> 110	19	***7.9***	10
V106A/P225H/Y318F/K65R	1.0	1.4	1.8	2.4	7.7	12	1.6	> 210	4.8	0.7	1.0
V106I/F227C	0.2	0.7	1.0	0.7	2.8	3.1	0.3	> 105	2.5	***4.0***	3.4
V106I/H221Y/F227C/M184V	0.2	0.8	1.1	3.9	> 100	> 100	0.4	> 96	1.7	1.5	1.2
V106M/F227C/K65R/M184V	0.1	0.5	1.5	2.8	> 100	> 100	0.4	> 98	11.0	0.6	0.4
Y188L/M184V	0.5	0.8	1.6	2.9	> 100	> 100	0.8	> 181	> 120	***3.4***	11

Orange shading denotes **resistance**. Green shading denotes **susceptibility**. Bolded italics indicate ***partial sensitivity***.

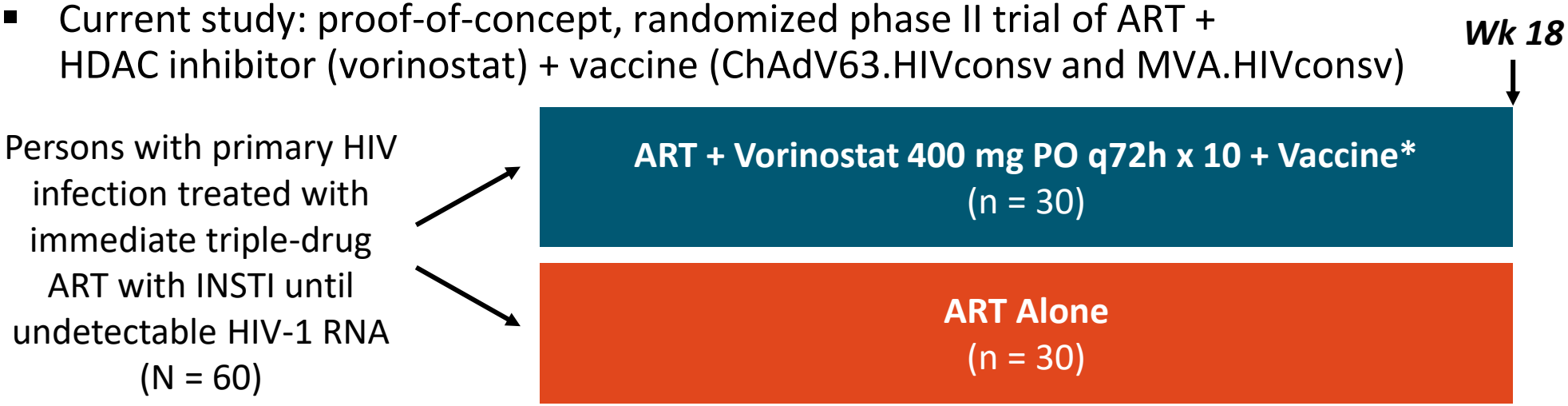
Lai M-T, et al. AIDS 2018. Abstract THPDB101.

Slide credit: clinicaloptions.com

RIVER: Akut HIV enfeksiyonunda ART ± vorinostat ile Prime/Boost Aşısı

RIVER: ART ± Vorinostat With Prime/Boost Vaccine in Primary HIV Infection

- Background: total HIV DNA predicts time to viral rebound after stopping treatment
- Current study: proof-of-concept, randomized phase II trial of ART + HDAC inhibitor (vorinostat) + vaccine (ChAdV63.HIVconsv and MVA.HIVconsv)



*Prime: ChAdV63.HIVconsv at randomization, boost: MVA.HIVconsv at Wk 8.

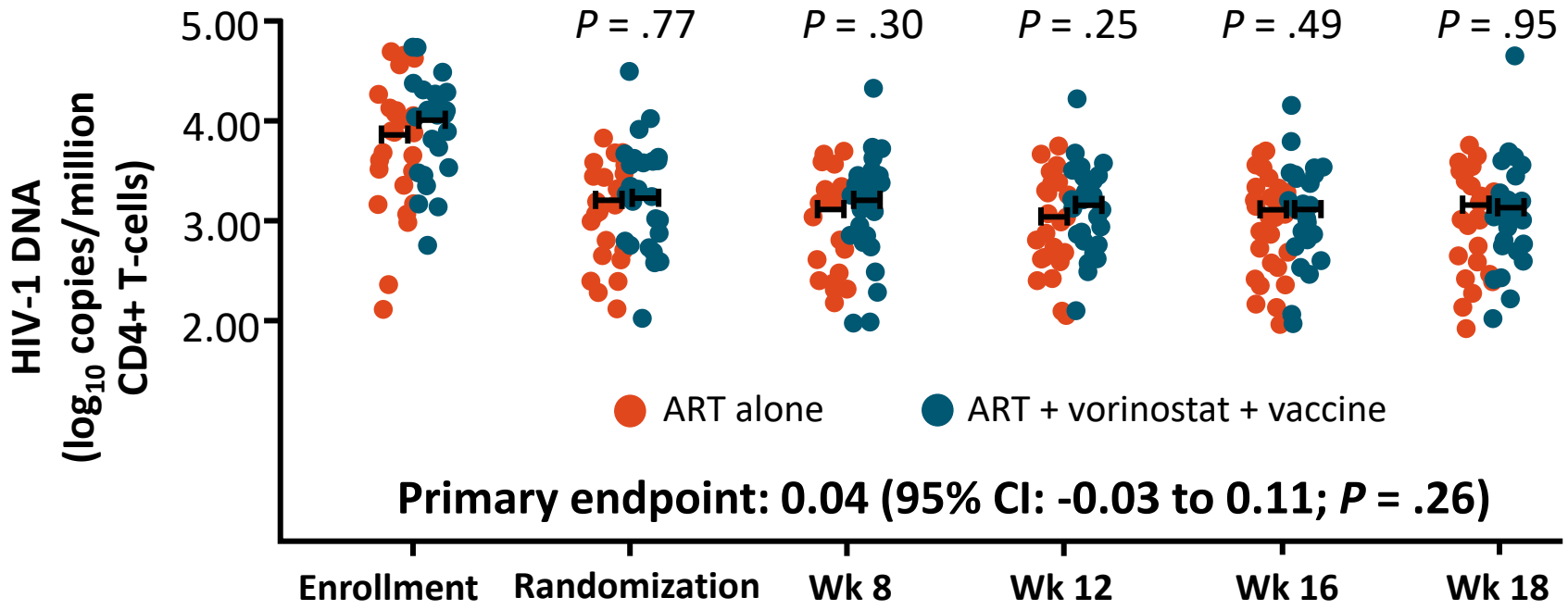
- Predominantly MSM (92%); median age: 32 yrs
- Primary endpoint: difference between arms in mean $\log_{10}$ HIV-1 DNA copies/million CD4+ T-cells averaged across Wks 16 and 18
- Secondary endpoint: HIV-specific T-cell responses by intracellular cytokine staining

Fidler S, et al. AIDS 2018. Abstract TUAA0202LB.

Slide credit: clinicaloptions.com

RIVER: HIV-1 DNA in CD4+ T-Cells

- No significant difference in proviral DNA reservoir in CD4+ T-cells at Wks 16-18



- Combination of HDAC inhibitor vorinostat + vaccine + ART safe and immunogenic and had no significant effect on proviral DNA reservoir vs ART alone
- More research needed

Fidler S, et al. AIDS 2018. Abstract TUAA0202LB.

Slide credit: clinicaloptions.com

HIV Cure Research: α4β7 Integrin

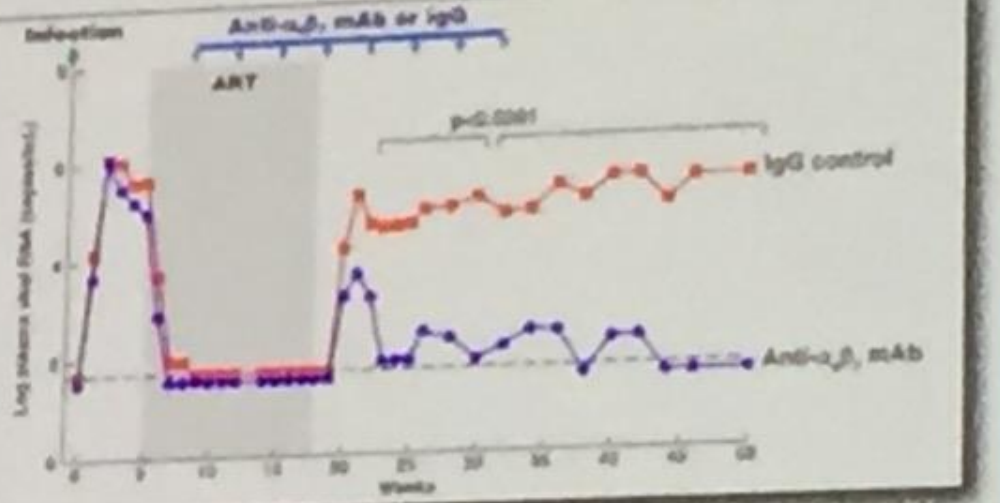
- In vitro, CD4+ T-cells with high vs low levels of **α4β7 integrin** more susceptible to HIV infection[1]
- Promising signals in SIV-infected nonhuman primates[2]
  - Treatment with **ART + primatized mAb against α4β7 integrin** associated with durable virologic suppression and normal CD4+ cell count, even after stopping treatment
  - However, confirmatory study with same design showed **no effect** on virologic suppression after stopping treatment[3]
- Vedolizumab: humanized mAb against **α4β7 integrin**[4]
  - FDA approved for Crohn's disease and ulcerative colitis in adults

1. Cicala C, et al. Proc Natl Acad Sci U S A. 2009;106:20877-20882. 2. Byrareddy SN, et al. Science. 2016;354:197-202.
3. Di Mascio M, et al. AIDS 2018. Abstract TUAA0206LB. 4. Vedolizumab [package insert]. 2018.

Science

Sustained Virologic Control in SIV+ Macaques after Anti-Retroviral and $\alpha_4\beta_7$ Antibody Therapy

SN Byrareddy et al.

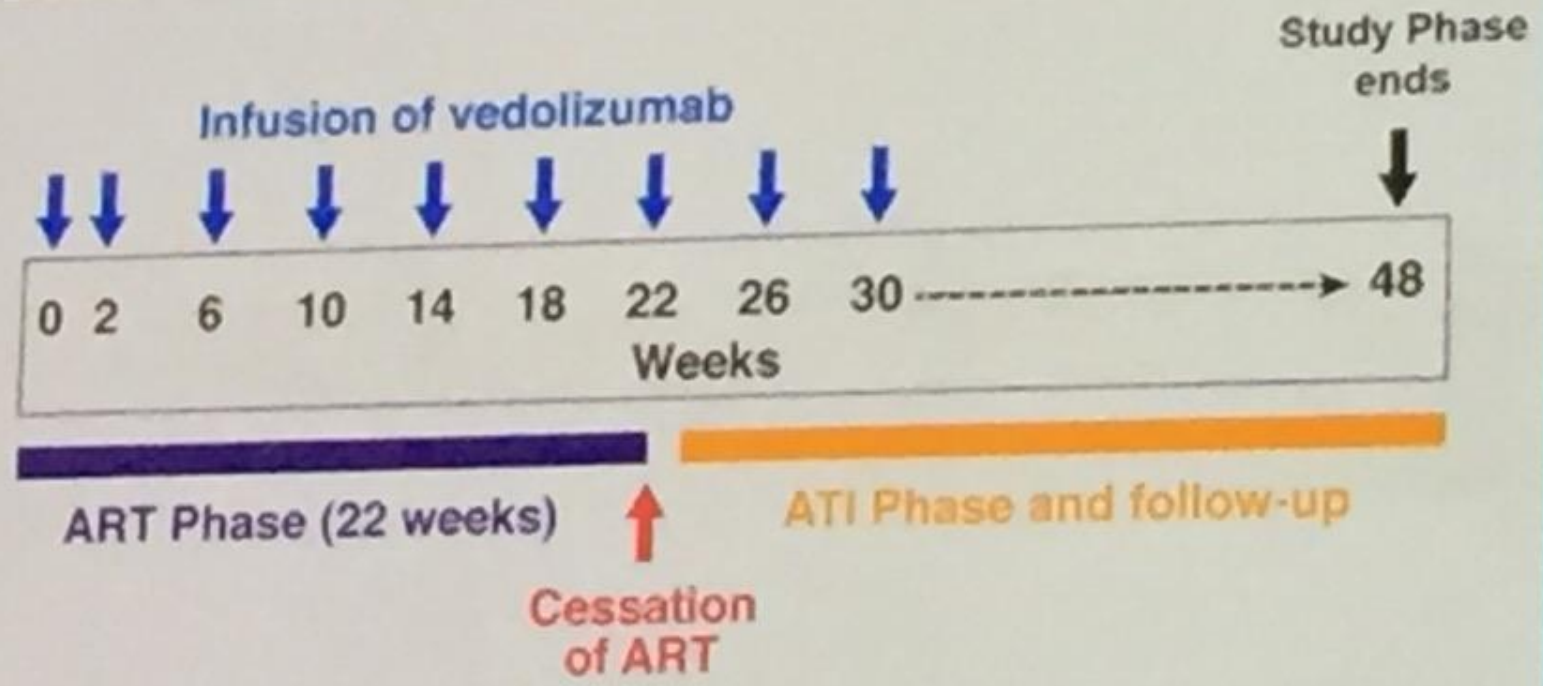


Follow-up studies

Repeat macaque study at NIH

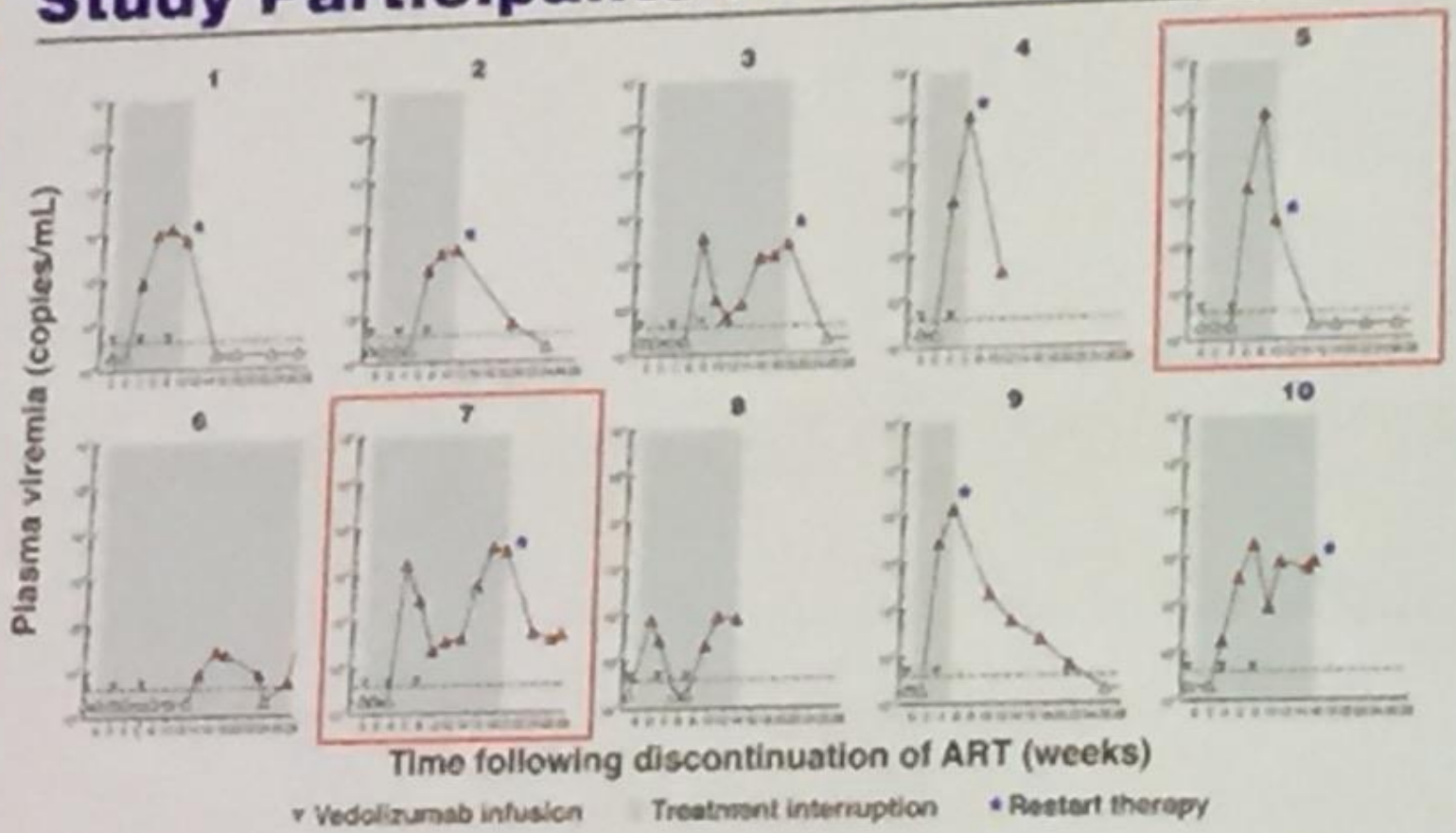
Initiate study in humans with vedolizumab

An Exploratory, Open-Label Study of Vedolizumab in Subjects wth HIV Infection Undergoing Analytical Treatment Interruption (ATI) of Antiretroviral Therapy (ART)



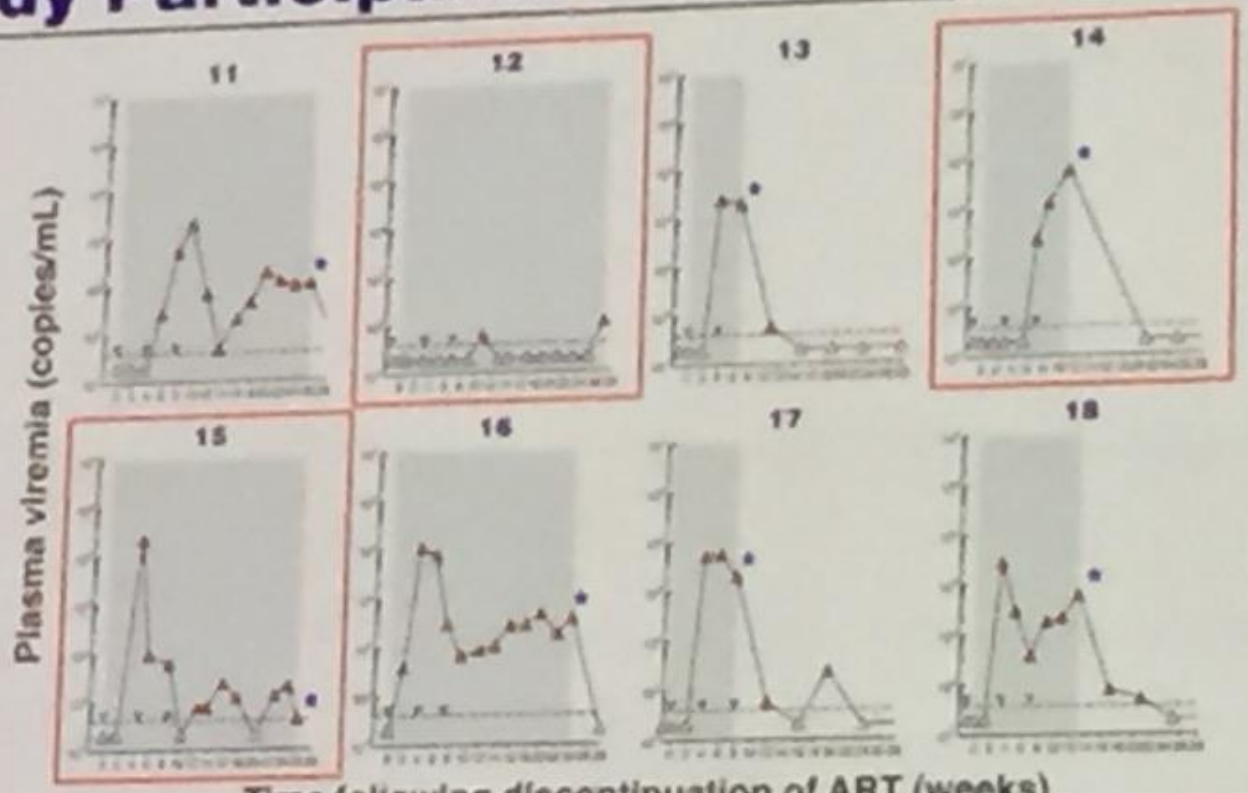
Infuse passive transfer of vedulizumab over infusions in 30 weeks.

Plasma Viremia of the Vedolizumab Study Participants Following ATI



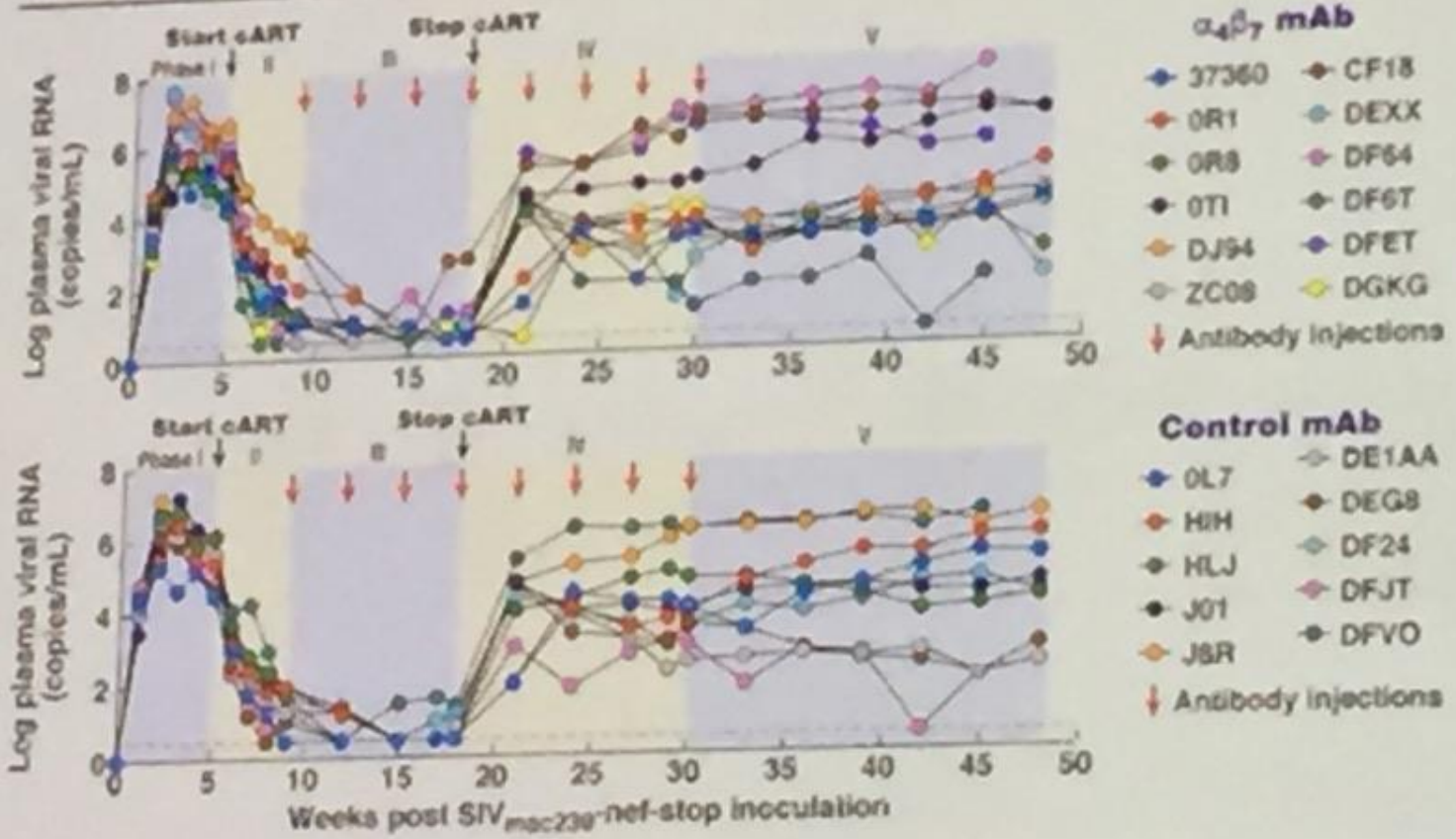
years.

Plasma Viremia of the Vedolizumab Study Participants Following ATI



interruption. Blue asterisk is when we triggered putting them

Effect of anti-$\alpha_4\beta_7$ Antibody on SIV-Infected Macaques



symposium. As Michaele showed, we didn't see the dramatic results at all. If you look at the IgG control at the bottom,

ÖZET

- PARTNER2: U=U
- ANRS Prevenir
  - gerektiğinde PrEP'in etkinliği
- DTG ve gebelik
  - konsepsiyonda kullanılabilir mi?
- DTG: monoterapi ✘ ama dual terapi ✓
- Kür arayışına devam...

HIV/AIDS KONGRESİ 2018

AIDS 2018

IAS-AIDS 2018

İLGİNİZ İÇİN TEŞEKKÜRLER!

DOÇ. DR. ULULHAN SILI

uluhan@hotmail.com

MARMARA ÜNİVERSİTESİ 1883

Tıp Fakültesi

How do further lower incidence?

- Treatment as prevention:
  - Use better regimens: TLD
  - Ensure adherence and monitor VL for suppression
- VMMC
- Pre-Exposure Prophylaxis for those at highest risk
- Targeted primary prevention programming for most vulnerable – DREAMS
- Condoms

Incidence monitoring using POC recency assay to target prevention activities

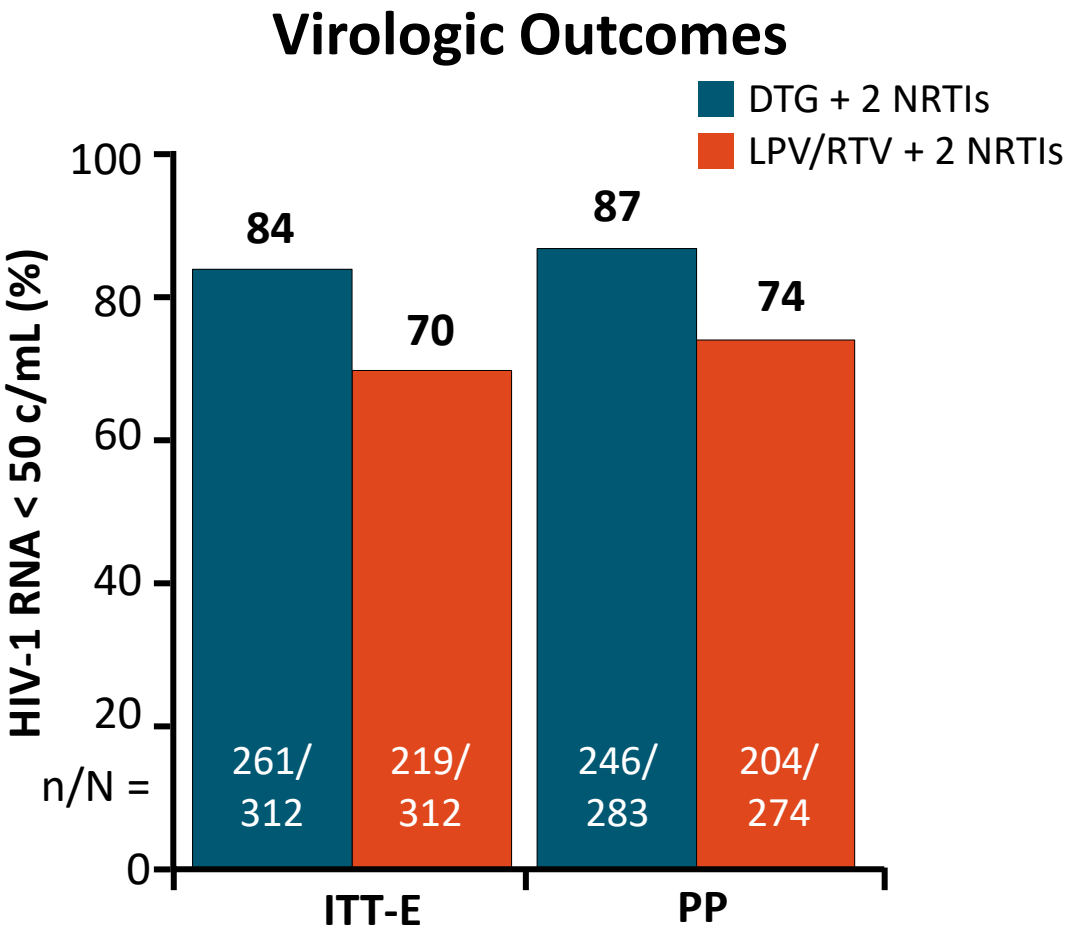
PEPFAR

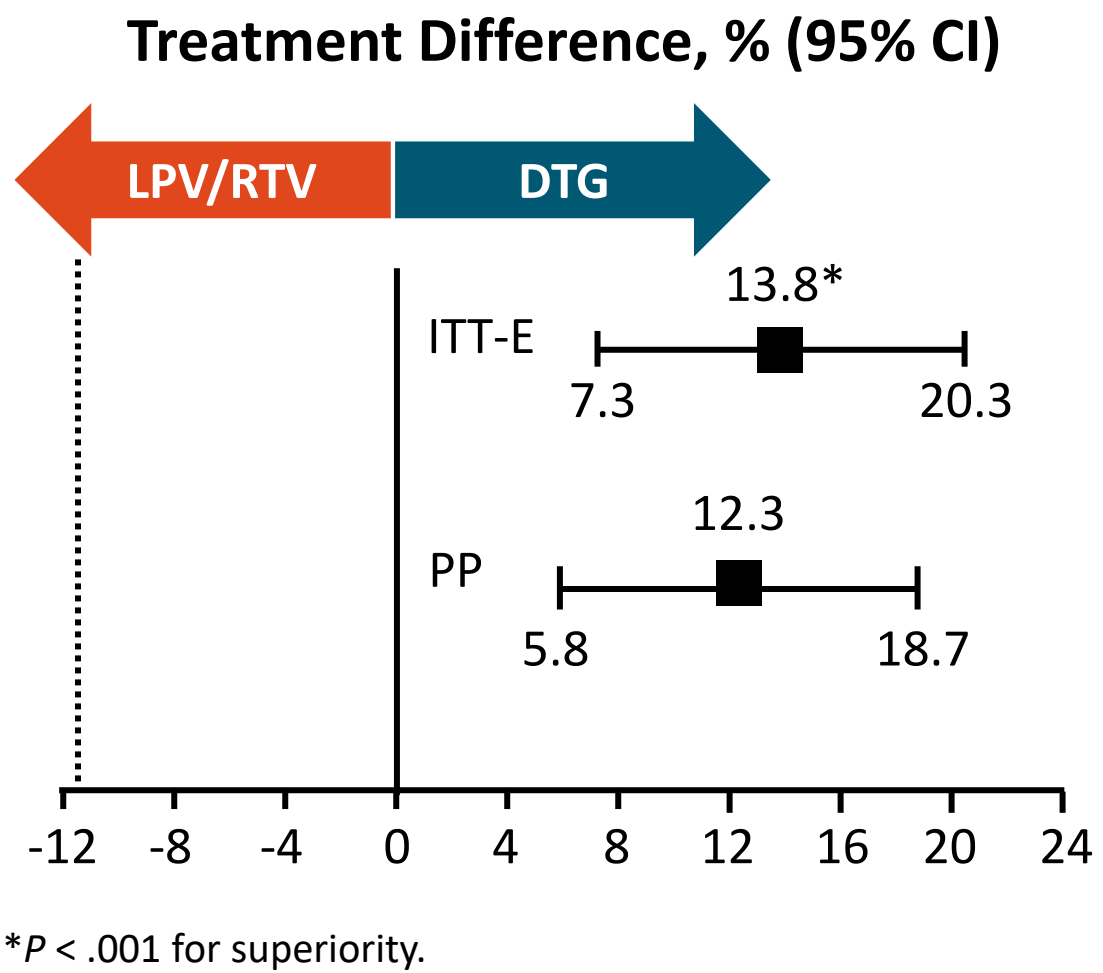
new incident cases. Part of what we need is better regimens,

İkincil ART

- DAWNING
  - 2 NRTI + DTG ile 2 NRTI + LPV/RTV'nin «devam ART» olarak karşılatırılması
  - Uluslararası, randomize, açık etiketli faz3b «non-inferiority» çalışması
  - Başlangıç NNRTI başarısızlığı
    - genotipik direnç analizi sonucuna göre ≥1 tam aktif NRTI

DAWNING: Virologic Response at Wk 48





*P < .001 for superiority.

Aboud M, et al. AIDS 2018. Abstract THPEB040.

Slide credit: clinicaloptions.com

DAWNING: Virologic Withdrawal and Treatment-Emergent Mutations

VW and Treatment-Emergent Mutations by BL NRTI Resistance	DTG + 2 NRTIs (n = 314)*			LPV/RTV + 2 NRTIs (n = 310)		
	VW, n/N	INSTI, n	NRTI, n	VW, n/N	PI, n	NRTI, n
M184I/V only	3/77	0	0	10/85	0	0
M184I/V + others, including K65R	4/184	2[†]	1[†]	10/167	0	2[‡]
K65R ± others, but not M184I/V	1/16	0	0	2/17	0	0
Others, excluding K65R and M184I/V	1/7	0	0	0	0	0
None	2/30	0	0	8/33	0	1[§]

*Includes 2 subjects randomized to LPV/RTV but treated with DTG.
[†]Emergent G118R (INSTI) + D67N (NRTI) in n = 1; H51H/Y, G118R, E138E/K, and R263R/K (all INSTI) in n = 1.
[‡]BL K65R + M184I/V in both with emergent K219K/Q or K219K/E + K70K/Q/R. [§]Emergent K70K/R + M184V.

- Met criteria for virologic withdrawal: DTG, n = 11; LPV/RTV, n = 30
  - Treatment-emergent resistance: DTG, n = 2; LPV/RTV, n = 3
- Fewer drug-related AEs with DTG vs LPV/RTV

Wang R, et al. AIDS 2018. Abstract THPEB071. Aboud M, et al. AIDS 2018. Abstract THPEB040.

BRIGHTE: Dirençli hastalarda Fostemsavir (gp120 inhibitörü)

- HIV'in hedef hücreye bağlanmasını ve girişini önlüyor
- Çoğul dirençli virüsü olan hastalarda
- Tek başına verildiğinde 1 haftada viral yükü -0.79 $\log_{10}$ kopya/ml düzeyinde düşürüyor (plasebo ile düşüş -0.17 $\log_{10}$ kopya/ml)

- OBT (optimized background regimen) ile 24. haftada hastaların %50 – 60'ında HIV RNA saptanamaz düzeyde

Vedolizumab Study: Criteria for Re-Starting ART Following Treatment Interruption

- A sustained (> 4 weeks) plasma HIV RNA >1000 copies/mL
- A >30% decline in baseline $CD4^+$ T-cell count or an absolute $CD4^+$ T-cell count <350 cells/mm^3
- Any HIV-related symptoms (e.g., acute retroviral syndrome, OI) or pregnancy

Vedolizumab Protocol in HIV-Infected Individuals

Secondary Objective: To evaluate the effect of vedolizumab on plasma viral rebound following ATI

Evaluation: Open-label study designed to detect a dramatic effect as seen in Byrareddy et al. macaque study.

Durable control of viremia not observed

In the absence of dramatic effect, no randomized control with which to compare

Results compared in post-hoc analysis to placebo arms of published ATI studies

objective was met. There were no infusion associated adverse

Vedolizumab in Virologically Suppressed Adults

- Open-label, single-arm, exploratory study of adults with virologic suppression on ART, CD4+ cell count > 450 copies/mm^3 (N = 18)
  - ART discontinued at Wk 22
  - Vedolizumab infusions at Wks 0 and 2, and then every 4 wks through Wk 30
- **Primary endpoint:** no infusion-related AEs or vedolizumab-related serious AEs before or after ART interruption
- **Secondary endpoint:** no difference in plasma viral rebound necessitating ART restart* with vedolizumab vs historical untreated controls through Wk 48
  - HR: 0.95 (95% CI: 0.42-2.13)
  - Historical untreated control data from published studies of ART interruption for post hoc analysis

*ART restart criteria: > 4 wks of HIV-1 RNA > 1000 copies/mL, decrease in CD4+ cell count by > 30% from baseline or decrease to < 350 cells/mm^3, HIV-related symptoms, or pregnancy.

Fauci AS, et al. AIDS 2018. Abstract WESS0102.