NUH HIV PROGRAMME

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HIV conference and treatment guidelines updates

Dr Dariusz P. Olszyna, MD, PhD, FAMS

National University Health Systems

Singapore

15 May 2018

Disclosures

Travel and subsistence fees from:
World Health Organization (WHO)
Janssen / Johnson & Johnson

Outline:

- newly approved agents
- dual ART
- rapid ART
- changes in guidelines
- TasP / U=U

ARVs available in Indonesia

TDF

ABC (only children?)

AZT

d4T

TDF/FTC (FDC)

Efavirenz

Rilpivirine

Nevirapine

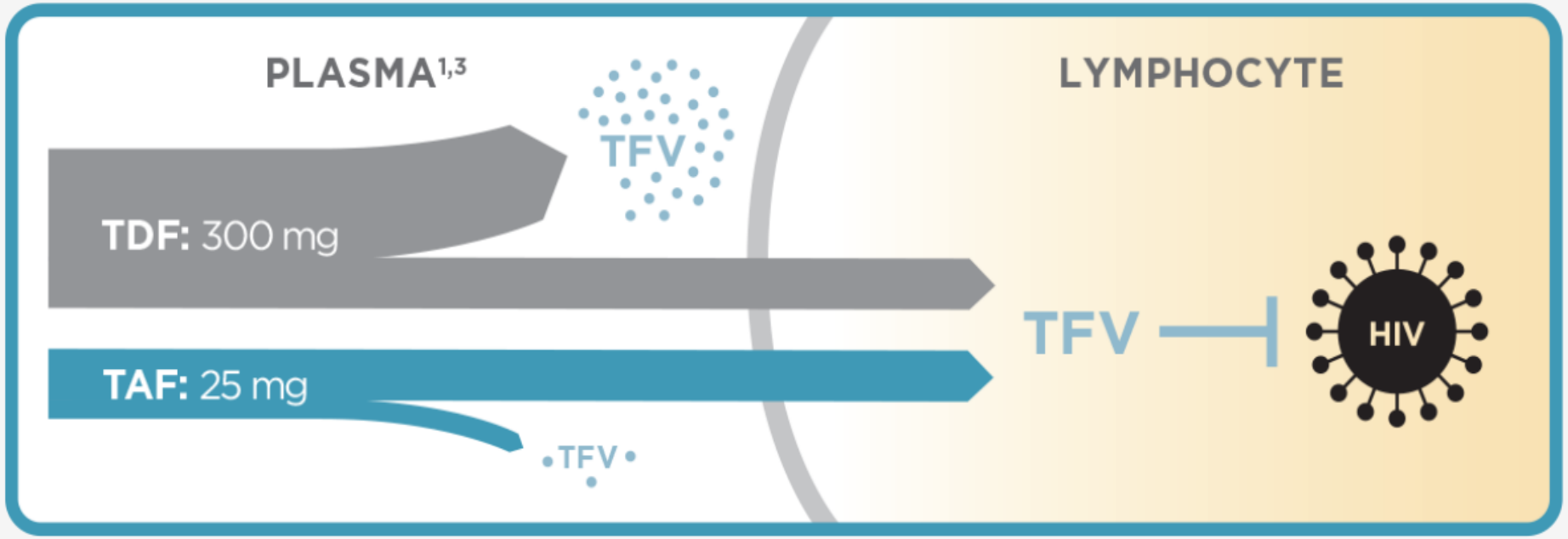
Lopinavir/r

Newly approved agents

Tenofovir alafenamide *(TAF)*

- Not really new, but we are prescribing it more and more.
- TAF causes less renal and bone toxicity than TDF
- Available in Indonesia soon?
- Currently prescribed to those with TDF-related tubulopathy or osteoporosis; especially if coinfected with HBV.
- Can be used in patients with CKD with CrCl > 15 ml/min

Tenofovir alafenamide *(TAF)*



>90% reduction of plasma TFV concentration

Tenofovir alafenamide

Descovy 200mg/ 25mg
Emtricitabine 200mg Tablet/
Tenofovir Alafenamide 25mg

Descovy 200mg/ 10mg
Emtricitabine 200mg Tablet/
Tenofovir Alafenamide 10mg

Tenofovir alafenamide

Dose of Descovy	Third agent in HIV treatment regimen (see section 4.5)
Descovy 200/10 mg once daily	Atazanavir with ritonavir or cobicistat Darunavir with ritonavir or cobicistat[1] Lopinavir with ritonavir
Descovy 200/25 mg once daily	Dolutegravir, efavirenz, maraviroc, nevirapine, rilpivirine, raltegravir

Regular dose: 25mg daily

Use TAF 10mg qd when combining with ritonavir or cobicistat

TAF has not been approved for PrEP!

Bictegravir

Bictegravir *(Gilead)*

novel unboosted INSTI (co-formulated):

- bictegravir/emtricitabine/TAF (STR)

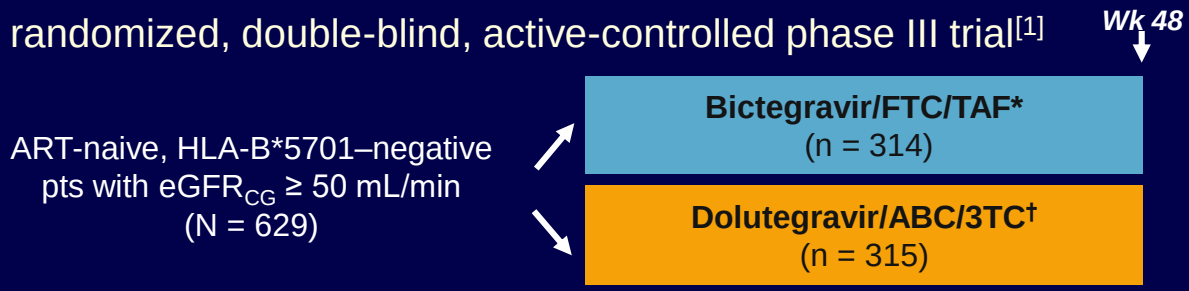
high barrier to resistance

competitor to DGV/3TC/ABC (Triumeq)

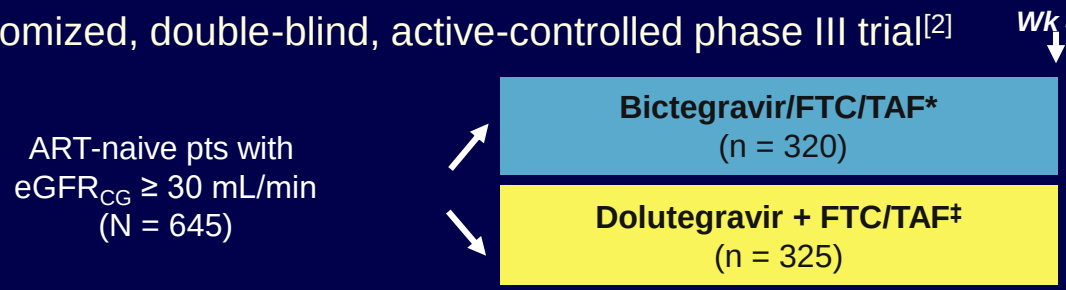
Approved by FDA in February 2018

Bictegravir/FTC/TAF vs Dolutegravir-Containing Regimens for Treatment-Naive Pts

- **Bictegravir**: novel QD unboosted INSTI coformulated with FTC/TAF
- GS-1489: randomized, double-blind, active-controlled phase III trial[1]



- GS-1490: randomized, double-blind, active-controlled phase III trial[2]



All pts also received placebo tablets for comparator regimen (eg, pts in GS-1489 who received BIC/FTC/TAF also received DTG/ABC/3TC placebo). *BIC/FTC/TAF, 50/200/25 mg PO QD. †DTG/ABC/3TC, 50/600/300 mg PO QD. ‡DTG + FTC/TAF, 50 + 200/25 mg PO QD

1. Gallant J, et al. IAS 2017. Abstract MOAB0105LB. 2. Sax PE, et al. IAS 2017. Abstract TUPDB0201LB.

BIC/FTC/TAF vs DTG-Containing Regimens: Selected Baseline Characteristics

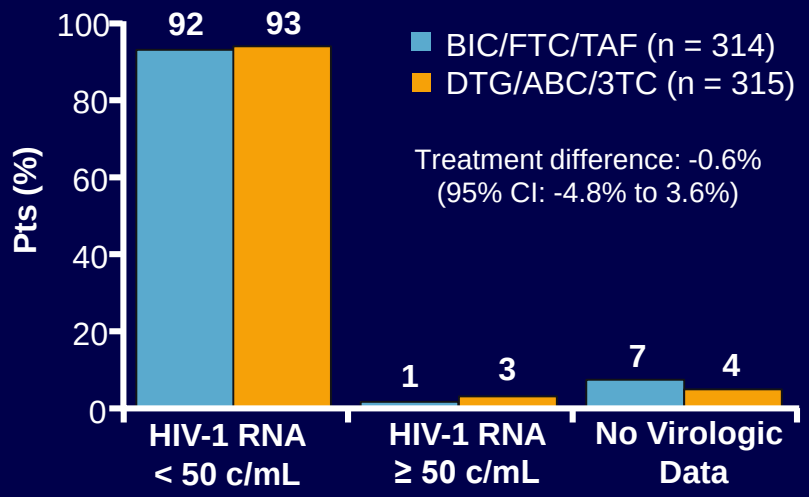
Baseline Characteristic	GS-1489[1]		GS-1490[2]	
	BIC/FTC/TAF (n = 314)	DTG/ABC/3TC (n = 315)	BIC/FTC/TAF (n = 320)	DTG + FTC/TAF (n = 325)
Median age, yrs (range)	31 (18-71)	32 (18-68)	33 (18-71)	34 (18-77)
Male, %	91	90	88	89
Median HIV-1 RNA, log_{10} copies/mL (IQR)	4.42 (4.03-4.87)	4.51 (4.04-4.87)	4.43 (3.95-4.90)	4.45 (4.03-4.84)
▪ HIV-1 RNA > 100,000 copies/mL, %	17	16	21	17
Median CD4+ cell count, cells/mm^3 (IQR)	443 (299-590)	450 (324-608)	440 (289-591)	441 (297-597)
▪ CD4+ cell count < 200 cells/mm^3, %	11	10	14	10

1. Gallant J, et al. IAS 2017. Abstract MOAB0105LB. 2. Sax PE, et al. IAS 2017. Abstract TUPDB0201LB.

Slide credit: clinicaloptions.com

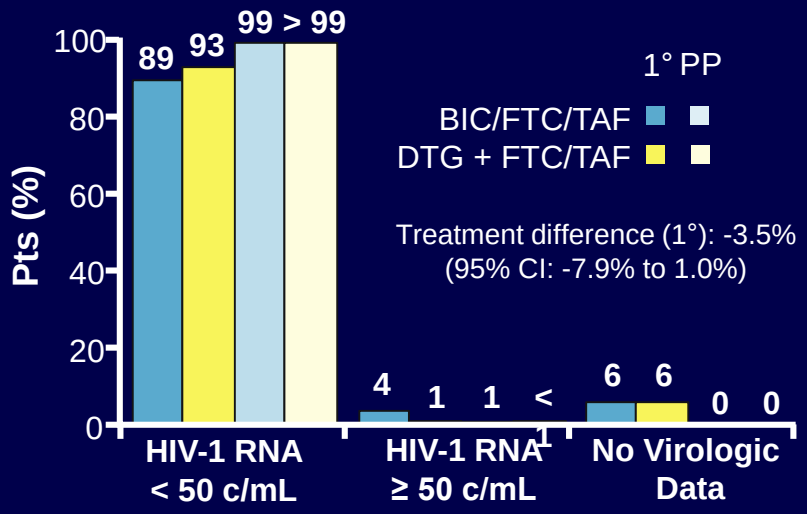
BIC/FTC/TAF vs DTG-Containing Regimens: Key Efficacy Findings

GS-1489: Wk 48 Virologic Efficacy[1]



- No resistance for any regimen components detected for either group

GS-1490: Wk 48 Virologic Efficacy[2]



- No resistance for any regimen components detected for either group

1. Gallant J, et al. IAS 2017. Abstract MOAB0105LB. Reproduced with permission.
2. Sax PE, et al. IAS 2017. Abstract TUPDB0201LB. Reproduced with permission.

Slide credit: clinicaloptions.com

BIC/FTC/TAF vs DTG-Containing Regimens: Key Safety Findings

Outcome Through Wk 48	GS-1489[1]		GS-1490[2]	
	BIC/FTC/TAF (n = 314)	DTG/ABC/3TC (n = 315)	BIC/FTC/TAF (n = 320)	DTG + FTC/TAF (n = 325)
Diarrhea, %	12.7	13.0	11.6	12.0
Headache, %	11.5	13.7	12.5	12.3
Nausea, %	10.2	22.9*	7.8	8.9
Upper respiratory tract infection, %	6.4	10.8	4.7	7.1
Median $eGFR_{CG}$ Δ from BL, mL/min	-10.5	-10.8†	-7.3	-10.8‡
Mean BMD Δ from BL, % spine/hip	-0.83/-0.78	-0.60/-1.02†	NR	NR
D/c for AE, n (%)	0	4 (1.3)	5 (1.6)	1 (0.3)

*P < .001. †P = NS. ‡P = .02.

- GS-1489: similar changes in lipids and proteinuria between groups; some pt-reported neuropsychiatric (eg, anxiety, depression) and sleep-related symptoms (eg, disturbance) more frequent with DTG/ABC/3TC
- No d/c for renal AEs and no proximal tubulopathy for any regimen

1. Gallant J, et al. IAS 2017. Abstract MOAB0105LB. 2. Sax PE, et al. IAS 2017. Abstract TUPDB0201LB.

Switching from DGV to BGV
Molina JM, e.a. (CROI 2018)

- Phase III study
- Patients virologically suppressed on DGV/3TC/ABC switched to BGV/FTC/TAF
- 48-week results showed noninferiority in virological suppression, but no advantage over existing DGV/3TC/ABC
- Same safety parameters

Dual ART

rilpivirine/dolutegravir (STR)
SWORD-1 and SWORD-2 trials

- First dual treatment in history approved by FDA in November 2017
- smallest STR on the market

"The U.S. FDA approved DGV/RPV as a complete regimen for the treatment of HIV-1 infection in adults who are virologically suppressed (HIV-VL <50 copies/mL) on a stable ART regimen for at least six months with no history of treatment failure and no known mutations associated with resistance to DGV or RPV"

Rilpivirine/dolutegravir (STR)
SWORD-1 and SWORD-2 trials

- it is clear now that you do not need three drugs to control HIV
  - Better compliance with fewer pills
  - Less side effects to be expected in long-term with fewer agents
- reasonable to switch patients who have been virologically suppressed for >6 months on a triple ART to DGV/RPV if they fit the same population criteria as in the SWORD studies

- cannot be used in patients with viral replications:
  - treatment naïve patients
  - patients failing their current ART regimen
  - Patient with (cross)resistance to DGV or RPV

DTG/RPV FDA Approved for Maintenance Therapy

- Once-daily single-tablet regimen of DTG and RPV
  - First 2-drug STR FDA approved for use as a complete regimen in the US

Key US Label Information	
Indication	▪ For patients who have been virologically suppressed for ≥ 6 mos, with no history of treatment failure and no resistance to DTG or RPV
Administration requirements	▪ Must be taken with a meal
Key DDIs	▪ Separate dose of DTG/RPV and antacid/polyvalent cation–containing medications ▪ Avoid PPIs (eg, omeprazole, pantoprazole), dexamethasone
Dose adjustments	▪ None required for patients with mild/moderate renal impairment; in patients with CrCl < 30 mL/min, increase monitoring for AEs

DTG/RPV [package insert]. November 2017.

Slide credit: clinicaloptions.com

Other TDF- and ABC-Sparing ART Strategies

Study	Initial or Switch From Suppr. ART	N	Regimen	Results
PADDLE[1,2]	Initial	20	DTG + 3TC	Small study; encouraging efficacy
ACTG 5353[3]	Initial	120	DTG + 3TC	Encouraging efficacy; 1 patient with resistance at VF
LAMIDOL[4]	Switch	110	DTG + 3TC	Encouraging efficacy
SALT[5]	Switch	286	ATV/RTV + 3TC	Similar efficacy as ATV/RTV + 2 NRTIs
ATLAS-M[6]	Switch	266	ATV/RTV + 3TC	Noninferior and superior efficacy vs ATV/RTV + 2 NRTIs
NEAT001/ANRS143[7]	Initial	805	DRV/RTV + RAL	Similar efficacy as DRV/RTV + FTC/TDF
ANDES[8]	Initial	145	DRV/RTV + 3TC	Similar efficacy as DRV/RTV + 3TC/TDF at interim
NA[9]	Switch	48	DRV/RTV + 3TC	Small study; encouraging efficacy

References in slidenotes

Slide credit: clinicaloptions.com

Rapid ART


CROI 2018
Conference on Retroviruses
and Opportunistic Infections

Current Recommendations for Initiating ART

- DHHS, IAS-USA, and WHO guidance recommend ART for all HIV-infected pts worldwide, regardless of CD4+ cell count
- ART initiation recommended as soon as possible by DHHS and IAS-USA[1,2]
  - WHO recommends ART be offered on day of diagnosis where feasible[3]
- Guidelines note importance of educating pts on ART benefits, considerations, and strategies for optimizing adherence

1. DHHS Guidelines. October 2017. 2. Günthard HF, et al. JAMA. 2016;316:191-210.
3. WHO. July 2017.

Rapid ART Program for HIV Diagnoses (RAPID) in San Francisco

- ART initiation recommended as soon as possible by DHHS and IAS-USA; WHO recommends ART be offered on day of diagnosis where feasible[1-3]
- San Francisco Getting to Zero Consortium's Citywide RAPID program: accelerated ART initiation for newly diagnosed HIV[4]
  - All new confirmed HIV diagnoses linked to care within 5 working days
  - First care visit: baseline labs collected, counseling, medical/psychosocial assessment, ART started unless risk for fatal IRIS
  - ART: (INSTI or DRV/RTV) + FTC/TDF (4-drug regimen optional if HIV infection suspected to have occurred while on PrEP)
  - Dissemination: HIV clinics identified using HIV surveillance data, linkage navigators utilized RAPID Provider Directory to identify best clinic for each patient

1. DHHS Guidelines. October 2017. 2. Günthard HF, et al. JAMA. 2016;316:191-210.
3. WHO. July 2017. 4. Bacon O, et al. CROI 2018. Abstract O93.

RAPID ART in San Francisco: Care Linkage, ART Initiation, and Virologic Suppression

Significance of RAPID ART:
People with HIV become practically non-infectious two months from the diagnosis!

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Median time from diagnosis to care entry, d	8	7	5	-38
Median time from first care visit to ART initiation, d	27	17	6	1	-96
Median time from ART start to HIV-1 RNA < 200 c/mL, d	70	53	50	38	-46
Median time from diagnosis to HIV-1 RNA < 200 c/mL, d	134	92	77	61	-54

- Time to ART start and first viral suppression decreased in vulnerable populations, including racial/ethnic minorities and homeless patients, although disparities still exist for some outcomes

Bacon O, et al. CROI 2018. Abstract O93.

Slide credit: clinicaloptions.com

Changes in Treatment Guidelines

EACS Guidelines Updated to Version 9.0: Summary of Changes to ART Recommendations

Initial ART

- Older agents (LPV/RTV) removed
- Regimen order updated to reflect preference based on available data
- Footnotes added: when TAF preferred over TDF, potential CVD toxicity of DRV, ATV and renal toxicity

Virologic Failure

- Definition revised to differentiate incomplete suppression from virologic rebound
- Note added on importance of considering all available resistance tests when choosing new regimen for pts with virologic failure

Switch Strategies

- Indications for switch added: HCV treatment, renal/bone toxicity
- DTG + RPV added as switch option
- DTG monotherapy added as NOT recommended

- EFV warning removed
- EFV, RAL, RPV, or DRV/RTV can be continued during pregnancy
- Women on EVG/COBI need to be informed that more monitoring of HIV-1 RNA and drug levels may be necessary during pregnancy
- Added recommendation against initial use of TAF and COBI
- Added recommendation against breastfeeding

EACS Guidelines. Version 9.0. October 2017.

Slide credit: clinicaloptions.com

US DHHS Guidelines Updated October 2017: Summary of Initial ART Recommendations

Recommended Initial Regimens for Most People With HIV
▪ DTG/ABC/3TC ▪ DTG + FTC/(TAF or TDF) ▪ EVG/COBI/FTC/(TAF or TDF) ▪ RAL + FTC/(TAF or TDF)

- Recommendations may differ based on baseline HIV-1 RNA, CD4+ count, CrCl, eGFR, HLA-B*5701 status, HBsAg status, and osteoporosis status
- Separate list of *Recommended Initial Regimens in Certain Clinical Situations* includes PIs, NNRTIs, and other INSTI combination regimens

DHHS ART Guidelines. October 2017.

Slide credit: clinicaloptions.com

Increasing HIV-1 Pretreatment Resistance to NNRTIs in Low- and Middle-income countries

Armstrong WS, e.a.

Lancet Infect Dis 2018 Mar

WHO Guidelines 2016

- Recommended NNRTI-based regimen

- Systematic review and meta-regression analysis
- 56,044 patients
- 63 countries (five regions)

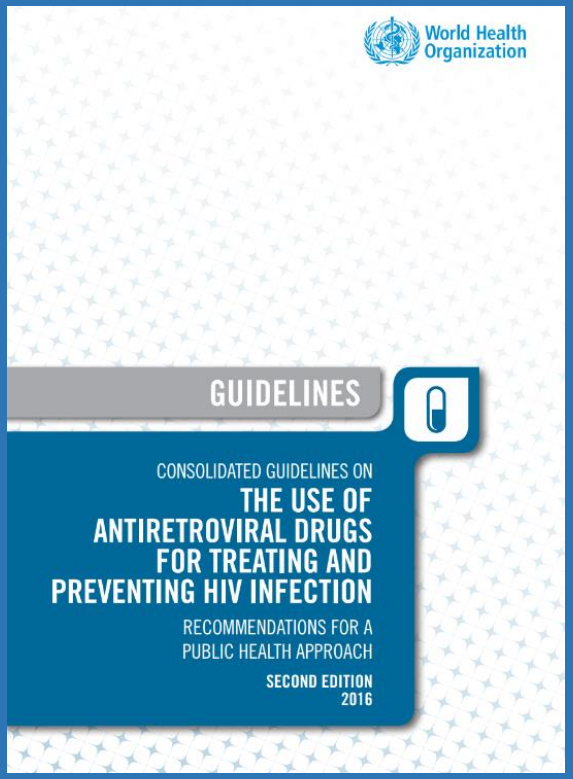
- No change in NRTI resistance
- Significant annual *increase* of NNRTI resistance:
  - 23% in Southern Africa
  - 11% in Asia
- Estimates of *absolute* pretreatment drug resistance in 2016:
  - Southern Africa: 11%
  - Eastern Africa: 10.1%

What does that mean?

- NNRTIs are not recommended as empirical treatment (without Genotypic Resistance Testing) in areas with pretreatment resistance >10%
- We will all need GRT sooner or later
- For now there needs to be country wide surveillance of the pretreatment NNRTI resistance in countries such as Indonesia
- We will need access to generic dolutegravir for first line treatment soon

WHO Guidelines 2017

WHO amended its guideline in 2017 recommending urgent consideration of a non-NNRTI containing regimen for areas with >10% pretreatment resistance



TasP / U=U

Partner Study (2016)

- 1,166 HIV serodiscordant couples (61.7% heterosexual and 38.3% MSM) in 14 European countries
- HIV+ partner on ART and undetectable (<200 cp/mL)
- 1,238 eligible couple-years of follow up
- acts of condomless penetrative sex:
  - MSM couples: 22,000
  - heterosexual couples: 36,000

PARTNER

Partner Study (2016)

58,000 acts of condomless penetrative sex

ZERO HIV transmissions!

PARTNER

Opposites Attract Study

Opposites Attract Study

- 343 HIV serodiscordant gay couples
- HIV+ partner on ART and undetectable
- 73.8% couples reported condomless anal sex (318 cumulative years of follow-up data)
  - 16,889 acts of condomless anal sex

Opposites Attract Study

16,889 acts of condomless anal sex:

- in 5,000 acts HIV negative participant was on PrEP

12,000 acts of condomless anal sex

ZERO HIV transmissions!

STIs diagnosed in:

- 14.3% HIV+ participants
- 11.7% HIV- participants

Opposites Attract Study

12,000

Undetectable: HIV-VL <200 cp/mL

PARTNER

58,000

12,000

70,000 acts of condomless penetrative sex

ZERO HIV transmissions!

Bottom line…

There has never been a recorded case of HIV transmission from an HIV-positive person to their HIV-negative sexual partner when HIV-positive partner had undetectable viral load

There has never been a more hopeful time in the history of AIDS. Revolutionary advances in HIV prevention and treatment can now bring the epidemics of HIV stigma and HIV to a halt.

Source: Prevention Access Campaign

"U=U is a simple but hugely important campaign based on a solid foundation of scientific evidence. It has already been successful in influencing public opinion, causing more people with HIV (and their friends and families) to comprehend that they can live long, healthy lives, have children, and never have to worry about passing on their infection to others."

The Lancet (November, 2017)

"These scientific findings require that we step back and re-assess what we thought we knew for the last 36 years. At United States Conference on AIDS and in discussions we've been having for about a year with internal and external stakeholders, it is clear that people living with HIV are leading the way, and they are more than ready for others to follow."

Richard Wolitski, Ph.D., Director, Office of HIV/AIDS and Infectious Disease Policy, U.S. Department of Health and Human Services (September, 2017)

Source: Prevention Access Campaign

prevention access campaign

Endorsements Updated: January 28, 2018
Issued: July 21, 2016

RISK OF SEXUAL TRANSMISSION OF HIV FROM A PERSON LIVING WITH HIV WHO HAS AN UNDETECTABLE VIRAL LOAD

Messaging Primer & Consensus Statement

Editor's Note 1/10/18: The term "negligible" is not effective in public health messaging to describe the risk of HIV sexual transmission when a person with HIV has an undetectable viral load and is taking ART as prescribed. "Negligible" is often misconstrued as still a risk to take into consideration in sexual and reproductive health decisions. Please see the messaging guide with examples of the words used in public health messaging to convey the risk including "effectively no risk", "cannot transmit" and "do not transmit." It is imperative that language instills confidence rather promote unnecessary fear about sexual transmission when a person with HIV has an undetectable viral load and is taking ART as prescribed.

There is now evidence-based confirmation that the risk of HIV transmission from a person living with HIV (PLHIV), who is on Antiretroviral Therapy (ART) and has achieved an undetectable viral load in their blood for at least 6 months is negligible to non-existent. (Negligible is defined as: *so small or unimportant as to be not worth considering; insignificant.*) While HIV is not always transmitted even with a detectable viral load, when the partner with HIV has an undetectable viral load this both protects their own health and prevents new HIV infections.[i]

However, the majority of PLHIV, medical providers and those potentially at risk of acquiring HIV are not aware of the extent to which successful treatment prevents HIV transmission.[ii] Much of the messaging about HIV transmission risk is based on outdated research and is influenced by agency or funding restraints and politics which perpetuate sex-negativity, HIV-related stigma and discrimination.

The consensus statement below, addressing HIV transmission risk from PLHIV who have an undetectable viral load, is endorsed by principal investigators from each of the leading studies that examined this issue. It is important that PLHIV, their intimate partners and their healthcare providers have accurate information about risks of sexual transmission of HIV from those successfully on ART.

At the same time, it is important to recognize that many PLHIV may not be in a position to reach an undetectable status because of factors limiting treatment access (e.g., inadequate health systems, poverty, racism, denial, stigma, discrimination, and criminalization), pre-existing ART treatment resulting in resistance or ART toxicities. Some may choose not to be treated or may not be ready to start treatment.

Understanding that successful ART prevents transmission can help reduce HIV-related stigma and encourage PLHIV to initiate and adhere to a successful treatment regimen.

Source: Prevention Access Campaign

BHIVA
British HIV Association

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BHIVA endorses 'Undetectable equals Untransmittable' (U=U) consensus statement

Wednesday 12 July 2017

The British HIV Association (BHIVA), today announces its endorsement for the 'Undetectable Equals Untransmittable' (U=U) Consensus Statement produced by the Prevention Access Campaign.

BHIVA Chair, Professor Chloe Orkin, said: "As the UK's leading voice for HIV health professionals, our backing for U=U is unequivocal. There should be no doubt about the clear and simple message that a person with sustained, undetectable levels of HIV virus in their blood cannot transmit HIV to their sexual partners.

"This fact is a testament to the preventive impact of effective HIV treatment and highlights the need to maximise access to treatment in order to minimise and ultimately eradicate HIV transmission. Spreading the U=U message is also an important way to help reduce the stigma experienced by people living with HIV, whose sexual partners may fear infection unnecessarily."

The U=U statement is based on evidence from the PARTNER study (published in the Journal of the American Medical Association, 12 July 2016) which reported that the risk of HIV transmission with effective treatment is negligible.

Ends

For further information, please contact Curium Communications:
Jon Cope: 07867 508212
jon@curium.cc

Dear Colleague: September 27, 2017

Dear Colleague

INFORMATION FROM CDC'S DIVISION OF HIV/AIDS PREVENTION

September 27, 2017

Dear Colleague,

Today is National Gay Men's HIV/AIDS Awareness Day. On this day, we join together in taking actions to prevent HIV among gay and bisexual men and ensure that all gay and bisexual men living with HIV get the care they need to stay healthy. Gay and bisexual men are severely affected by HIV. More than 26,000 gay and bisexual men received an HIV diagnosis in 2015, representing two-thirds of all new diagnoses in the United States, and diagnoses increased among Hispanic/Latino gay and bisexual men from 2010 to 2014.

However, recent trends suggest that prevention efforts are slowing the spread of HIV among some gay and bisexual men. From 2010 to 2014, HIV diagnoses fell among white gay and bisexual men and remained stable among African American gay and bisexual men after years of increases.

Scientific advances have shown that antiretroviral therapy (ART) preserves the health of people living with HIV. We also have strong evidence of the prevention effectiveness of ART. When ART results in viral suppression, defined as less than 200 copies/ml or undetectable levels, it prevents sexual HIV transmission. Across three different studies, including thousands of couples and many thousand acts of sex without a condom or pre-exposure prophylaxis (PrEP), no HIV transmissions to an HIV-negative partner were observed when the HIV-positive person was virally suppressed. This means that people who take ART daily as prescribed and achieve and maintain an undetectable viral load have effectively no risk of sexually transmitting the virus to an HIV-negative partner.

However, according to a recent *Morbidity and Mortality Weekly Report*, too many gay and bisexual men living with HIV are not getting the care and treatment they need. Among gay and bisexual men living with diagnosed HIV, 61% have achieved viral suppression, more than in previous years, but well short of where we want to be. More work is needed to close this gap and to address the barriers that make it more difficult for some gay and bisexual men, including African American and Hispanic/Latino men, to get HIV care and treatment. For example, socioeconomic factors such as lower income and educational levels and cultural factors such as stigma and discrimination may affect whether some gay and bisexual men seek and are able to receive HIV treatment and prevention services.

Across three different studies, including thousands of couples and many thousand acts of sex without a condom or pre-exposure prophylaxis (PrEP), no HIV transmissions to an HIV-negative partner were observed when the HIV-positive person was virally suppressed. This means that people who take ART daily as prescribed and achieve and maintain an undetectable viral load have effectively no risk of sexually transmitting the virus to an HIV-negative partner.

Caveats of U=U

- HIV+ partner should be under continuous medical care
- No adherence problems (to ensure continuing viral suppression)
- What about viral blips?
- What about STIs which could facilitate easier HIV transmission?

Significance of Partner and Opposites Attract Studies

People with HIV can now have fulfilling relationships with their partners without fear of infecting them.

For the first time in more than three decades KAPs such as gay men can enjoy sex without fear.

Important tool in fighting stigma

90-90-90 Millennium Goals

HIV Conference Updates

Take Home Messages

TAF on the market and building more experience (useful in patients on TDF with CKD/tubulopathy or osteoporosis)

Lower dose of TAF from 25mg to 10mg when combining with ritonavir or cobicistat

Bictegravir: a new STR co-formulated with hepB active and kidney-”friendly” backbone of FTC/TAF

DGV/RPV dual treatment now available as switch therapy for suppressed patients.

Moving towards “RAPID ART”.

Treatment guidelines now recommend INSTI-based regimens as first line (no PIs or NNRTI-based combinations)

Pregnancy warning now removed from both EACS and DHHS guidelines for efavirenz.

Increase in transmitted NNRTI resistance in low- and middle income countries.

TasP/U=U means people with HIV do not sexually transmit the virus.