IAS 2015 Report Back

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Disclosures

None

Some slides adapted from Clinical Care Options (CCO) Highlights of IAS 2015
Slide Deck: clinicaloptions.com/hiv

Original slide sets can be downloaded from pag.ias2015.org

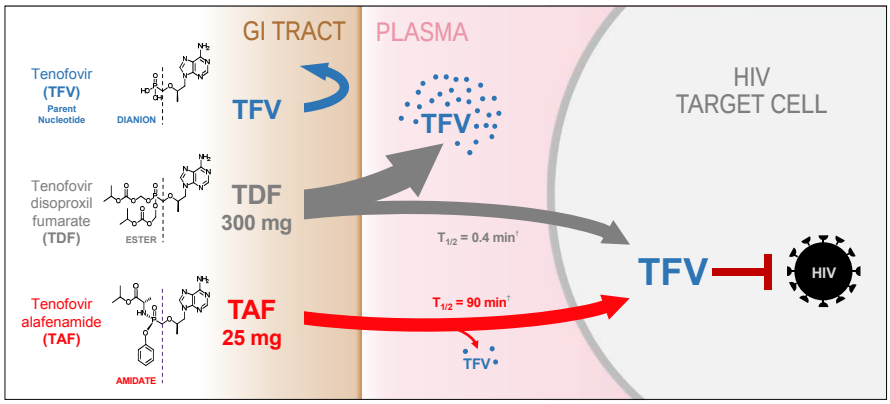
Outline

- Antiretroviral Therapeutics
- HCV
- HIV Prevention
  - Treatment as Prevention (TasP)
  - PrEP
- The Global HIV Epidemic
  - Getting to 90-90-90

Antiretroviral Therapeutics

- TAF
  - GS109 Switch Study
  - GS 112 Switch Study in Adults with Renal Impairment
  - TAF in Patients with HIV/HBV Coinfection
- Doravarine
  - Efficacy and Safety Study
- 2nd Generation Maturation Inhibitor, BMS 176
  - Dose Ranging study with Atazanavir

Tenofovir Alafenamide (TAF): Novel Prodrug of Tenofovir



- **91% lower plasma TFV levels minimize renal and bone effects while maintaining high potency for suppressing HIV**

† $T_{1/2}$ based on *in vitro* plasma data.

1. Lee WV et. *Antimicr Agents Chemo* 2005;49(5):1898-1906. 2. Birkus G et al. *Antimicr Agents Chemo* 2007;51(2):543-550. 3. Babusis D, et al. *Mol Pharm* 2013;10(2):459-66. 4. Ruane P, et al. *J Acquir Immune Defic Syndr* 2013; 63:449-5. 5. Sax P, et al. *JAIDS* 2014. 2014;67(1):52-8. 6. Sax P, et al. *Lancet* 2015;385:2606-15.

2015 Snapshot of the Current TAF Landscape

Treatment Naïve
GS 104 & 111
Wohl and Sax CROI 201, Sax Lancet 2015

Results:
E/C/F/TAF **non-inferior** to E/C/F/TDF
Less decline in BMD, eGFR, and less alteration in tubular function

Switch to E/C/F TAF Renal Impairment
GS 112
48 week data Pozniack CROI 2015

Results:
92% retained virologic suppression, no change in eGFR, improvement in markers of tubular function and BMD.

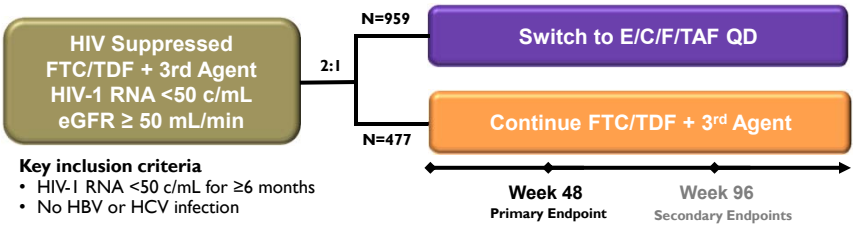
IAS 2015

TAF Switch Study
GS 109

Efficacy and Comorbidities in Subpopulations:
- GS 112 Renal Impairment- stratified by pre switch TDF use
- HBV/HIV Coinfected

Study 109: Switch from a TDF-containing regimen to E/C/F/TAF

Phase 3, 96-week, multi-centered, randomized, open label, active-controlled



Key inclusion criteria
- HIV-1 RNA <50 c/mL for ≥6 months
- No HBV or HCV infection

TDF-containing regimens
- Stribild (32%), Atripla (26%), RTV or boosted (cobi or ritonaivr) ATV+FTC/TDF (42%)

Primary Endpoint :
Non-inferiority (12% margin) of switch to E/C/F/TAF vs continuation of baseline regimen by FDA Snapshot analysis (HIV-1 RNA <50 copies/mL at week 48)

Secondary Endpoints:
Efficacy through Week 96
Safety and tolerability through Week 48 and Week 96"

E/C/F/TAF: single-tablet regimen elvitegravir 150mg/ cobicistat 150mg/ emtricitabine 200mg/ tenofovir alafenamide 10mg
STB = Stribild = single-tablet regimen elvitegravir 150mg/ cobicistat 150mg/ emtricitabine 200mg/ tenofovir DF 300mg
ATR = Atripla = single-tablet regimen efavirenz 600mg/ emtricitabine 200mg/ tenofovir DF 300mg
ATV = atazanavir, COBI = cobicistat, RTV = ritonavir

ClinicalTrials.gov Identifier: NCT01815736

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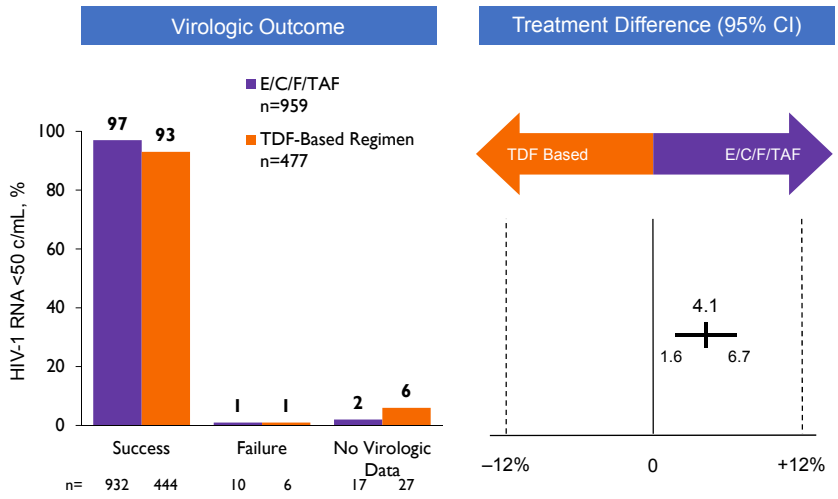
Mills A, et al. IAS 2015, Vancouver, Canada. Oral # TUAB0102

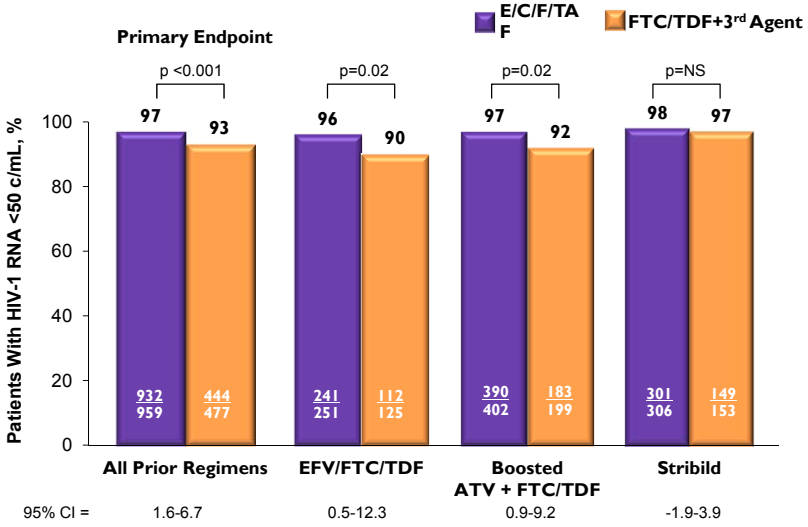
Primary Outcome

HIV-1 RNA <50 Copies/mL at Week 48



Mills A, et al. IAS 2015, Vancouver, Canada. Oral # TUAB0102

Virologic Outcome: By Prior FTC/TDF-Based Regimens



Study 109: Suppressed Adults Switched from a TDF-containing regimen to E/C/F/TAF

Mills A, et al. IAS 2015, Vancouver, Canada. Oral # TUAB0102

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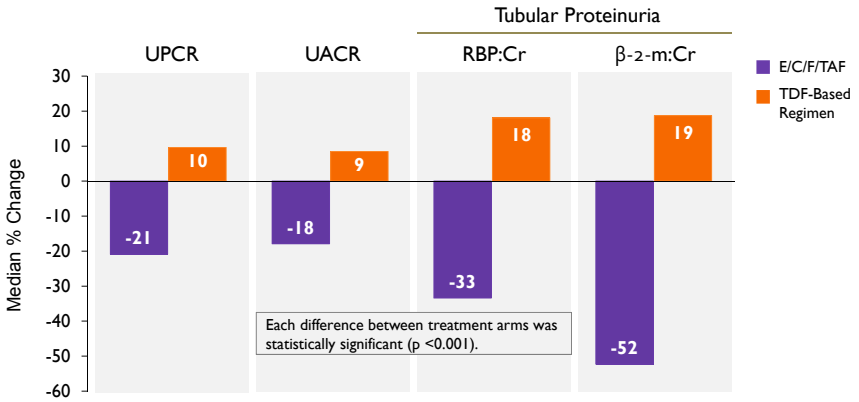
GS-US-292-0109
Renal Safety Results



- **Statistically significant improvements for participants who switched from either E/C/F/TDF or from boosted ATV + FTC/TDF**
  - Serum creatinine (p <0.001); eGFR (p <0.001)
  - Fractional excretion of phosphate, FEPO4 (p=0.05); fractional excretion of uric acid, FEUA (p <0.001)
- **Changes began by Week 2 and persisted to Week 48**

UPCR: urine protein: creatinine ratio; UACR: urine albumin: creatinine ratio; RBP, retinol-binding protein; β-2-m:Cr , beta-2 microglobulin.

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Study 109: Suppressed Adults Switched from a TDF-containing regimen to E/C/F/TAF

AEs Leading to Discontinuation

	E/C/F/TAF n=959	FTC/TDF+3rd Agent n=477
Participants, % (n)	**0.9 (9)**	**2.5 (12)**
Renal Events	• Acute renal failure† • Interstitial nephritis‡	• Chronic kidney disease • Elevated serum creatinine • Fanconi syndrome, mild jaundice • Increased creatinine • Nephretic colic (nephrolithiasis)
All Other Events	• Depression • Leg swelling, impaired concentration • Memory loss, speech disturbance, lack of motivation • Nausea, vomiting, headache • Panic attack • Reiter syndrome • Suicide attempt	• Abnormal dreams • Depression, insomnia, irritability • Depression, insomnia, nightmares • Elevated bilirubin • Icterus (n=2) • Increased forgetfulness

†After cancer chemotherapy, participant hospitalized with neutropenia, sepsis, and multi-system organ failure
‡Recurrent hematuria on treatment, subsequent off-treatment diagnosis of Hodgkin's Lymphoma

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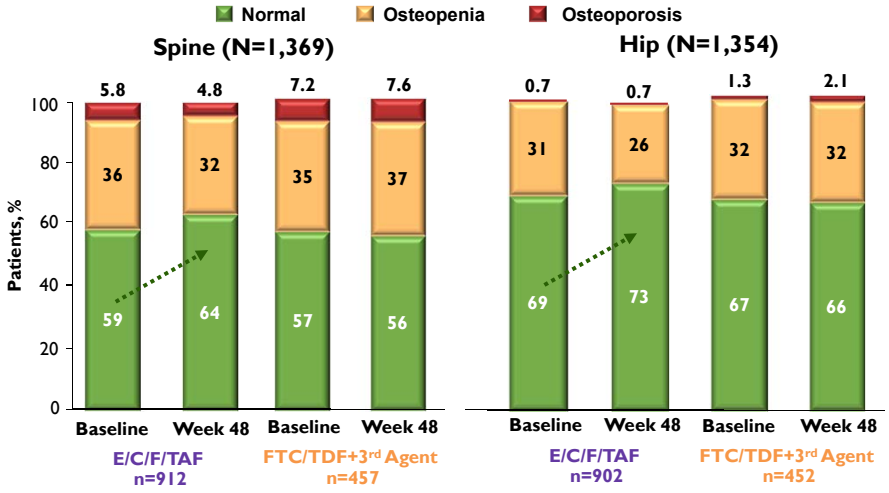
Mills A, et al. IAS 2015, Vancouver, Canada. Oral # TUAB0102

Change in Diagnosis of Osteopenia/Osteoporosis Through Week 48 (As Defined by T-Score)



Differences between E/C/F/TAF and TDF-based regimens were statistically significant ($p < 0.001$)

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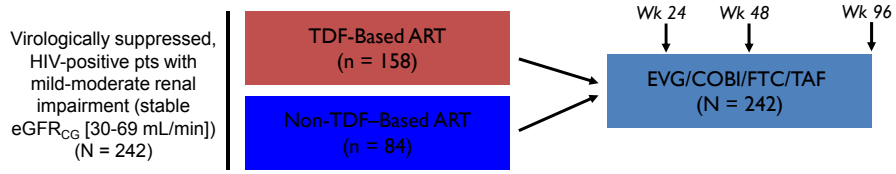
Mills A, et al. IAS 2015, Vancouver, Canada. Oral # TUAB0102

How will this change practice?

- We know the switch is safe
- There are less bone and renal effects
- The clinical significance remains unclear.
  - Correlation between subclinical markers and overt clinical disease.
  - Correlation between declines in BMD and osteoporosis and fractures
  - Are there subgroups that benefit most, older patients, vasculopaths?
- Will the answer be in post marketing studies?
- Justify the cost?

GS-112: Switching to a TAF-Based Regimen in Pts With Renal Impairment

- Multicenter, open-label phase III trial



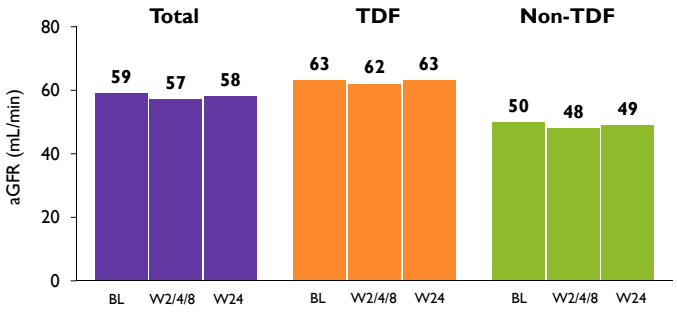
Pre-Switch ART Use

	PI	NNRTI	INSTI	CCR5 Antag.	TDF	ABC	Other NRTI	No NRTI
ART use,%	44	42	24	3	65	22	7	5

Gupta S, et al. IAS 2015. Abstract TUAB0103.

Slide from CCO

Actual GFR by Iohexol Clearance through Week 24



		GLSM Ratio, % (90% CI)*
TDF (n=21)	Week 2, 4, or 8 vs baseline	98 (94, 102)
	Week 24 vs baseline	100 (96, 105)
Non-TDF (n=10)	Week 2, 4, or 8 vs baseline	96 (86, 108)
	Week 24 vs baseline	98 (87, 111)

*Lack of alteration boundary: 80–125% (GLSM).

- Actual GFR unaffected by E/C/F/TAF switch, regardless of previous regimen

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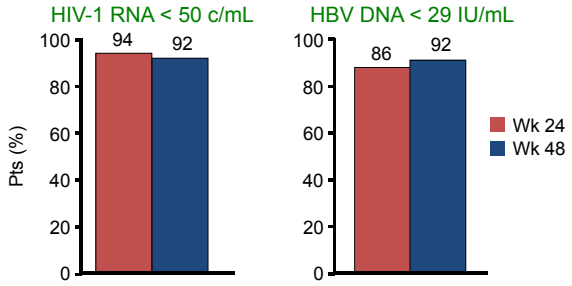
Conclusions

- No change in actual GFR, regardless of whether TDF in prior regimen
- Improvement in mean BMD if TDF in prior regimen, but not if on a non-TDF regimen pre-switch
- Safe
- Promising for a single tablet regimen
- Significance of improvement in renal markers unclear among those previously on TDF unclear.
- Caution: Big difference between CrCL of 30 & 69. More analyses for those between 30-50?

Is TAF effective with HIV/HBV Coinfection?

Switching Patients With HIV/HBV Coinfection to a TAF-Based Regimen

- International, multicenter, single-arm, open-label phase IIIb trial (N = 72)
  - Pts with virologically suppressed HIV infection on any regimen, chronic HBV coinfection, and eGFR > 50 mL/min switched to EVG/COBI/FTC/TAF for 48 Wks



- By Wk 48, 2/70 (3%) pts lost HBsAg/gained HBsAb; 2/30 (7%) pts had lost HBeAg; 1/30 (3%) pts gained HBeAb
- Significant improvement in median Wk 48 *FibroTest* score with switch (-.04; *P* = .018)

Gallant J, et al. IAS 2015. Abstract WELBPE13.

Slide from CCO .

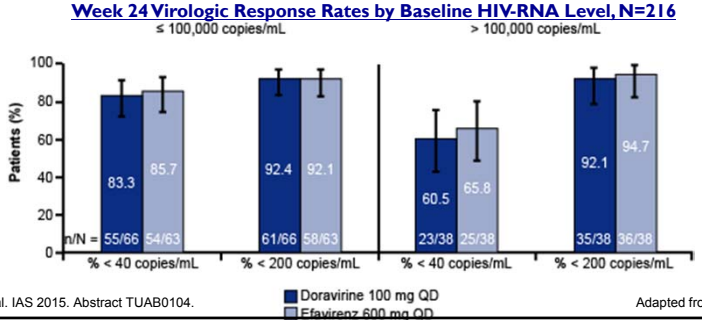
Phase 2b Efficacy and Safety of Doravirine vs. Efavarinz

Why is Doravirine of Interest?

- Excellent potency for suppressing K103N and Y181C mutants
- NNRTI, unique resistance pathway
- Fewer DDI: not an inducer or an inhibitor of CYP34A
- Daily Dosing

Phase 2B Results:

- **Primary outcome: No difference in VL <40 at 24 weeks: 73% DOR vs. 72% EFZ** , N=205
- 24 week virologic response similar between arms, regardless of baseline HIV RNA
- Doravirine plus TDF/FTC was well tolerated and associated with fewer AEs and discontinuations.



Gatell JM, et al. IAS 2015. Abstract TUAB0104.

Adapted from from CCO

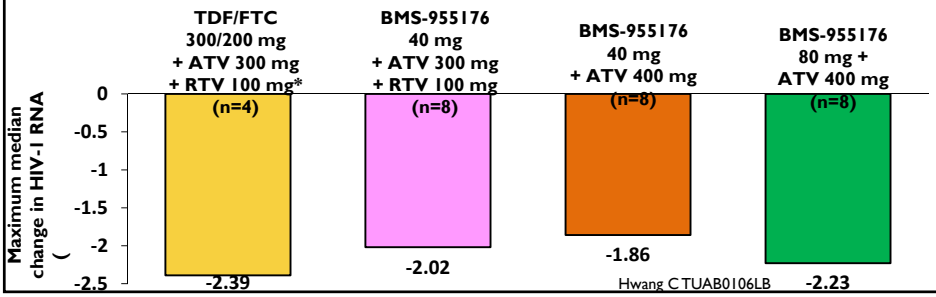
Activity and Safety of 2nd Generation Maturation Inhibitor plus ATV/r

Why is BMS 176 of Interest?

- Novel Mechanism: Inhibits the last protease cleavage event (between capsid protein p24 and spacer peptide 1 in Gag), resulting in the release of immature non-infectious virions.
- Long half life allows for once daily dosing
- NRTI sparing regimen?

Methods and Results : 28 Day Dosing Ranging Study

- N=26, Treatment naïve (<1 week of ART) or experienced (but PI and MI naïve)
- ATV/r + 40mg & unboosted ATV+ 80 mg of BMS-176 comparable to control.
- No As leading to discontinuation

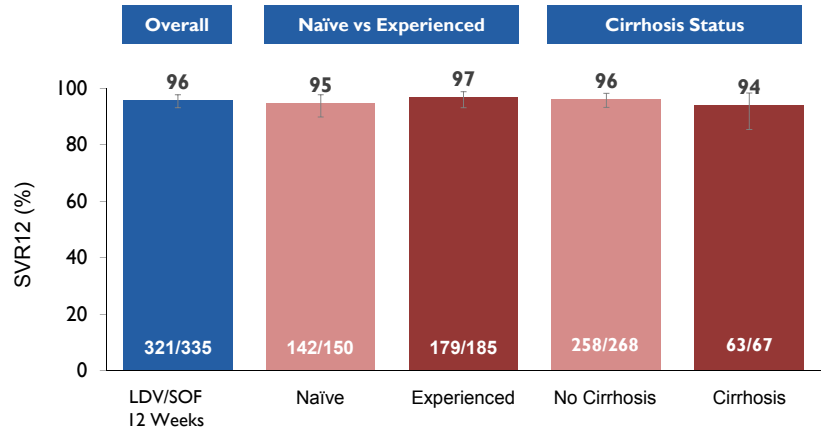


Hepatitis C Treatment: The Good News Continues

- ION-4
  - LDV/SOF in genotype 1/4 HIV/HCV-coinfected patients
- C-EDGE Coinfection Study
  - Grazoprevir/Elbasvir for patients coinfected with HIV/HCV, genotypes 1/4/6

SVR12 by Prior Treatment Experience and Cirrhosis Status

HIV-HCV (ION-4)



Error bars represent 95% confidence intervals.

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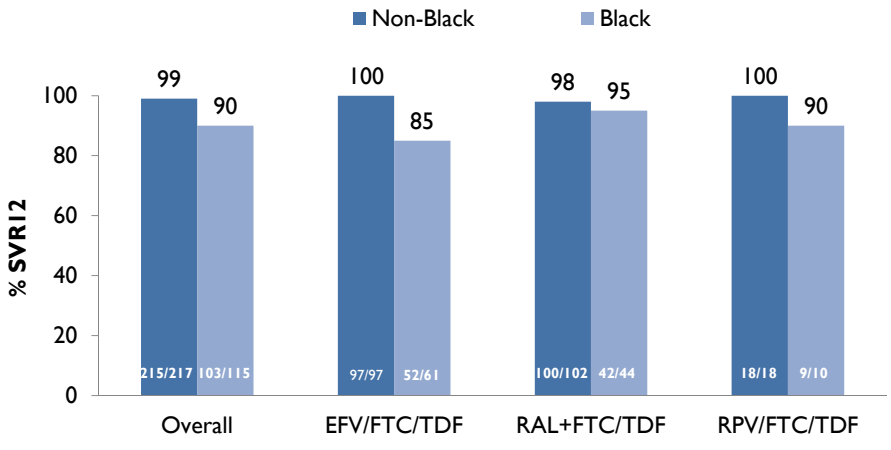
ION-4 – LDV/SOF in HIV/HCV

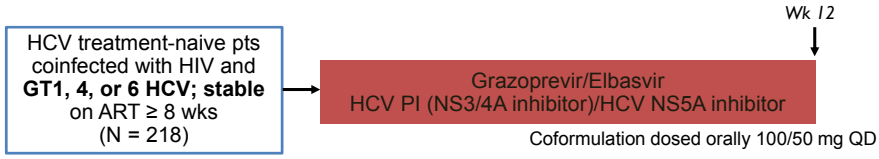
SVR12 by ARV Regimen and Race



C-EDGE Coinfection: Grazoprevir/Elbasvir for Patients Coinfected With HIV/HCV

Methods

- Multicenter, single-arm, open-label phase III trial



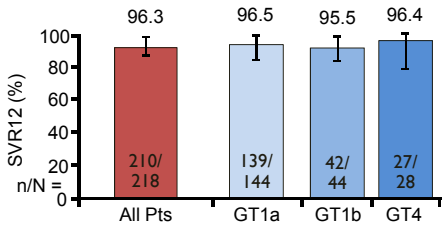
- 66% GT1a HCV, 60% had HCV RNA > 800,000 IU/mL, **16% cirrhotic**

Baseline ART Characteristic, %	Grazoprevir/Elbasvir (N = 218)
Undetectable HIV-1 RNA on ART	**96.8**
ART regimen	
Abacavir containing	**21.6**
TDF containing	**75.2**
Raltegravir	**51.8**
Dolutegravir	**27.1**
Rilpivirine	**17.4**

Rockstroh JK, et al. IAS 2015. Abstract TUAB0206LB. Rockstroh JK, et al. Lancet HIV. 2015;2:e319-e327.

C-EDGE Coinfection: Key Findings

SVR12 With 12 Wks GZR/EBV According to Genotype



Discontinued*	1	0	1	0
Relapse	5	4	0	1
Reinfection	2	1	1	0

*Unrelated to virologic failure.

- High rates of SVR.
  - No subgroup provided efficacy advantage or disadvantage, including ART regimen
  - 100% of cirrhotics with SVR 12
- New NS3, NS5A RAVs detected at failure in 4 of 5 pts who relapsed
- Short-lived HIV-1 RNA increases in 2 pts on ART during GZR/EBV treatment
  - Both suppressed HIV-1 RNA without change of ART
- During GZR/EBV Tx, no significant changes in CD4+ cell count
- GZR/EBV well tolerated: no pt discontinued for AEs and no serious treatment-related AEs

Rockstroh JK, et al. IAS 2015. Abstract TUAB0206LB. Rockstroh JK, et al. Lancet HIV. 2015;2:e319-e327.
Slide from CCO

Combination HIV Prevention

- TaSP
  - Final Results from HPTN 052
- PrEP

Final HPTN 052 Results:
ART for Prevention of HIV Transmission in Serodiscordant Couples

	Overall (April 2005 - May 2015)	
Partner Infections, n (rate/100 PY)	Early (4314 PY F/U)	Delayed (4180 PY F/U)
All	19 (0.44)	59 (1.41)
Linked	3 (0.07)	43 (1.03)
Risk Reduction With Early ART, %		
All infections	69	--
Linked infections	93	--

- No linked HIV transmissions observed when index participant stably suppressed on ART, N=1763 couples
- 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 patient
- Unlinked partner infection rates similar between study arms

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

PrEP in Non-Clinical Settings and in Diverse Populations

Key Topics at IAS

- PReP in the Real World: Implementation Success and Challenges
  - Demo Projects from US, Brazil, Youth
  - Open Label Extension Bostswana
- Feasibility of Intermittent Dosing in Diverse Patient Populations
  - ADAPT/HPTN 067

The time for debate on the effectiveness of PrEP is over.

US PrEP Demo
Implementation of Daily PrEP by US MSM/TGW

- The first US multi-site, open-label study assessing PrEP delivery in 2 STD clinics (SF, Miami) and 1 community health clinic (Washington, DC) (N = 557)
  - Enrolled HIV-negative MSM (98%) and TGW (1.3%) who met behavioral risk criteria; participants offered daily TDF/FTC as PrEP for up to 48 wks
- Retention rates declined from 93% at Mo 1 to 78% at Mo 12
  - Participants with prior PrEP knowledge and those who reported condomless receptive anal sex at baseline had higher retention rates
- 63% of participants had protective TFV DBS levels at all study visits (consistent with ≥ 4 doses/wk)
  - Odds of protective blood levels lower in Miami (aOR 0.32), black participants (aOR 0.28), higher in those who had ≥ 2 condomless sex partners in 3 months (1.8), higher for those who own or rent (aOR 2), no difference by age, drug use, or education
  - PrEP dispensation interrupted in 15% participants most commonly due to side effect concerns or low perceived risk
- No evidence of risk compensation, but high background rate of STIs.
- HIV incidence rates low at 0.43/100 PY (95% CI: 0.05-1.54)
  - 3 acute infections at enrollment, M184V in one patient
  - 2 during follow up, both with low or undetectable drug levels throughout the study

Liu A, et al. IAS 2015. Abstract TUAC0202.

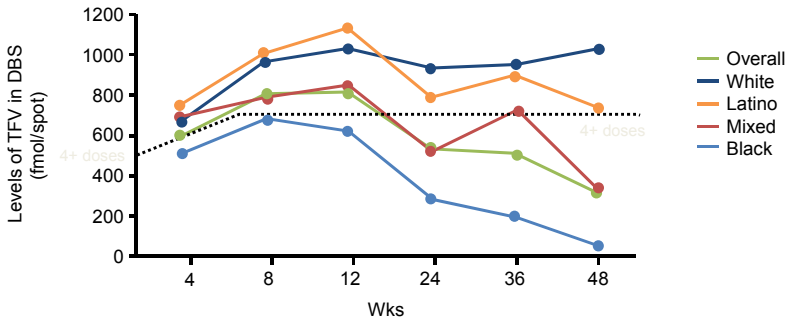
US PrEP Demo Project: Implications for Scaling-up PrEP in the US

- These data show relatively high PrEP adherence among MSM.
- PrEP was safe, no major adverse events
  - 23 creatinine elevations in 13 patients (2.3%), all grade 1, all resolved without stopping PrEP.
- Implementations questions moving forward
  - Do we need as frequent lab monitoring?
  - Who type of counseling should be provided by whom and how often?
  - Effects of cost and insurance on adherence and uptake.
- High rates of sexually transmitted infections supports need for quarterly screening
- Interventions to address racial and geographic disparities and housing instability may increase PrEP impact in the US.
- We need to understand of why adherence was lower in African American participants and in Miami.

  -elucidate role of medical mistrust, health literacy, privacy concerns, acculturation factors, social support, and unmet medical/social-structural needs in these health disparities

ATN 110: TDF/FTC PrEP for Young US MSM, N=200

- Adherence decreased from baseline to Wk 48
  - Undetectable levels of DBS TFV occurred in < 10% of pts at Wk 4 and ~ 30% of pts at Wk 48
- Black pts had decreased adherence compared with other races
  - Sample comprised of 53% black, 17% Latio
- 4 seroconversions in 48 weeks, drug levels undetectable



Hosek S, et al. IAS 2015. Abstract TUAC0204LB.

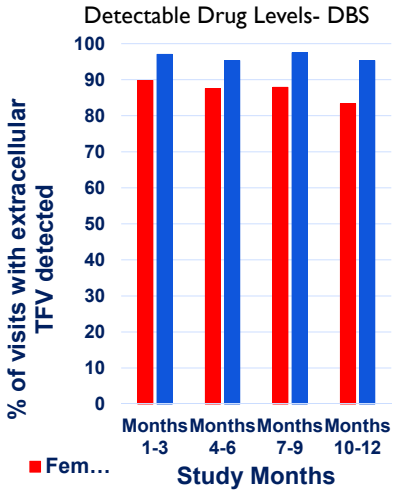
Slide from Clinical Care Options

First PrEP Demonstration in Middle Income Country

- High uptake 51% (409/798)
- Highest among those at increased risk and awareness of PrEP
- 6% of participants were trans women.
  - Targeted Trans community education activities and environment can play major role in getting Trans people to access PrEP services.

Grizstejn et al. , et al. IAS 2015. Vancouver, Canada. Oral #TUAC0205LB

TDF-2 OLE Botswana



Overall, TFV was detected at ~93% of visits.

- TDF 2: 62% protective efficacy (Thigpen NEJM 2012)
- TDF2 OLE 2013-2014 to assess safety, effectiveness, behavioral risk compensation, adherence
  - 86% Eligible started Truvada, N=229
- High adherence to daily PrEP among both heterosexual men and women at risk for HIV
- Mean number of condomless sex acts decreased by 39%
- No HIV infections observed (expected 5-6 based on TDF2 incidence rate)
- Supports recent findings that women and men who are at risk for HIV can adhere to daily PrEP

N=120, lower limit of detection= =5ng/ml

A Phase II, Randomized, Open-label, Pharmacokinetic And Behavioral Study Of The Use Of Intermittent Oral Emtricitabine/Tenofovir Disoproxil Fumarate Pre-exposure Prophylaxis (PrEP)

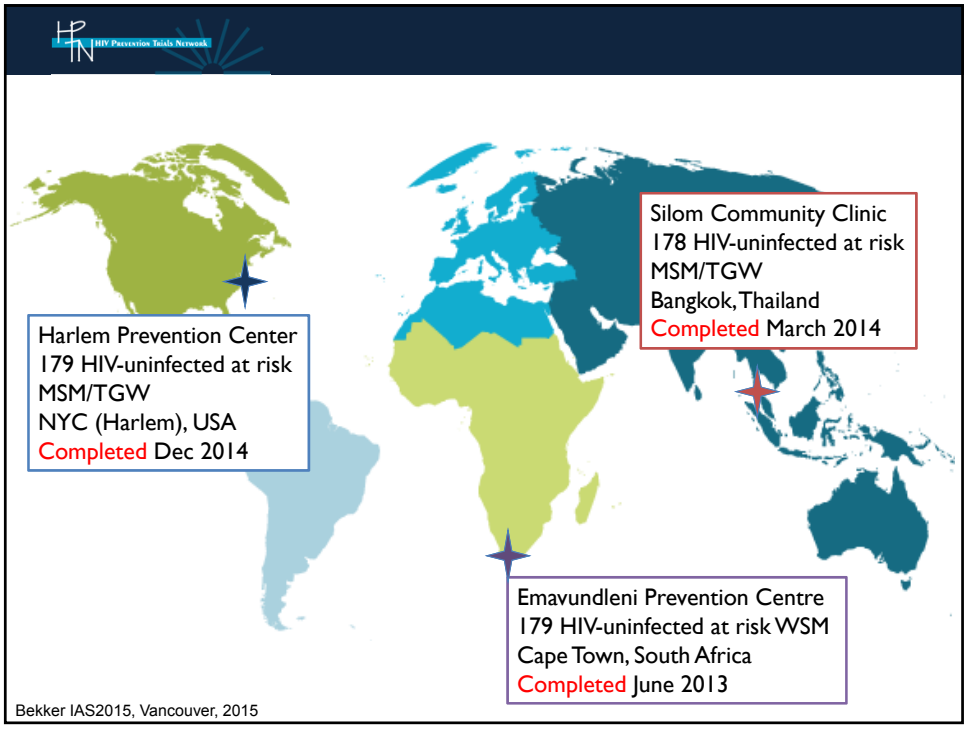
Alternative
Dosing to
Augment PrEP
Pill
Taking

HPTN 067 ADAPT

HPTN 067 ADAPT Study Primary Objective

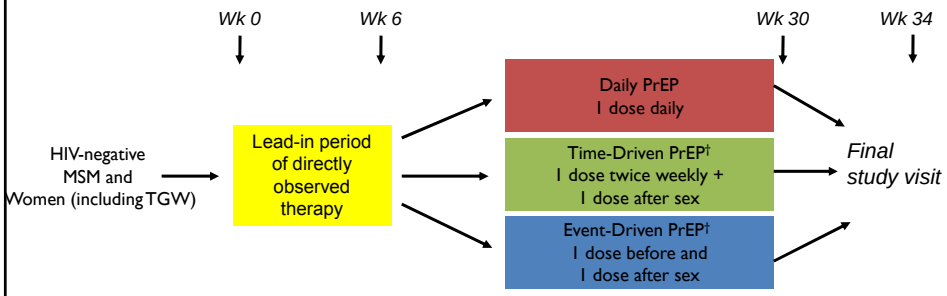
To assess whether recommending non-daily oral FTC/TDF PrEP, compared with daily, is associated with:

- Equivalent coverage of sex events with pre- and post-exposure dosing
- Lower number of tablets needed
- Decreased self-reported symptoms/side effects



HPTN 067/ADAPT

- International, randomized, open-label phase II trial



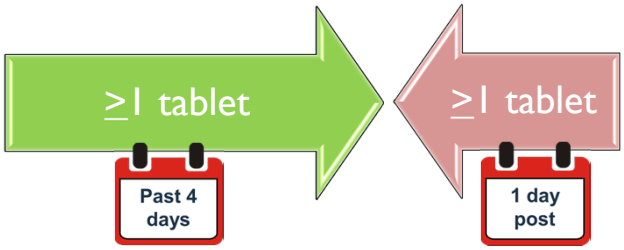
TDF/FTC PrEP given at standard dose and dispensed using an electronic monitoring device.
Adherence and sexual risk behavior assessed by weekly interview conducted by phone or in person.
Inclusion criteria for MSM and TGW: reported anal intercourse and ≥ 1 other risk factor for HIV infection in last 6 mos; creatinine clearance > 70 mL/min.

†Participants instructed to take no more than 2 doses daily or 7 doses/wk.

Slide from Clinical Care Options

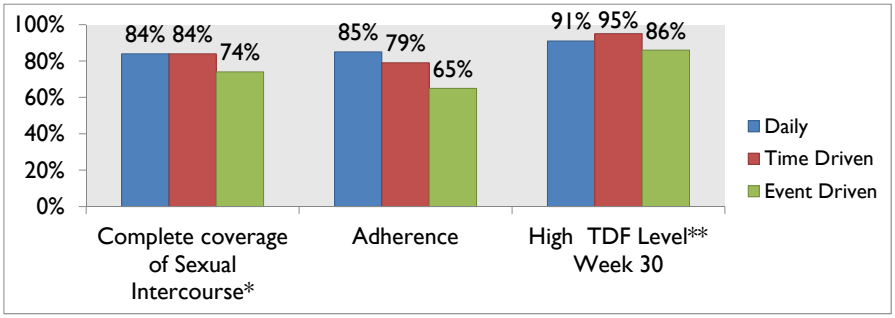
Definition: Covered sex event

Coverage for all arms:
≥1 pill taken in the 4 days before sex
≥1 pill taken in the 24 hours after sex



Bekker IAS2015, Vancouver, 2015

HPTN 067/ADAPT: Results Bangkok Cohort N=178



- Compared to daily and time driven dosing, coverage lower in event driven arm.
- Drug levels similar across dosing arms
- 2 HIV seroconversions during pre randomization directly observed dosing phase
  - Both associated with undetectable or low levels of FTC or TFV in plasma/PBMCs

• Complete coverage taking taking ≥ 1 PrEP dose within 4 days before sex and ≥ 1 dose within 24 hrs after sex
**>9.1 fmol/million PBMC, 2 tablets per week

T. Holtz, IAS 2015 ,Vancouver, # MOSY0104

Event-driven regimen

Patterns of sex
- Have infrequent sex events
- Ability of sex planning / have control over planning for sex with sexual partners

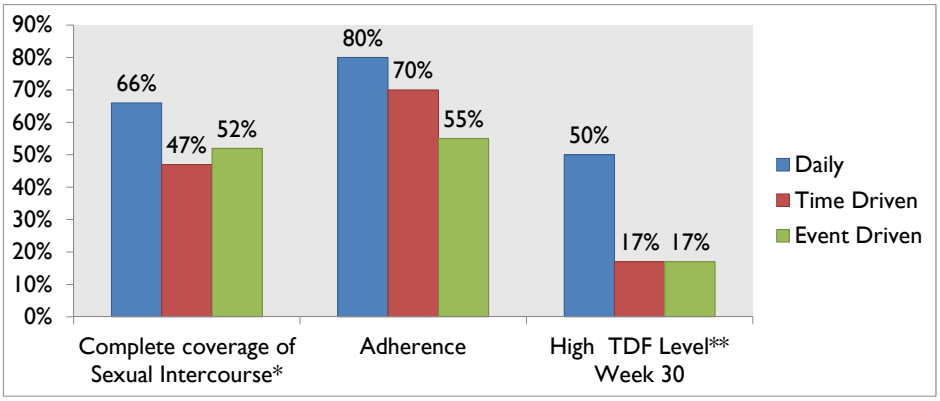
Pro
- Fewer doses (less concerns about side effects)

Cons
- Need sex planning
- Need to carry tablets at all times (pre/post-sex dose)
- Difficult to hide tablets from sexual partners
- Regimen confusion (need to count by the hour)
- Complicated regimen (No more than 1 dose in a 2 hour window)

"I always ask for sex from my boyfriend. Sometimes, he says yes. Sometimes, he's tired. But, if I'm really horny I would take a tablet and get what I want." (FGD/Event-driven arm)

"After coming back from the bar, I took a tablet at 2 am right before having sex and I had to wait 2 hours to take post sex dose at 4 am. I already fell asleep by then." (KII/Event-driven arm)

HPTN 067/ADAPT: Harlem Cohort



- **70% African American, young- one third less than 25 years**
- **Daily dosing resulted in higher coverage of sex events, higher drug concentrations, higher adherence.**
- Suboptimal coverage and drug levels.
- HIV seroconversion seen in 2 pts
  Both pts had low or undetectable TDF in dried blood spots/plasma at study visits

• Complete coverage taking taking ≥ 1 PrEP dose within 4 days before sex and ≥ 1 dose within 24 hrs after sex.**
**>350 fmol DBS, includes participants reportingsex in last 7 days

S. Mannheimer, IAS 2015, Vancouver, #MOSY01015

PrEP and Stigma
ADAPT- Harlem Qualitative Study

HIV-related Stigma

"Even if I told them it was a study, maybe some of them wouldn't believe it, and put some ideas into people's heads that I did have HIV".

"My partners would be like, "Why are you taking those pills?" [and] sometimes it would never get to the intercourse part. It would just stop the night. They would be mad and leave."

Promiscuity-related stigma

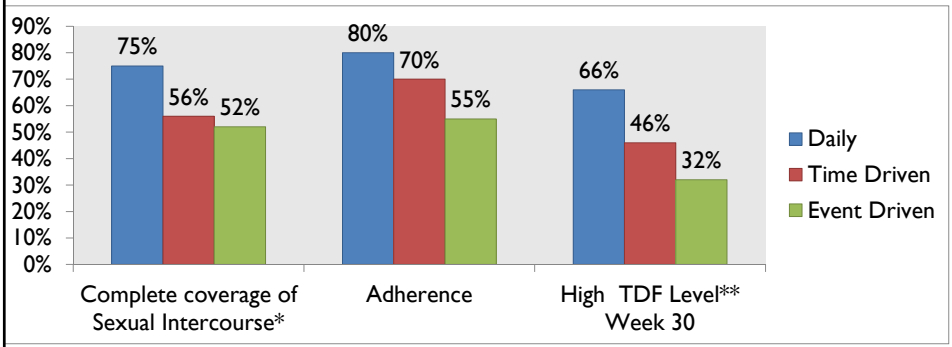
"One of my partners was like, "Whoa. What does this mean? What are you doing? " Indicating that taking the pill means that I'm willy-nilly having unprotected sex"

Stigma and Adherence, Challenges for Sex-Dependent Dosing

"My partners would be like, "Why are you taking those pills?" [and] sometimes it would never get to the intercourse part. It would just stop the night. They would be mad and leave."

J. Franks, IAS 2015, Vancouver, #MOSY0108

HPTN 067/ADAPT: South African Women



- Majority of young, predominantly single, South African women took oral PrEP when made available in an open label study
- Daily dosing resulted in higher coverage of sex events, higher drug concentrations, and higher adherence.
- 2 seroconversion in DOT phase, 5 during self-administered PrEP phase (5.4/100PY)

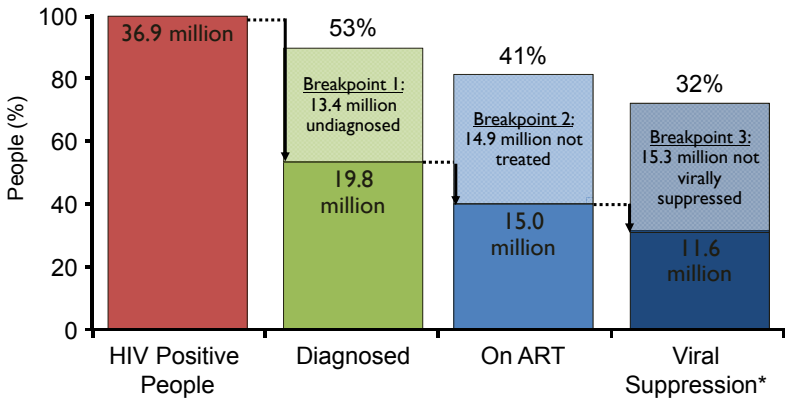
• Complete coverage taking taking ≥ 1 PrEP dose within 4 days before sex and ≥ 1 dose within 24 hrs after sex.**
**>350 fmol DBS

Bekker IAS 2015, Vancouver, 2015

Implications for PrEP Implementation

- In general daily dosing looks better for coverage, adherence, and drug levels except in Bangkok.
- Different strategies might wok better with different subpopulations and individuals.
- Would drug levels have been better if IPERGAY dosing is used.
- More data is needed for adherence in African American MSM and Trans women

UNAIDS: 90-90-90 Global Estimated Gaps

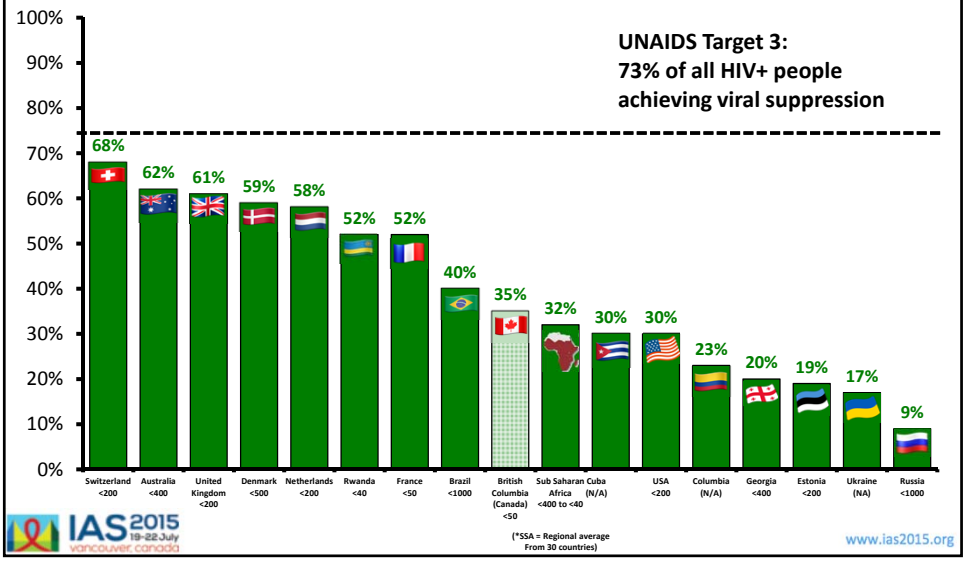


*HIV-1 RNA < 1000 copies/mL.

Levi J, et al. IAS 2015. Abstract MOAD0102.

Slide from Clinical Care Options

Target 3 – Percentage of HIV+ People with HIV RNA suppression - Results



IAS 2015 19-22 July vancouver, canada

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How do we get to 90-90-90?

Highlights of Innovative Studies

Image avert.org