UPDATE ON ANTIRETROVIRAL THERAPIES

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Disclosures

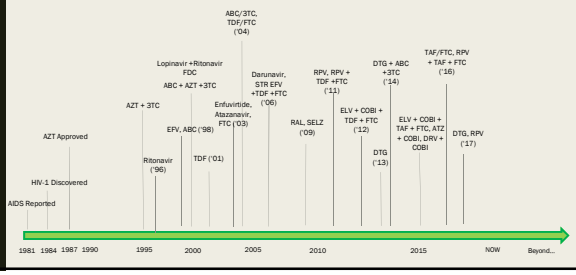
- Janssen Therapeutics- Community Speaker's Bureau
- Viiv Healthcare- Pharmacy Advisory Board

Learning Objectives

- Identify newly approved ART regimens and discuss appropriate use of these agents
- Describe new approaches for treating PLWH

KNOWING THE PAST

TO UNDERSTAND THE PRESENT AND PLAN FOR THE FUTURE



Initial ART Selection

A. Boosted DRV plus tenofovir/FTC
B. DTG/ABC/3TC
C. DTG plus tenofovir/FTC
D. EVG/c/tenofovir/FTC
E. RPV/tenofovir/FTC
F. RAL HD/tenofovir/FTC
G. I like something else
H. It depends

NEW OPTIONS FOR INITIAL TREATMENT

Bictegravir/TAF/FTC

- **Indications:**
  - *Initial treatment in adults with HIV infection*
  - *Replacement therapy in persons who have achieved virologic suppression (<50 copies per mL) for at least 3 months and have no history of treatment failure or known resistance to its components*
- **Pharmacology and dosing:**
  - *One-pill, once a day, with or without food*
  - *Half-life 17.3 hours*
  - *Excretion- feces 60.3%, urine 35%; Not recommended if CrCL <30 mL/minute*
- **Drug resistance:**
  - *Active in vitro against HIV isolates that carry some integrase resistance mutations*
  - *Efficacy in people with prior INSTI failure or resistance is unknown*

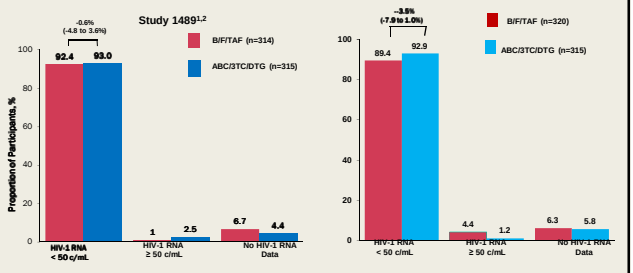
https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210251s000lbl.pdf; http://www.gilead.com/~/media/files/pdfs/medicines/hiv/biktarvy/biktarvy_pi.pdf?la=en

Bictegravir/TAF/FTC

- **Drug-Drug Interactions:**
  - ***Contraindications:*** *Rifampin; Dofetilide*
  - ***Special considerations:***
  - *Medications or oral supplements containing polyvalent cations; 2 hours before antacids, simultaneously with food with Ca++ or FeSO4 supplements*
  - *Metformin AUC increased 39%; assess risk vs. benefit*
- **Side effects:**
  - *Diarrhea, nausea and headache*
  - *Inhibition of tubular secretion → increase in serum creatinine (median 0.1 mg/dL)*

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210251s000lbl.pdf; http://www.gilead.com/~/media/files/pdfs/medicines/hiv/biktarvy/biktarvy_pi.pdf?la=en

Bictegravir/TAF/FTC: Treatment Naïve Trials



BIC non-inferior to DTG- containing regimen in terms of virologic suppression at Week 48[1,2]

Gallant Jet al, Lancet 2017; Sax P et al Lancet 2017

Bictregravir (BIC)

- Unboosted Integrase Inhibitor (INSTI)
- High genetic barrier to resistance
- Low potential for drug-drug interactions
- Co-formulated with TAF/FTC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Home > HIV/AIDS News > Department of Health and Human Services Adults and Adolescents Antiretroviral Guidelines Panel* Classifies a Fixed-Dose Combination Product of Bictegravir/Tenofovir Alafenamide/Emtricitabine as One of the Recommended Initial Regimens for Most People with HIV

Department of Health and Human Services Adults and Adolescents Antiretroviral Guidelines Panel* Classifies a Fixed-Dose Combination Product of Bictegravir/Tenofovir Alafenamide/Emtricitabine as One of the Recommended Initial Regimens for Most People with HIV

Date: March 27, 2018
Source: AIDSinfo

Introduction

Bictegravir (BIC) is a new HIV-1 integrase strand transfer inhibitor (INSTI) that has been approved by the U.S. Food and Drug Administration for initial therapy in adults with HIV as part of a single-tablet, once-daily regimen that includes tenofovir alafenamide and emtricitabine (BIC/TAF/FTC).[1] BIC/TAF/FTC is not recommended for individuals with creatinine clearance <30 mL/min or with severe liver impairment. It is not approved for persons younger than 18 years of age, and there is insufficient safety information regarding its use in pregnant women.

A.C.

- 32 y/o AAF diagnosed with HIV 3 years ago after ex-husband passed away from AIDS-related illness. Tx naïve, "doesn't like taking pills." Urged to come in by new partner who is not HIV-infected.
- PMH: HTN- previously on medication, but took it intermittently and finally stopped completely ~ 5 months ago. Depression- untreated
- SH: Single mother with 3 small children (6mo,2y,8y); some assistance from family members; Works as a manager at a fast food restaurant, works all shifts; limited transportation; no tob, ETOH, or illicit drug use.

Bictegravir/TAF/FTC: Virologically Suppressed Switch

- Randomized switch studies in virologically suppressed persons:
  - *Switching to BIC/FTC/TAF non-inferior to continuing boosted PI[1] or a DTG, ABC, 3TC-containing regimen[2]*

[1]Daar E et al IDWeek 2017; [2]Molina J-Met al, CROI 2018 abstract 22

K.B.

- 20 y/o AAM presents for initial visit after being diagnosed 2 weeks ago. He decided to get tested after he learned that his current partner has been living with HIV since 2006. He goes on to share that since his diagnosis, he and his partner now communicate more regularly about HIV. His partner has been helping him learn about different treatment options, and suggested K.B. start with one pill, but stay away from "the one that causes weird dreams." You also learn that K.B.'s partner had problems with adherence on "that one."
- PMH: No history
- SH: In a monogamous relationship now, currently a junior in college studying music, smokes ½ ppd, social drinker, lives off fast food

Doravirine (DOR)

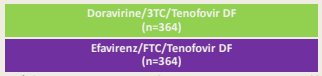
- New NNRTI
- Active in vitro against HIV that is resistant to first-generation NNRTI (K103N, Y181C, G190A, E138K, K103N/Y181C)[1]
- Metabolized by CYP3A4, but not an inhibitor or inducer
- Not impacted by PPIs
- No specific food requirements

[1]Lai AAC 2014;58:1652-1663

DRIVE-AHEAD: DOR/3TC/TDF in Treatment-Naïve PLWH

Phase 3

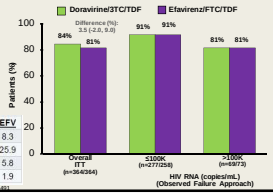
Double-blind, Randomized 1:1, 96 Wk
HIV RNA ≥1000 copies/mL
Stratified by:
- **HIV RNA (</> 100K) and**
- **Hepatitis B/C co-infection**



- Primary outcome: HIV RNA <50 copies/mL (FDA snapshot algorithm)
- Non-inferior efficacy
  - DOR (84%); EFV (81%)
- Virologic failures in DOR arm (6%)
  - Primary NNRTI resistance: (1.6%)
  - Primary NRTI resistance (1.4%)
- Superior safety profile for neuropsychiatric events and lipids

AEs %	DOR	EFV
Nightmares	5.6	8.3
Dizziness	6.5	25.9
≥ Grade 1 LDL	2.0	5.8
≥ Grade 2 TG	0	1.9

DOR/3TC/FDF and DOR submitted Jan 2018, PDUFA Oct 2018



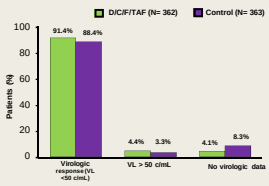
Squires KE, et al. J Int AIDS Soc. 2017;20(suppl 4):110-111. Abstract TUAB0204LB; Orkin C et al. CROI 2018, abstract 491

DRIVE with DORAvirine

- **DRIVE-AHEAD**
  - *DOR/3TC/TDF vs. EFV/FTC/TDF*
- DRIVE-FORWARD
  - *DOR vs. DRV/r (non-inferior, lipids)*
- **DRIVE-SHIFT**
  - *Switch to DOR/3TC/TDF*

AMBER: PI-based STR for Initial Therapy

- Phase 3 randomized, double-blind study designed to assess safety and efficacy of DRV/c + 3TC/TAF vs. DRV/c + 3TC/TDF
- Primary endpoint: non-inferiority of STR vs. control to achieve vial suppression (VL < 50 copies/mL) at 48 weeks



AE leading to D/C- Rash @ 2%
One- M184V

Orkin EACS 2017

Early Initiation/Rapid Start/TNT

- No, we need resistance testing before initiating treatment.
- Yes, my preferred regimen is Boosted DRV/tenofovir/FTC.
- Yes, my preferred regimen is DTG/ABC/3TC.
- Yes, my preferred regimen is DTG/tenofovir/FTC.
- No, I prefer to schedule to patient for a visit later to begin treatment.
- What, people do that?

Challenging Tradition: 2-drug Therapies

Nukes getting Nuked?

- Initial therapy
  - *LPV/r + 3TC (GARDEL)*
  - *DRV/r + RAL (NEAT001)*
  - *DTG + 3TC (PADDLE; ACTG A5353; GEMINI-1,2)*
  - *DRV/r +3TC (ANDES)*
- Switch therapy
  - *LPV/r + 3TC/FTC (OLE)*
  - *ATV/r + 3TC (SALT, ATLAS-M)*
  - *DRV/r + 3TC (DUAL)*
  - *DRV/r + RPV*
  - *DTG + RPV*
  - *DRV/r + DTG (DUALIS)**
  - *DTG + 3TC (LAMIDOL, ASPIRE, TANGO*)*

* Currently being studied

Dolutegravir + 3TC

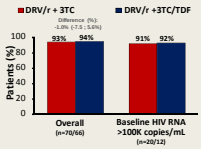
- **PADDLE**: open-label, single arm study, 20 patients, ARV-naïve, VL >5000<100K copies/mL, CD4 >200 cells/mL, **HBV negative**; primary endpoint <50 copies/mL at week 48 (FDA snapshot algorithm) outcome: 90% at week 48
- **ACTG A5353**: Phase 2 single-arm study, 120 patients, VL >1000<500K copies/mL, at week 24: 90% at <50 copies/mL, no difference in VL, VF uncommon (adherence n=1)
- **GEMINI-1,2**: Large RCT, phase III; results likely summer 2018

Figueroa MI et al, 15th EACS, 2015. Taiwo BO et al, Clin Infect Dis, 2017.

ANDES: DRV/r + 3TC

- DRV/r + 3TC **vs.** DRV/r + 3TC/TDF
  - *Randomized, open-label, phase IV*
  - *Primary endpoint: VL < 50 copies/mL at week 48 (FDA snapshot algorithm)*
  - *145 patients: DT (n=75),TT (n=70)*

HIV RNA <50 (ITTe)



Adverse Events

AEs/%	Dual Therapy	Triple Therapy
Gastrointestinal (GI)	7%	14%
Rash	8%	7%
TC	19%	4%
LDL	14%	6%
TRG	25%	14%

- Discontinuation rare, similar
- No SAEs or death

Figueroa et al, CROI 2018, Abstract 489

Challenging Tradition: 2-drug Therapies

Nukes getting Nuked?

- Initial therapy
  - *LPV/r + 3TC (GARDEL)*
  - *DRV/r + RAL (NEAT001)*
  - *DTG + 3TC (PADDLE; GEMINI-1,2)*
  - *DRV/r +3TC (ANDES)*
- Switch therapy
  - *LPV/r + 3TC/FTC (OLE)*
  - *ATV/r + 3TC (SALT, ATLAS-M)*
  - *DRV/r + 3TC (DUAL)*
  - *DRV/r + RPV*
  - *DTG + RPV*
  - *DRV/r + DTG (DUALIS)**
  - *DTG + 3TC (LAMIDOL, ASPIRE, TANGO*)*

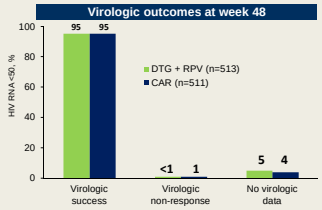
* Currently being studied

Dolutegravir + RPV

- Approved November 2017
- First complete treatment regimen with only two drugs
- Co-formulated INSTI + NNRTI
- Switch/maintenance therapy

SWORD-1 and 2: Switching to DTG + RPV

- Stable on standard 3DR suppressive ART, VL <50 for >6 mo., no h/o VF or resistance to DTG or RPV
- Randomized 1:1 to continue CAR or switch to DTG +RPV
- Primary endpoint: # of subjects VL <50 copies/mL at Wk 48
- Non-inferiority to CAR



Llibre JM et al. CROI 2017; Abstract 44LB.; Llibre JM et al. Lancet 2018

DTG + RPV

- **Indications:**
  - *Replacement therapy in persons who have achieved virologic suppression (<50 copies per mL) for at least 6 months and have no history of treatment failure or known resistance to its components*
- **Pharmacology and dosing:**
  - *One-pill, once a day with **a meal***
  - *Can be used in patients with severe renal impairment, increased monitoring for AEs*
- **Drug-Drug Interactions:**
  - ***Contraindications:** Dofetilide, Rifampin, PPIs*
  - ***Special considerations:***
  - *Rifabutin requires additional 25-mg of RPV with DTG/RPV*
  - *Antacids, administer DTG/RPV 4 hours before or 6 hours after; H2RA, administer DTG/RPV 4 hours before or 12 hours after*
  - *Metformin dose limited to 1000 mg when starting DTG/RPV or metformin*
- **Side effects:**
  - *Diarrhea, headache*

https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Juluca/pdf/JULUCA-PI-PIL.PDF#page1

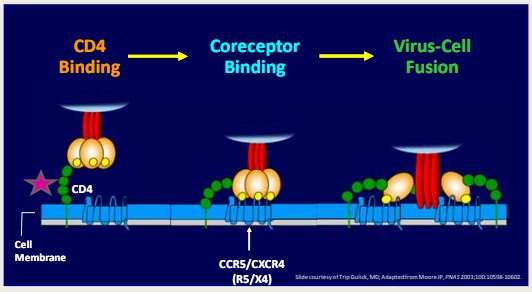
S.S.

- 56 y/o AAM presents for follow-up after being discharged from the hospital. While in hospital, patient was diagnosed with ESRD requiring dialysis. Current ART of DTG + TAF/FTC.
- PMH: Cryptococcal meningitis (2001, 2014), Genital Herpes (2014), CKD (2010), Depression, R DVT (2015), HTN (2015)
- Medications: Rivaroxaban, Hydralazine, Amlodipine, Fluconazole, Valacyclovir
- SH: Married, wife is supportive, past smoker 1 ppd, social drinker

What can TWO do?

- "Nuc-sparing" Rationale
  - *Renal disease*
  - *TFV or ABC intolerance*
  - *Minimize ARV exposure*
    (Aging population, co-morbidities)
  - *Cost*
    (Less agents)

Ibalizumab



Ibalizumab

- Approved March 6, 2018
- Humanized monoclonal Ab
- Binds CD4 on the host cell to block HIV entry into the cell (post-attachment inhibitor)[1]
- Active against CCR5 and CXCR4 tropic HIV

[1]Emu B et al, Abstract 1686, IDWeek 2017

Ibalizumab

- **Indications:**
  - *Treatment in heavily treatment-experiences adults with multidrug resistant HIV infection failing their current regimen*
  - *In combination with other antiretroviral(s)*
- **Pharmacology and dosing:**
  - *Administered intravenously, Infusion time 15-30 minutes*
  - *Diluted in 250 mL of 0.9% Sodium Chloride Injection*
  - *2000 mg loading dose (10 vials), followed by 800 mg q 2 weeks (4 vials)*
  - *Half-life 2.7-64 hours*
- **Drug resistance:**
  - *No cross resistance with any classes of ART*
  - *Active against HIV resistant to all approved antiretroviral agents*

https://drive.google.com/viewerng/viewer?embedded=true&url=https://theratechnologies.s3.amazonaws.com/prod/media/TrogarzoPrescribingInformation.pdf

Ibalizumab

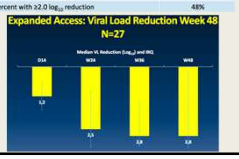
- **Drug-Drug Interactions:**
  - *None*
- **Side effects:**
  - *Diarrhea, dizziness, nausea and rash*

https://drive.google.com/viewerng/viewer?embedded=true&url=https://theratechnologies.s3.amazonaws.com/prod/media/TrogarzoPrescribingInformation.pdf

Ibalizumab at Work

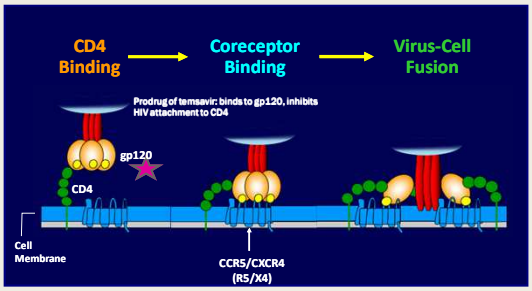
- Phase 3: 40 patients with 3-class ARV resistance, at least 1 active drug
- Primary Endpoint: VL drop > 0.5 $\log_{10}$ c/mL
  - *3% during control period*
  - *83% after loading dose*
- After loading dose, regimen optimized at day 14
  - *Week 24: 50% had VL <200*
  - *Expanded access: Week 48 viral suppression*

Week 24 Ibalizumab + OBR	
Percent with VL<50 copies	43%
Percent with VL<200 copies	50%
Mean VL decrease	1.6 $\log_{10}$
Percent with ≥1.0 $\log_{10}$ reduction	55%
Percent with ≥2.0 $\log_{10}$ reduction	48%



Emu B et al, Abstract 168b, IDWeek 2017; Weinheimer S et al, CROI 2018, #561

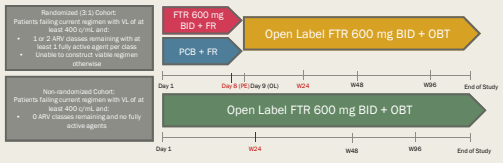
Fostemsavir (FTR)



Slide courtesy of Trip Gulick, MD; Adapted from Moore JP, PNAS 2003;100:10598-10602

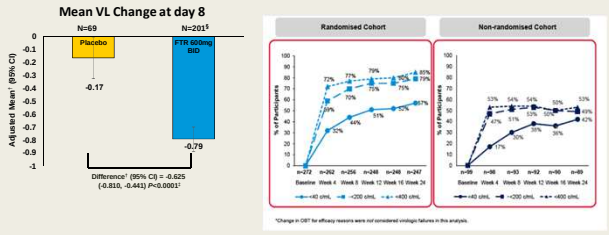
Fostemsavir (FTR): Oral Entry Inhibitor

Phase 3 trial with heavily treatment experienced patients with virologic failure (BRIGHTE)



Kozal M et al, 16th EACS, 2017

Fostemsavir (FTR): BRIGHTE Results



Week 24: 54% of randomized and 36% of non-randomized patients who received FTR + OBT achieved VL <40

Regulatory submission expected 2019/2020

https://www.viivhealthcare.com/media/press-releases/2017/october/viiv-healthcare-announces-positive-phase-3-results-from-the-brighte-study-of-fostemsavir-in-heavily-treatment-experienced-patients-with-hiv.aspx

Kozal M et al, 16th EACS, 2017
Slide courtesy of Rajesh Gharedi, Atlanta, GA, March 2018

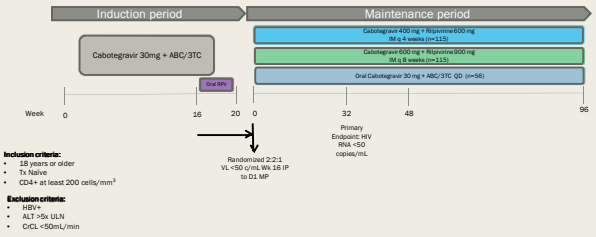
T.Y.

- 32 y/o AAF, poor to no adherence. Previous regimens: DRV/r + TDF/FTC, DTG + DRV/r, DTG + TDF/FTC, DRV/c + FTC/TAF, Current DTG + FTC/TAF. Continued non-adherence X 5 years.
- PMH: Depression, Developmental Delay
- SH: In a relationship, partner unaware of status, non-smoker, social drinker

Long-acting Injectable: CAB/RPV

- Cabotegravir (CAB) is an HIV-1 integrase inhibitor
  - *Oral 30 mg tablet ($t^{1/2}$, ~ 40 hours)*
  - *LA nanosuspension 200 mg/mL ($t^{1/2}$, ~ 20-40 days)*
- Rilpivirine (RPV) is an HIV-1 NNRTI
  - *Oral 25 mg tablet ($t^{1/2}$, ~ 50 hours)*
  - *LA nanosuspension 300 mg/mL ($t^{1/2}$, ~ 30-90 days)*
- Oral and injectable forms studied:
  - *LATTE-1: Oral CAB + RPV*
  - *LATTE-2: Oral induction, injection maintenance*

LATTE-2: Long-Acting Cabotegravir + Rilpivirine as Maintenance Therapy

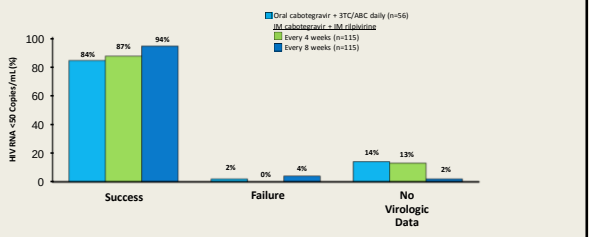


Inclusion criteria:
- 18 years or older
- Tx Naive
- CD4+ at least 200 cells/mm^3

Exclusion criteria:
- HBV+
- ALT >5x ULN
- CrCL <50mL/min

1. Spreen HIV Clin Trials 2013;14:192; 2. Spreen JAIDS 2014;67:481; 3. Margolis DA, et al. *Lancet*. 2017Jul 21. [Epub ahead of print].

LATTE-2: Long-Acting Cabotegravir + Rilpivirine as Maintenance Therapy at Week 96



1. Eron J, et al. *J Int AIDS Soc*. 2017;20(suppl 4):107-108. Abstract MOAX0205LB.; 2. Margolis DA, et al. *Lancet*. 2017Jul 21. [Epub ahead of print].

Long-Acting Cabotegravir + Rilpivirine as Maintenance Therapy

- Ongoing studies
  - *FLAIR, ATLAS: Q 4 week dosing (2018)*
  - *ATLAS-2M: Q 8 week dosing (2019)*

- NRTI
- Maturation Inhibitor
- Capsid Inhibitor
- Protease Inhibitor
- Entry Inhibitor
- Monoclonal antibodies
- Broadly neutralizing antibodies

Questions?