Present and future of ISTI

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Proc. Natl. Acad. Sci. USA
Vol. 90, pp. 2399–2403, March 1993
Pharmacology

Inhibitors of human immunodeficiency virus integrase

(retrovirus/AIDS/topoisomerase/zinc finger)

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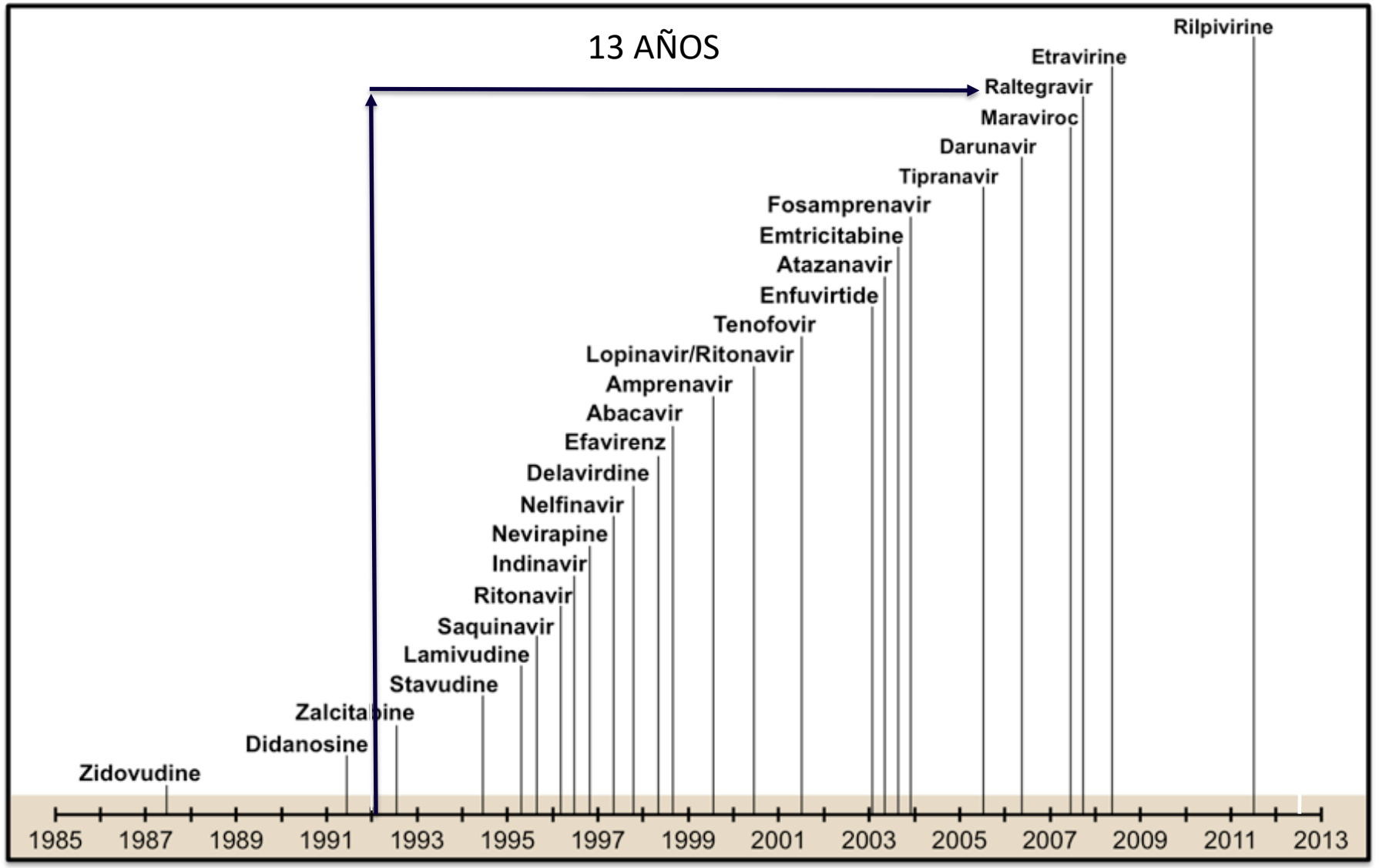
Laboratory of Molecular Pharmacology, Building 37, Room 5C25, Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, Bethesda, MD 20892

Communicated by Howard A. Nash, December 21, 1992


13 AÑOS
Rilpivirine
Etravirine
Raltegravir
Maraviroc
Darunavir
Tipranavir
Fosamprenavir
Emtricitabine
Atazanavir
Enfuvirtide
Tenofovir
Lopinavir/Ritonavir
Amprenavir
Abacavir
Efavirenz
Delavirdine
Nelfinavir
Nevirapine
Indinavir
Ritonavir
Saquinavir
Lamivudine
Stavudine
Zalcitabine
Didanosine
Zidovudine
1985
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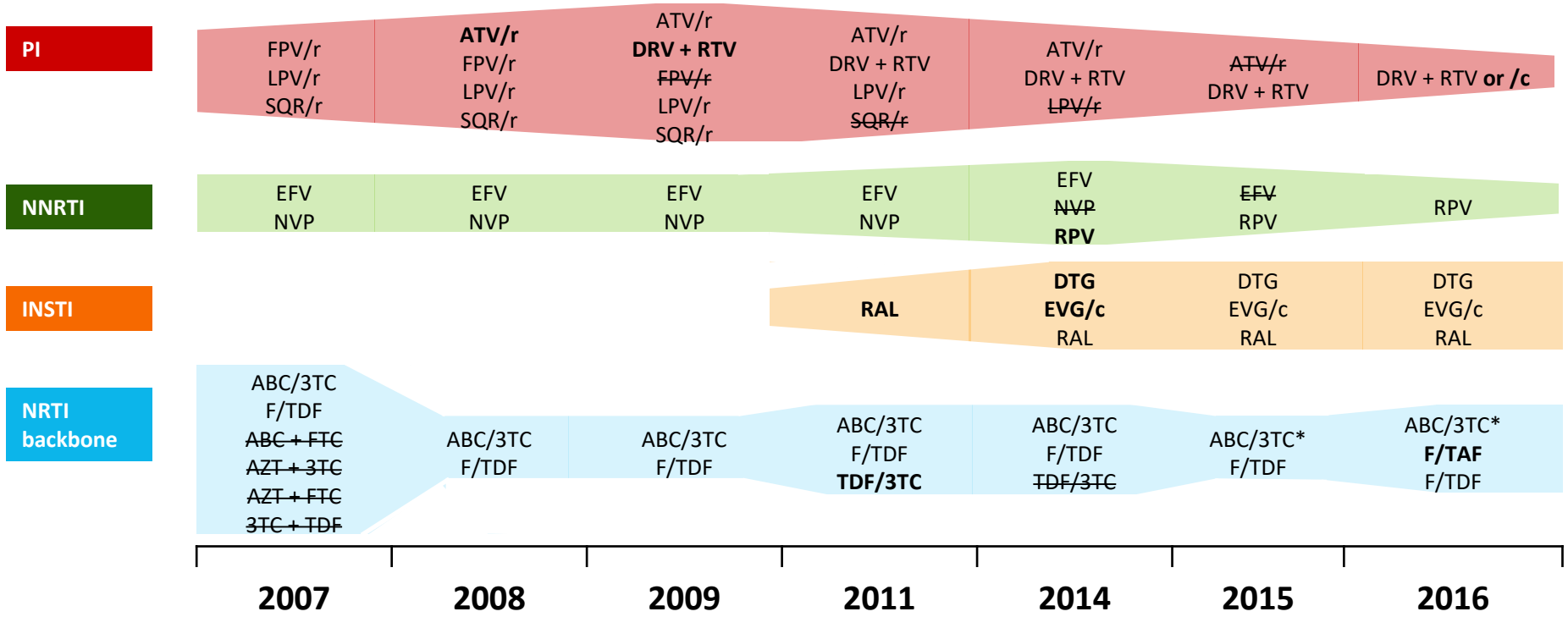
CLINICAL STUDIES OF RECOMMENDED FIRST-LINE INSTIS

Trial	INSTI Regimen	Comparator	Wks	Outcome vs Comparator
GS-1489[1]	**BIC**/FTC/TAF	DTG/ABC/3TC	96	Noninferior
GS-1490[2]	**BIC**/FTC/TAF	DTG + FTC/TAF	96	Noninferior
SINGLE[3]	**DTG** + ABC/3TC	EFV/FTC/TDF	144	Favors INSTI
FLAMINGO[4]	**DTG** + 2 NRTIs	DRV + RTV + 2 NRTIs	96	Favors INSTI
SPRING-2[5]	**DTG** + 2 NRTIs	RAL + 2 NRTIs	96	Noninferior
ARIA[6]	**DTG**/ABC/3TC	ATV + RTV + FTC/TDF	48	Favors INSTI
GEMINI-1/2[7]	**DTG** + 3TC	DTG + FTC/TDF	96	Noninferior
ACTG A5257[8]	**RAL** + FTC/TDF	ATV or DRV + RTV + FTC/TDF	96	Favors INSTI
STARTMRK[9]	**RAL** + FTC/TDF	EFV + FTC/TDF	240	Favors INSTI

Rates of discontinuation for AEs numerically lower with INSTIs vs PIs or NNRTIs and no BIC or DTG resistance detected in these trials

Source: 1. Wohl. Lancet HIV. 2019;6:e355. 2. Stellbrink. Lancet HIV. 2019;6:e364. 3. Walmsley. JAIDS. 2015;70:515.
4. Molina. Lancet HIV. 2015;2:e127. 5. Raffi. Lancet Infect Dis. 2013;13:927. 6. Orrell. Lancet HIV. 2017;4:e536.
7. Cahn. JAIDS. 2020;83:310. 8. Lennox. Ann Intern Med. 2014;161:461. 9. Rockstroh. JAIDS. 2013;63:77.

POSITION OF PREFERRED ANTIRETROVIRAL AGENTS IN EACS GUIDELINES FOR TREATMENT-NAÏVE INDIVIDUALS[1]



- EACS guidelines recommend initiation of ART, regardless of CD4 count, in part due to the evolution of drug development[1]
- Guidelines emphasise the importance of earlier ART to reduce mother-to-child and sexual transmission[1,2]

* Only in combination with DTG (ABC/3TC/DTG)[1]

3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; ATV, atazanavir; AZT, zidovudine; /c, cobicistat-boosted; DRV, darunavir; DTG, dolutegravir; EACS, European AIDS Clinical Society; EFV, efavirenz; EVG, elvitegravir; F or FTC, emtricitabine; FPV, fosamprenavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; LPV, lopinavir; PI, protease inhibitor; /r, ritonavir-boosted; RAL, raltegravir; RPV, rilpivirine; SQV, saquinavir; TAF, tenofovir alafenamide; TasP, treatment as prevention; TDF, tenofovir disoproxil fumarate

1. EACS. Guidelines Archive: http://www.eacsociety.org/guidelines/guidelines-archive/archive.html (accessed June 2017);
2. DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. January 2016: https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/0 (accessed August 2017)

Source: HIV/IHQ/17-02//1197j October 2017

PREFERRED/RECOOMMENDED FIRST-LINE ART REGIMENS FOR ART-NAÏVE

	EACS (Nov 2019)	US DHHS (Dec 2019)	IAS-USA (Jul 2018)	WHO (Jul 2019)
DTG	TAF/FTC or TDF/FTC or TDF/3TC + DTG	TAF/FTC or TDF/FTC or TDF/3TC + DTG	TAF/FTC-DTG	TDF+ 3TC (or FTC) + DTG
DTG	ABC/3TC + DTG ABC/3TC/DTG	ABC/3TC/DTG	ABC/3TC/DTG	
BIC	TAF/FTC/BIC	TAF/FTC/BIC	TAF/FTC/BIC	
RAL	TAF/FTC or TDF/FTC or TDF/3TC + RAL	TAF/FTC or TDF/FTC or TDF/3TC + RAL		
DTG	DTG/3TC	DTG/3TC		

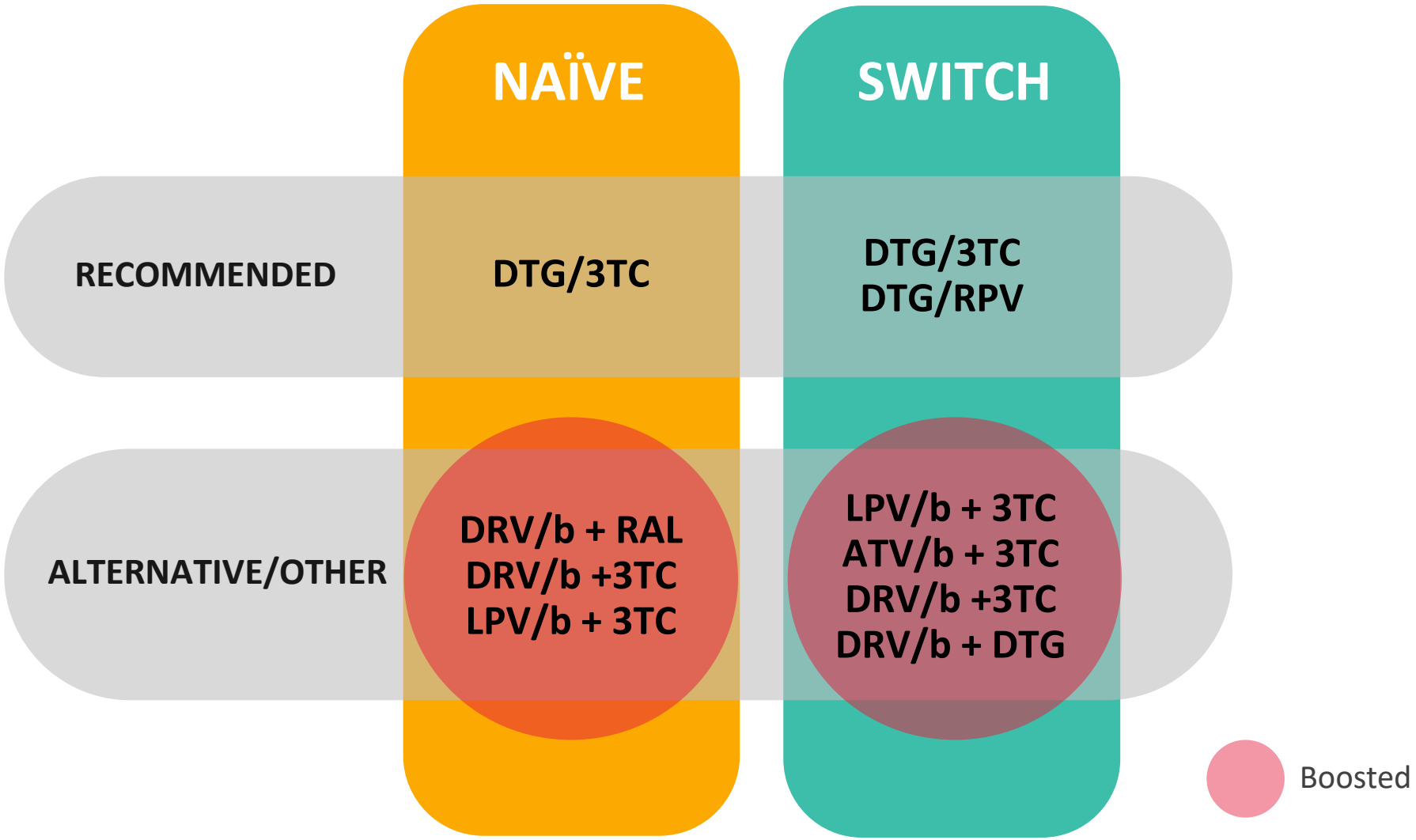
Source: https://www.eacsociety.org/files/2019_guidelines-10.0_final.pdf
https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf
https://www.iasusa.org/wp-content/uploads/guidelines/arv/arv_2018.pdf
https://apps.who.int/iris/bitstream/handle/10665/325892/WHO-CDS-HIV-19.15-eng.pdf?ua=1

CHOOSING AMONG INTEGRASE INHIBITORS FOR FIRST-LINE ART

Agent[1,2]	Advantages	Disadvantages
Bictegravir	• STR once daily with FTC/TAF • Few drug or food interactions • High barrier to resistance	• Least amount of data • Only available as an STR • Limited safety data in pregnancy
Dolutegravir	• STR once daily with 3TC or ABC/3TC • Also available as a single agent (eg, can be combined with other NRTIs) • Few drug or food interactions • High barrier to resistance • A preferred option for pregnant women	• ABC coformulation requires HLA-B*5701 testing • Increases metformin levels • Concerns regarding safety at conception/during early pregnancy
Raltegravir	• Longest experience • Few drug or food interactions • A preferred option for pregnant women	• Multiple pills (ie, no STR) • Lower barrier to resistance than BIC or DTG • Limited safety data at conception

Source: 1. DHHS ART Guidelines. December 2019. 2. Saag. JAMA. 2018;320:379.

LESS DRUGS. CURRENT OPTIONS FOR ORAL 2-DRUG ART



Source: DHHS Guidelines. December 2019. EACS Guidelines 10.0 November 2019

2-DRUG ART: NOT IF HBSAG+

HIV

CHB

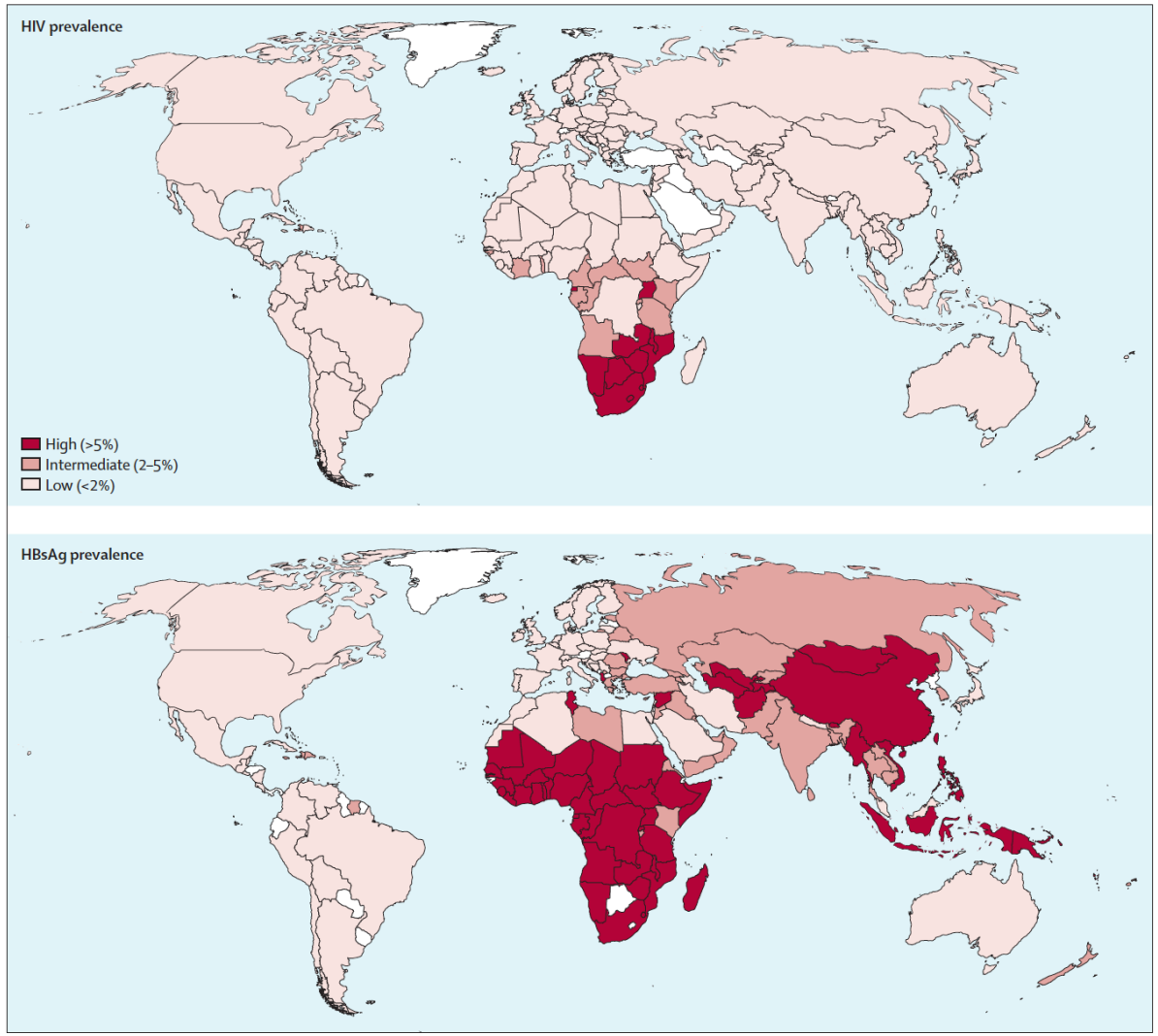


Figure: HIV and chronic hepatitis B virus infection prevalence
Data extracted from multiple sources.[62–70]

Source: Lancet HIV. https://doi.org/10.1016/S2352-3018(19)30342-X

DTG/3TC IN GUIDELINES – NAÏVE

EACS
(Nov 2019)

Recommended regimen

US DHHS
(Dec 2019)

Recommended Initial Regimens for Most People with HIV

Source: DHHS Guidelines. December 2019. EACS Guidelines 10.0 November 2019

DTG/3TC

	NAÏVE	SWITCH
KNOWNS	• Speed of response • Durability (Week 96) • Virological suppression < 50 (TND) = 3DR • No increased risk of resistance • Better bone/renal biomarkers and slightly worse lipid changes (vs TDF)	• Durability (Week 48) • Virological suppression < 50 (TND) = 3DR • No increased risk of resistance • vs TAF with and without boosters: bone, renal, inflmammatory biomarkers inconclusive, slightly better lipid changes
UNKNOWNS	• Advanced patients • Test and treat	• Impact of archived 3TC resistance • Durability (beyond wk 48)

- Pregnancy
- TB
- Long term weight impact

Source: Cahn P et al JAIDS 2020; 83:310–318. van Wyk J et al Clinical Infectious Diseases Published doi:10.1093/cid/ciz1243. Eron et al. J Acquir Immune Defic Syndr 2020; 84:60–65. Underwood M, et al. 26th CROI; Abst. 490. TND = Target not detected

DTG/RPV IN GUIDELINES – SWITCH

EACS
(Nov 2019)

Dual therapies supported by large randomized clinical trials or meta-analyses

US DHHS
(Dec 2019)

Reasonable option when the use of nucleoside reverse transcriptase inhibitors is not desirable

Source: DHHS Guidelines. December 2019. EACS Guidelines 10.0 November 2019

DTG/RPV IN SWITCH

SWITCH

KNOWNS

- Durability (3 years)
- Virological suppression < 50 (TND) = 3DR
- Slightly increased (0.6% of SWORD participants) risk of resistance (NNRTI not ISTI)
- Improvement bone/renal biomarkers (vs TDF)
- No consistent changes in inflammatory biomarkers

UNKNOWNS

- Impact of archived resistance
- Pregnancy
- Long term weight changes

Source: Aboud M et al. The Lancet HIV 2019; 6:e576–e587. Orkin et al C 25th BHIVA P008. Underwood M et al HIV Drug Therapy Glasgow 2018 P311

MANY ARV TOXICITIES ARE RECOGNIZED LATE

Drug / classgu	FDA approval	Toxicity/AE	Suspected strong signal	Delay (years)
Zidovudine	1987[1]	Lipoatrophy[10]	1999	12
Stavudine	1994[2]	Lipoatrophy[11]	1999	5
Nevirapine	1996[3]	Hepatotoxicity[12]	2001	5
Protease inhibitors	1995[4]	Myocardial infarction[13]	2003	8
Efavirenz	1998[5]	Suicidality[14]	2013	15
Abacavir	1998[6]	Myocardial infarction[15]	2008	10
Tenofovir disoproxil fumarate	2001[7]	Kidney disease[16]	2006	5
Tenofovir disoproxil fumarate	2001[7]	Fracture[17]	2012	12
Raltegravir	2007[8]	Myopathy[18]	2012	5
Dolutegravir	2013[9]	Psychiatric effects [19]	2015	2

Source: See slide notes for references

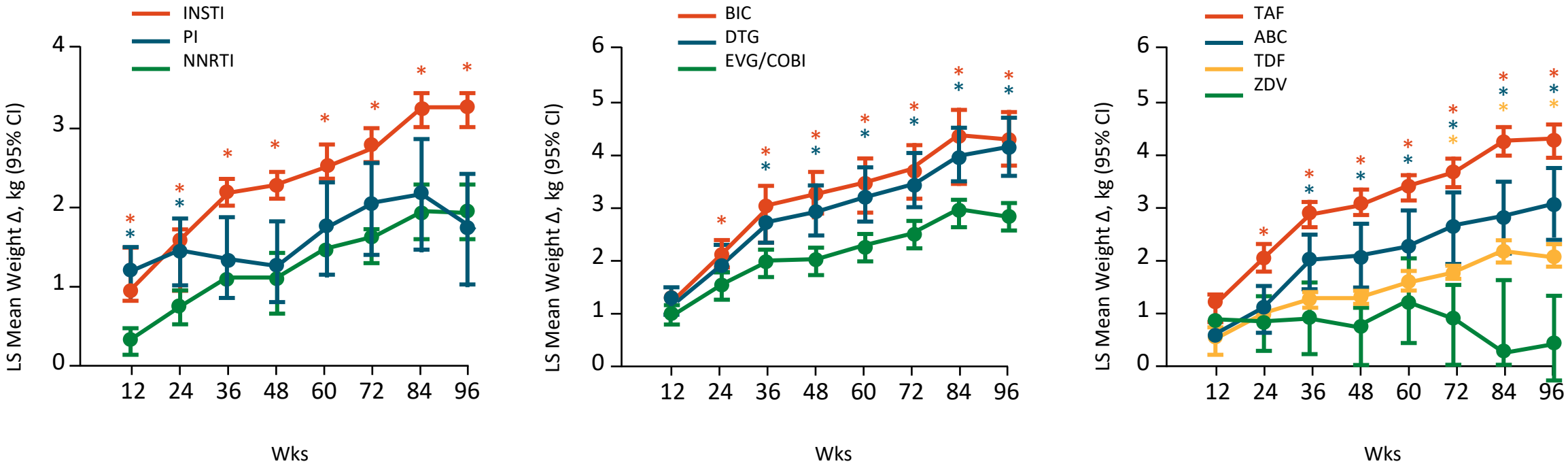
Fixed-dose combination bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir-containing regimens for initial treatment of HIV-1 infection: week 144 results from two randomised, double-blind, multicentre, phase 3, non-inferiority trials

	Study 1			Study 2	
	Bictegravir, emtricitabine, and tenofovir alafenamide (n=314)	Dolutegravir, abacavir, and lamivudine (n=315)	p value*	Bictegravir, emtricitabine, and tenofovir alafenamide (n=320)	Dolutegravir plus emtricitabine, and tenofovir alafenamide (n=325)
Any adverse event	300 (96%)	304 (97%)	..	291 (91%)	300 (92%)
Adverse event ≥10%					
Nausea	38 (12%)	76 (24%)	0·0001	31 (10%)	42 (13%)
Diarrhoea	54 (17%)	57 (18%)	..	66 (21%)	52 (16%)
Upper respiratory tract infection	43 (14%)	59 (19%)	..	43 (13%)	52 (16%)
Headache	44 (14%)	56 (18%)	..	56 (18%)	57 (18%)
Nasopharyngitis	40 (13%)	52 (17%)	..	50 (16%)	62 (19%)
Syphilis	39 (12%)	49 (16%)	..	33 (10%)	31 (10%)
Back pain	34 (11%)	38 (12%)	..	28 (9%)	38 (12%)
Fatigue	33 (11%)	38 (12%)	..	28 (9%)	36 (11%)
Insomnia	25 (8%)	35 (11%)	..	29 (9%)	24 (7%)
Oropharyngeal pain	21 (7%)	35 (11%)	..	20 (6%)	18 (6%)
Cough	34 (11%)	20 (6%)	..	25 (8%)	29 (9%)
Grade 3 or 4 adverse event	50 (16%)	50 (16%)	..	54 (17%)	43 (13%)
Serious adverse event	41 (13%)	53 (17%)	..	63 (20%)	40 (12%)
Study drug-related adverse event	94 (30%)	132 (42%)	0·0021	71 (22%)	95 (29%)
Study drug-related adverse event ≥5%					
Nausea	18 (6%)	56 (18%)	<0·0001	10 (3%)	17 (5%)
Diarrhoea	19 (6%)	13 (4%)	..	10 (3%)	10 (3%)
Headache	16 (5%)	16 (5%)	..	14 (4%)	10 (3%)
Study drug-related serious adverse event	2 (<1%)	1 (<1%)	..	3 (<1%)	3 (<1%)
Any adverse event leading to study drug discontinuation†	0	5 (2%)	..	6 (2%)	6 (2%)

Source: Lancet HIV 2020; 7: e389–400

MULTIVARIATE ANALYSIS OF WEIGHT GAIN FOLLOWING ART INITIATION IN RCTS

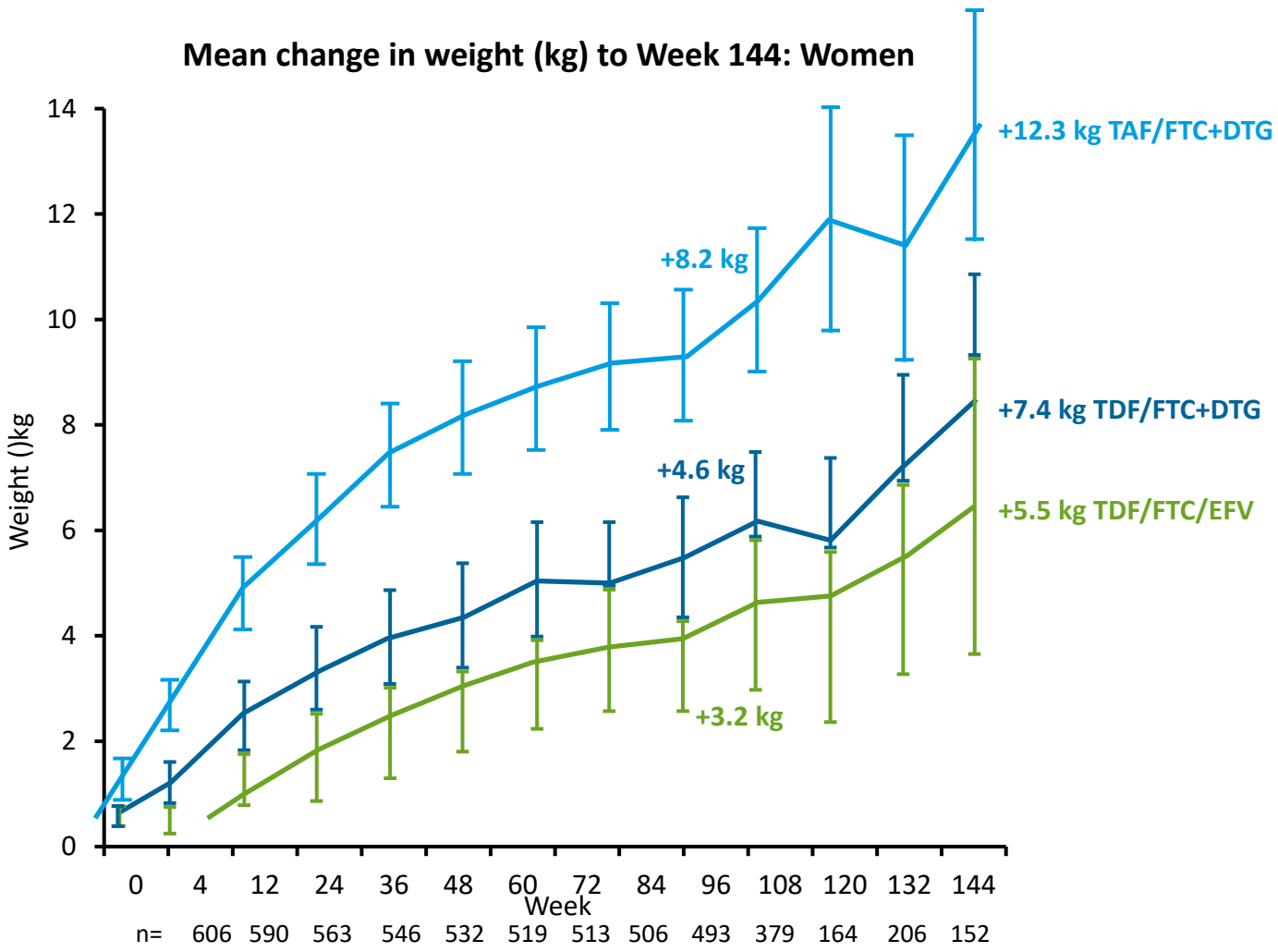
Pooled analysis of weight gain across 8 randomized phase III clinical trials of first-line ART initiation occurring in 2003-2015 (N = 5680)

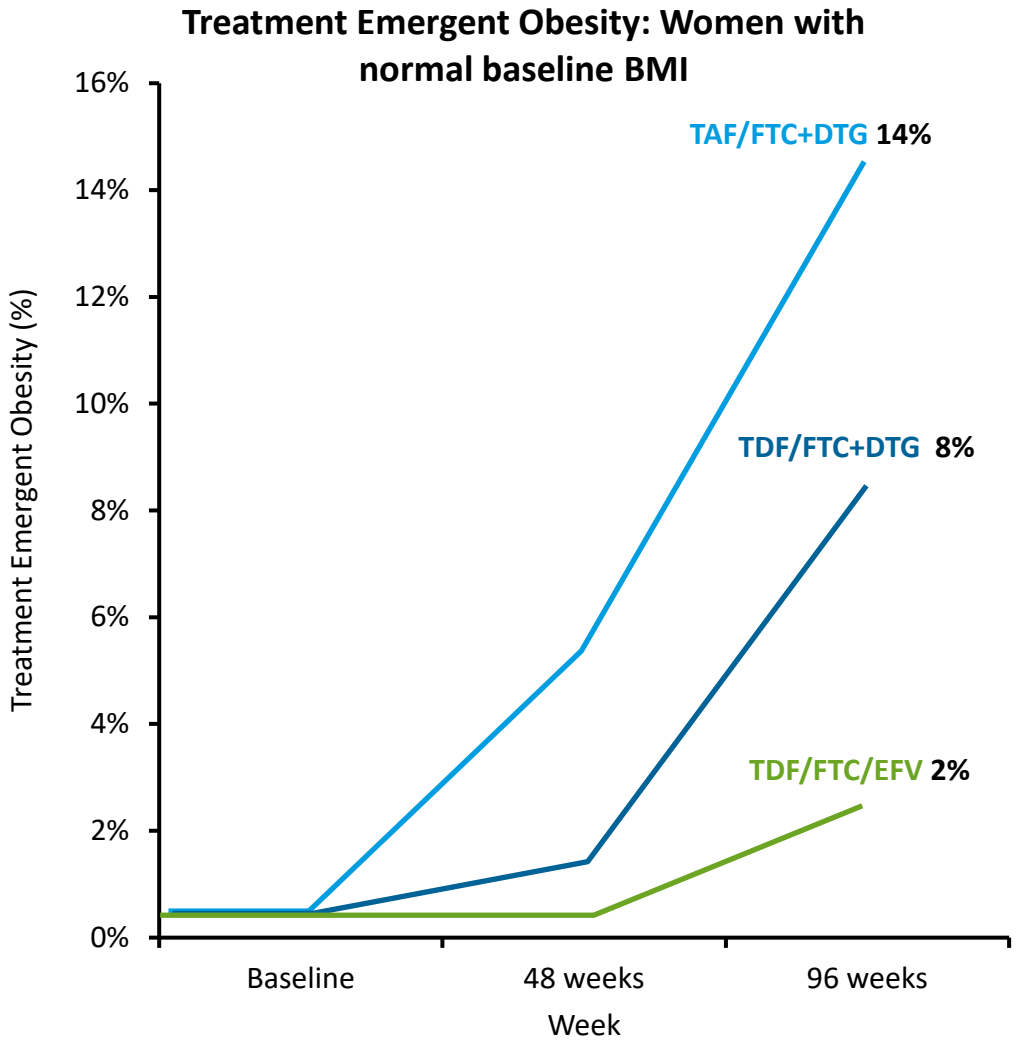


*Color-coded to match respective comparators, denoting P ≤ .05 vs NNRTI (first panel), EVG/COBI (second panel), or ZDV (last panel).

Source: Sax. Clin Infect Dis. 2019;[Epub].

ADVANCE 144WK: WEIGHT CHANGE AND OBESITY IN CIS-WOMEN





Source: Asif S, et al. AIDS 2020: Virtual; July 6-10, 2020. Abst. OABLB0103.

MANY ARV TOXICITIES ARE RECOGNIZED LATE

Drug / classgu	FDA approval	Toxicity/AE	Suspected strong signal	Delay (years)
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Raltegravir	2007[8]	Myopathy[18]	2012	5
Dolutegravir	2013[9]	Psychiatric effects[19]	2015	2
Dolutegravir	**2013[9]**	**Weight gain**	**2019**	**6**
Tenofovir alafenamide	**2016**	**Weight gain?**	**2019**	**3**
Bictegravir	**2018**	**Weight gain**	**2019**	**1**

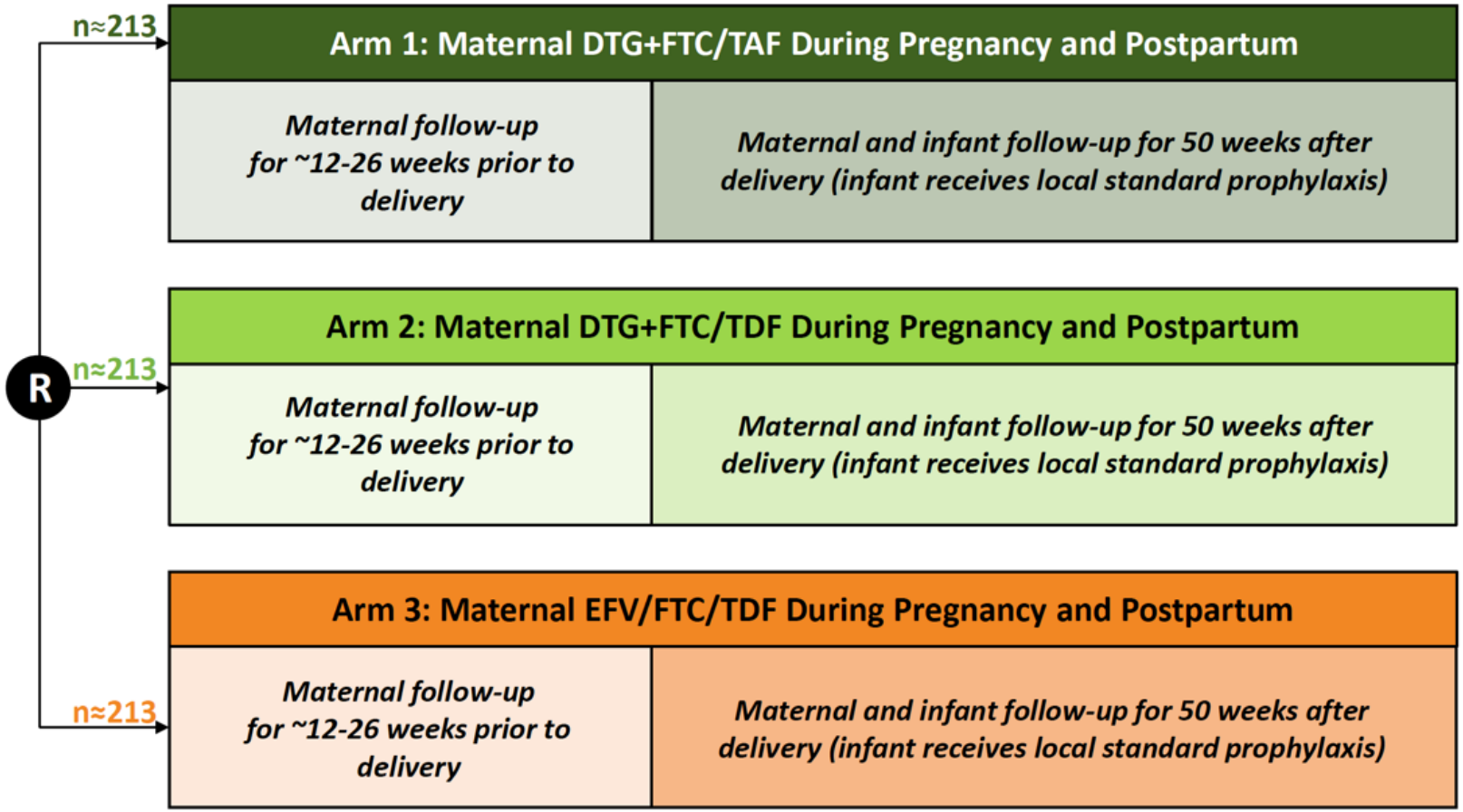
Source: See slide notes for references

TSEPAMO UPDATE: CONCLUSIONS

- With data collected through April 30, 2020, observed NTD prevalence among infants born to women with DTG exposure at conception appears to be stabilizing at ~ 2 cases per 1000 after decreasing from the initial analysis in May 2018
  - Initial analysis (May 2018): DTG vs non-DTG ART at conception, 0.94% vs 0.12%; prevalence difference 0.82% (95% CI: 0.24% to 2.30%)
  - Updated analysis (April 2019): 0.30% vs 0.10%; prevalence difference: 0.20% (95% CI: 0.01% to 0.59%)
  - Current analysis (April 30, 2020): 0.19% vs 0.11%; prevalence difference: 0.09% (95% CI: -0.03% to 0.30%)

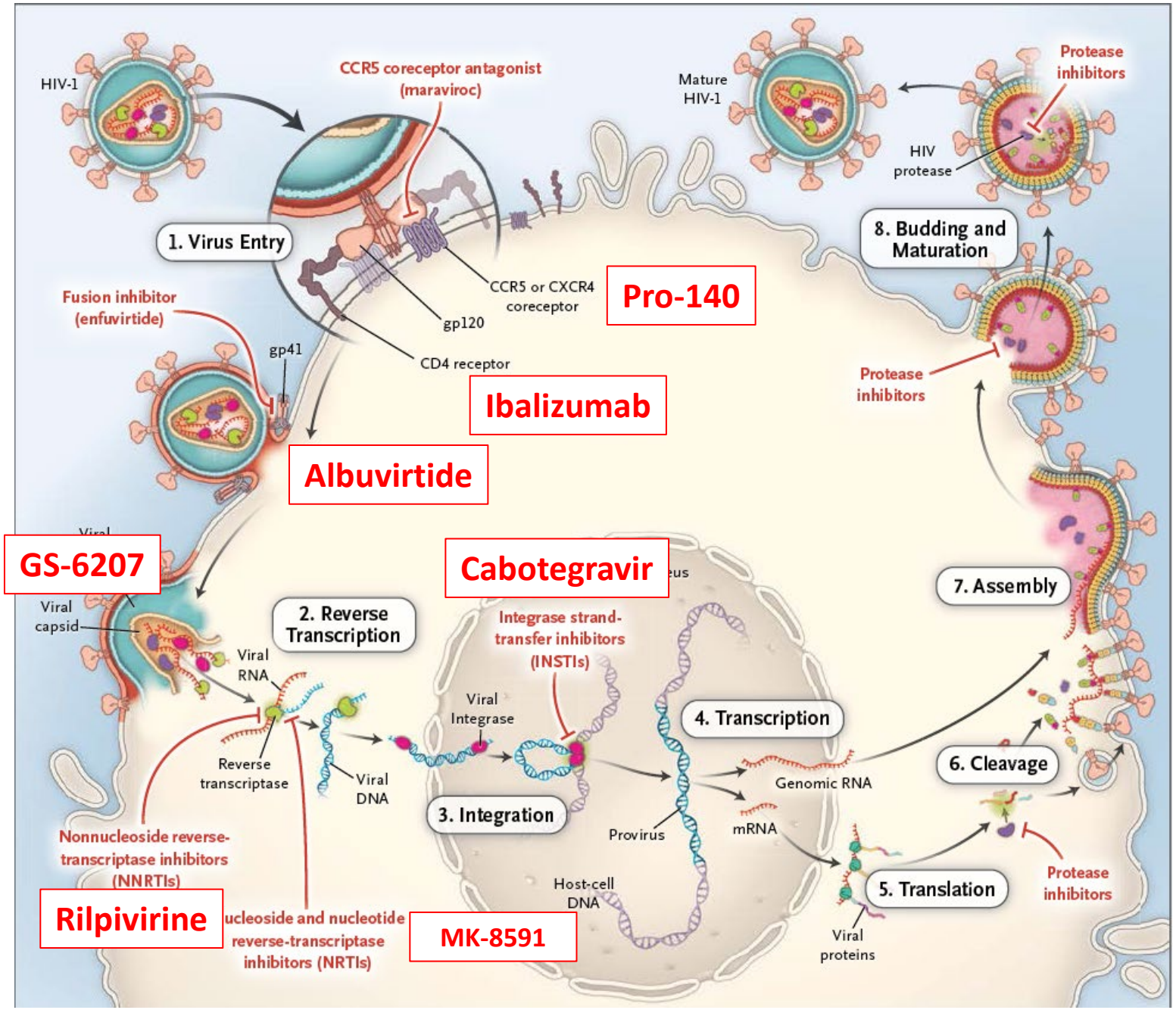
Source: Zash. AIDS 2020. Abstr OAXLB0102.

IMPAACT 2010: SAFETY AND EFFICACY OF DTG VS EFV AND TDF VS TAF IN PREGNANCY



- DTG containing ART had superior virologic efficacy at delivery compared to EFV/FTC/TDF
- DTG+FTC/TAF was associated with significantly fewer adverse pregnancy outcomes and fewer neonatal deaths than EFV/FTC/TDF

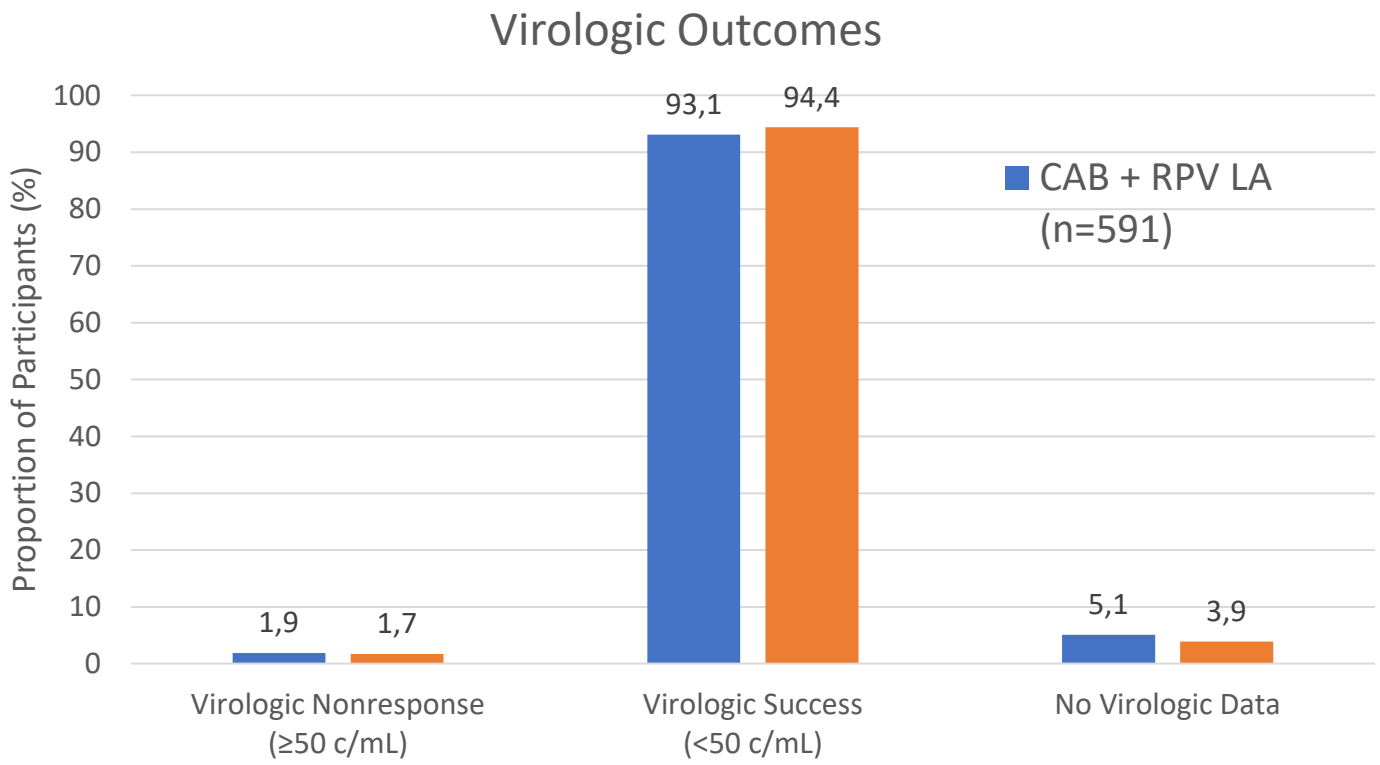
Source: Chinula. CROI 2020. Abstr 130LB.



Source: Adapted. Gandhi M, Gandhi RT. N Engl J Med 2014; 371:248–259

Present and future of ISTI

WEEK 48 POOLED ANALYSIS FROM (ATLAS AND FLAIR)



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Long-Acting Cabotegravir and Rilpivirine for Maintenance of HIV-1 Suppression

ORIGINAL ARTICLE

Long-Acting Cabotegravir and Rilpivirine after Oral Induction for HIV-1 Infection

6 failures A1. L74I

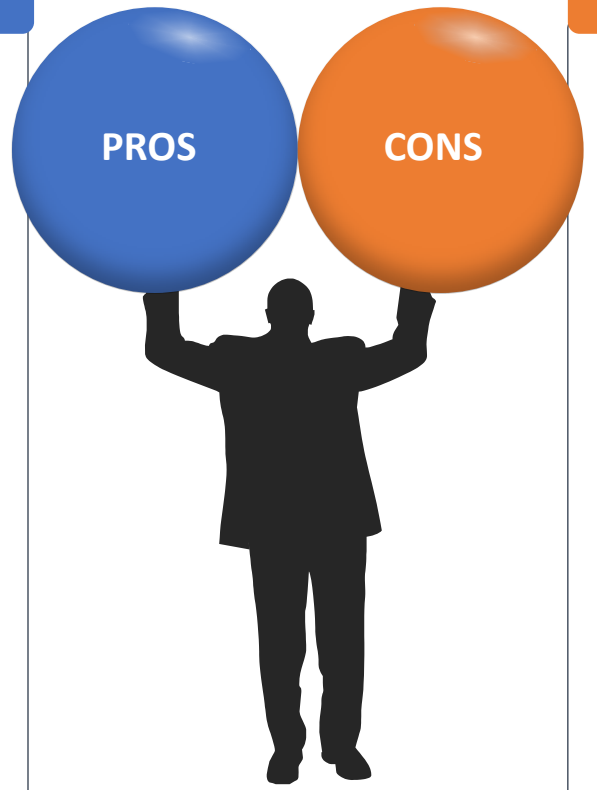
ATLAS 2M: Cabotegravir + rilpivirine **every 2 months** is noninferior to monthly dosing: week 48

CVF 8 (Q8W) vs 2 (Q4W)

Source: Overton ET et al. IAS 2019. MOPEB257. Overton et al. CROI 2020 Presentation 3334.
N Engl J Med 2020; 382:1112. N Engl J Med 2020; 382:1124

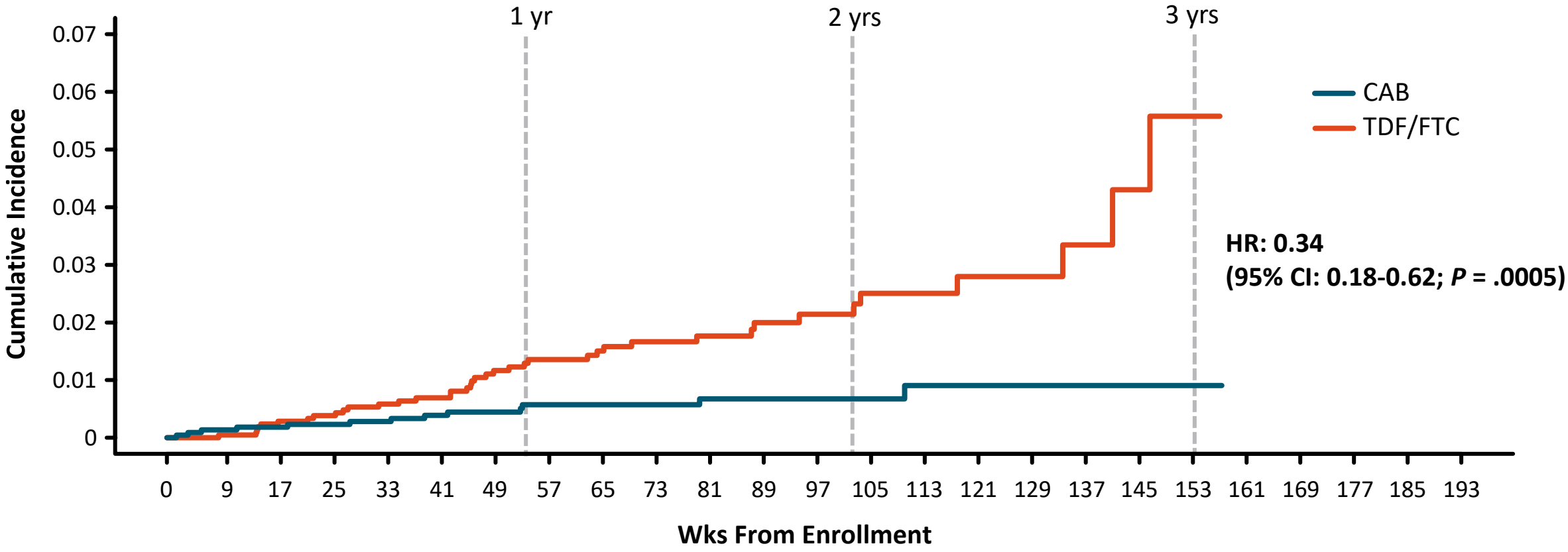
LA INJECTABLES: PROS AND CONS

- Less stigma
- Increased patient confidentiality
- Adherence
- Potential for DOT



- Hep B not covered
- Cold chain
- Oral lead in and bridge
- IM injection. Not self administered
- Long tail
- Adherence/Resistance
- ISR Long-term tolerability
- Difficulty with withdrawal of drug in the event of toxicity.
- Pregnancy
- Service capacity
- Cost

HPTN 083: HIV INCIDENCE (ITT) WITH LA INJECTABLE CAB VS DAILY ORAL TDF/FTC PREP



Source: Landovitz. AIDS 2020. Abstr OAXLB0101. Reproduced with permission.

Present and future of ISTI

- ISTI-based regimens are recommended in all international guidelines
- There is flexibility with the number of NRTIs that we need to include in an ISTI-based régimen
- Long-term impact of weight changes and metabolic consequences is an area of active research
- DTG related NTD signal is decreasing
- TAF/FTC-DTG new option for pregnant women
- The first long-acting regiment is ISTI based
- Exciting data about cabotegravir LA for PREP