The Future of ART

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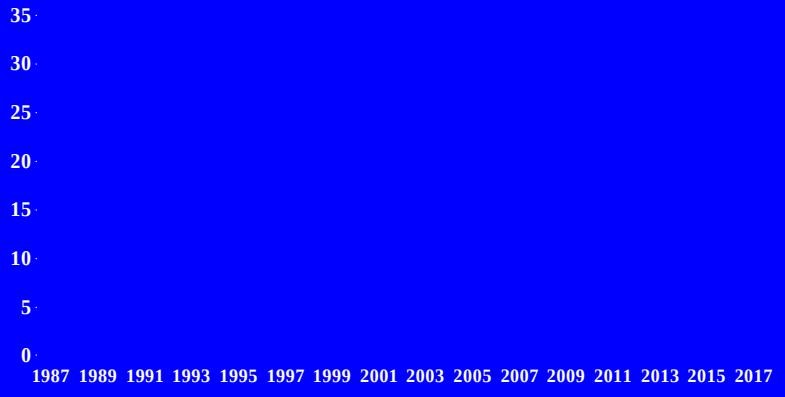
Disclosures

- none

ART in 2018

- Start ART at all CD4 cell counts
- 32 approved drugs
  - 5 broad mechanistic classes: NRTI, NNRTI, PI, INSTI, EI
- Up to 7 recommended first-line regimens worldwide
  - 1 standard strategy: 2 NRTI + [NNRTI, PI, or INSTI]
- ART Properties
  - Antiretroviral activity
  - Safety and tolerability
  - Convenience
  - Access and cost

Antiretroviral Drug Approval: 1987 - 2018



ART: What to Start? – Recommended/Preferred: 2 NRTI + 3rd Drug

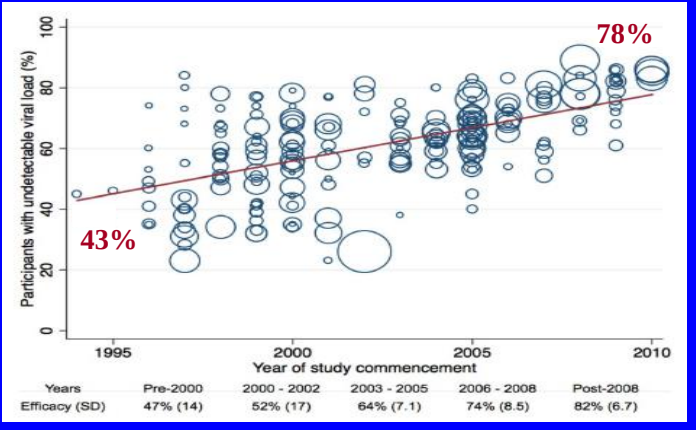
US DHHS 2018 www.aidsinfo.nih.gov
IAS-USA 2018 JAMA 2018;320:379
EACS 2017 www.europeanaidsclinicalsociety.org/
UK 2016 update www.bhiva.org
WHO 2018 http://www.who.int/hiv/pub/guidelines/ARV2018update/en/

+ only with DTG; * performs less well/not recommended for baseline HIV RNA >100,000 and/or CD4 <200

Antiretroviral Activity

ART Trials: Virologic Responses

114 studies through 2012, 1-3 years of f/u: ITT analyses



Carr PLoS One 2014;9:e97482

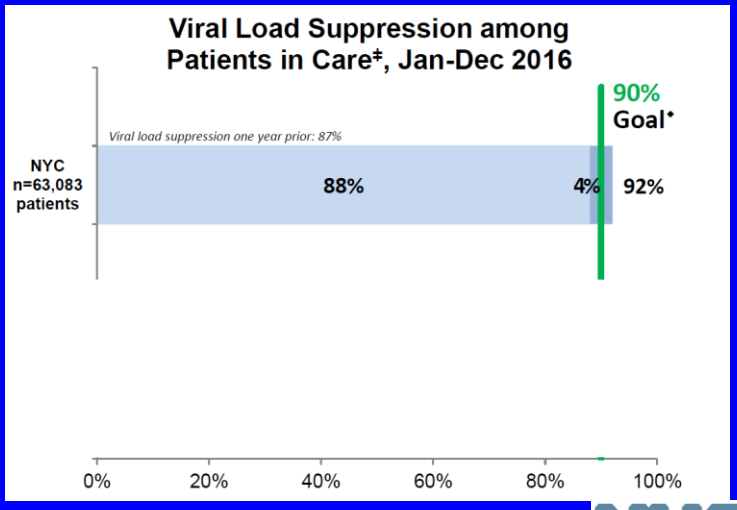
Virologic Responses – Newer Studies

Study (reference)	Study arm (N)	Regimen	HIV RNA <50 at 48 wks
GS-US-380-1490 Sax Lancet 2017;390:2074	**320** **325**	**TAF/FTC/BIC** **TAF/FTC + DTG**	**89%** **93%**
GS-US-380-1489 Gallant Lancet 2017;390:2063	**316** **315**	**TAF/FTC/BIC** **ABC/3TC/DTG**	**92%** **93%**
AMBER Eron AIDS 2018;32:1431	**362** **363**	**TAF/FTC/DRV/c** **TAF/FTC + DRV/c**	**91%** **88%**
GEMINI 1 Cahn IAS 2018 #TUAB0106LB	**356** **359**	**DTG+3TC** **TDF/FTC + DTG**	**90%** **93%**
GEMINI 2 Cahn IAS 2018 #TUAB0106LB	**360** **359**	**DTG+3TC** **TDF/FTC + DTG**	**93%** **94%**

Virologic Responses – Comparative Studies

Study (reference)	N	Regimen	VL <50 (96 wks)
ACTG 5257 Lennox Ann Intern Med 2014;161:461	**605**	**2 NRTI + ATV/r**	**88%**
	601	**2 NRTI + DRV/r**	**89%**
	603	**2 NRTI + RAL**	**94%***
SINGLE Walmsley NEJM 2013;369:1807 + JAIDS 2015;70:515	**414**	**ABC/3TC + DTG**	**80%***
	419	**TDF/FTC/EFV**	**72%**
FLAMINGO Molina Lancet 2014;383:2222 + Lancet HIV 2015;2:e127	**242**	**2 NRTI + DTG**	**80%***
	242	**2 NRTI + DRV/r**	**68%**

* = significant difference



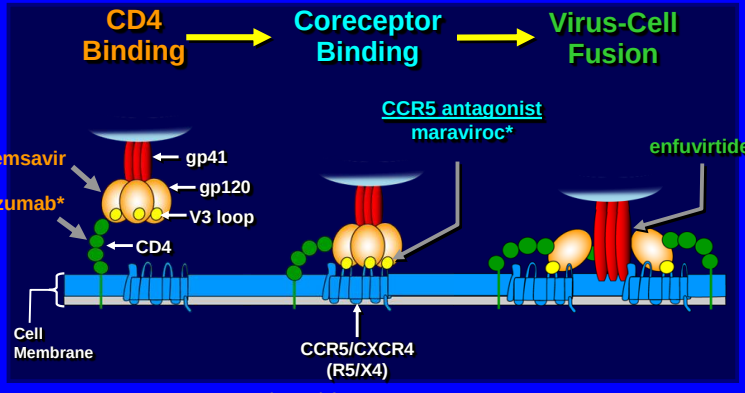
Multi-Class Failure on TAF/FTC + DRV/r + DTG

VL 87K
CD4 92

NRTI	Abacavir	Ziagen	Resistant	(4.5 - 6.5)	9.39	
	Didanosine	Videx	Resistant	(1.3 - 2.2)	2.67	
	Emtricitabine	Emtriva	Resistant	(3.5)	>MAX	
	Lamivudine	Epivir	Resistant	(3.5)	>MAX	
	Stavudine	Zerit	Resistant	(1.7)	2.57	
	Zidovudine	Retrovir	Resistant	(1.9)	4.80	
	Tenofovir	Viread	Partially Sensitive	(1.4 - 4)	1.62	
	NRTI Mutations		M41L, D67N, K70S, L74I, V75T, M184V, T215F, K219Q, N348I			
NNRTI	Delavirdine	Rescriptor	Resistant	(6.2)	>MAX	
	Efavirenz	Sustiva	Resistant	(3)	>MAX	
	Etravirine	Intelence	Resistant	(2.9 - 10)	18	
	Nevirapine	Viramune	Resistant	(4.8)	>MAX	
	Rilpivirine	Edurant	Resistant	(2)	>MAX	
	NNRTI Mutations		L100I, K103S, V179V/I, Y181Y/C, N348I			
PI	Atazanavir	Reyataz	Resistant	(2.2)	82	
	Atazanavir	Reyataz / r[a]	Resistant	(5.2)	82	
	Darunavir	Prezista / r[a]	Resistant	(10 - 90)	>MAX	
	Fosamprenavir	Lexiva / r[a]	Resistant	(4 - 11)	>MAX	
	Indinavir	Crixivan / r[a]	Resistant	(10)	77	
	Lopinavir	Kaletra[a]	Resistant	(9 - 55)	>MAX	
	Nelfinavir	Viracept	Resistant	(3.6)	162	
	Ritonavir	Norvir	Resistant	(2.5)	>MAX	
	Saquinavir	Invirase / r[a]	Resistant	(2.3 - 12)	>MAX	
	Tipranavir	Aptivus / r[a]	Resistant	(2 - 8)	16	
	PI Mutations		L10F, V11I, I13V, V32I, L33F, E35D, M36L, M46I, I47V, I54M, A71V, N83D, I84V, L			
INI	Dolutegravir	Tivicay	Resistant	(4 - 13)	50	
	Elvitegravir	Vitekta	Resistant	(3.5)	107	
	Raltegravir	Isentress	Resistant	(2.2)	153	
	INI Mutations		L74I/M, E138K, G140A, S147G, Q148R, V151I, I203M			

+ hx of failure on enfuvirtide!

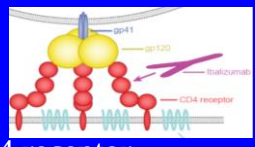
HIV Entry Inhibitors



* = FDA approved

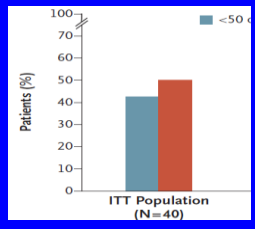
Adapted from Moore JP, *PNAS* 2003;100:10598-10602.

Ibalizumab (IBA): CD4 Post-Attachment Inhibitor



- Monoclonal antibody; parenteral; binds to CD4 receptor
- Phase 3
  - Study pop: VL>1000, ART >6 mos, 3-class resistance, ≥1 sens. drug (N=40)
  - Study treatment: continue ART, add IBA 2000 mg day 7
    - day 14: 60% VL 1 log ↓

  -- Day 14 optimize background, continue IBA 800 mg q2 weeks
    - week 24: 43% VL <50



Emu NEJM 2018;379:645

    - extension to week 48 (n=27): 59% VL <50

Emu IDWeek 2017 #1686

Fostemsavir (FTR): Oral Attachment Inhibitor

- Prodrug of **temsavir**; inhibits CD4 binding by binding to gp120
- Phase 1 dose-escalation: up to 1.5 log cps/ml ↓; ↓ baseline susceptibility in 12% of pts due to envelope polymorphisms

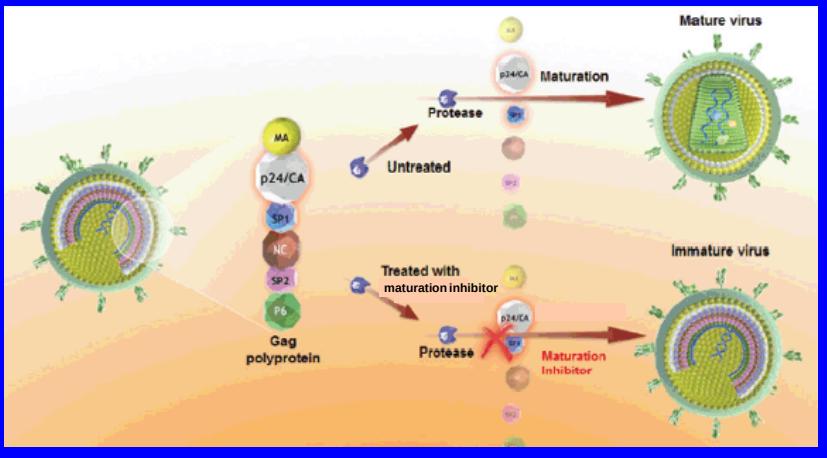
Nettles JID 2012;206:1002

- Phase 2b: modestly rx-experienced, screened for susc (N=254); week 48: 61-82% VL <50; week 96: 61% VL <50 (MITT)

DeJesus CROI 2016 #472 and Thompson Antivir Ther 2017;22:215

- Phase 3: heavily rx-experienced, NOT screened for susc (N=272 rand.; 99 non-rand.)
  - day 8: mean HIV RNA Δ: -0.2 (placebo) vs. -0.8 (FTR) log cps/ml
  - wk 24: VL <40: 54% (rand) vs. 36% (non-rand) Lataillade EACS 2017 #PS8/5
- FDA "breakthrough status" 2015; filing 2019-2020

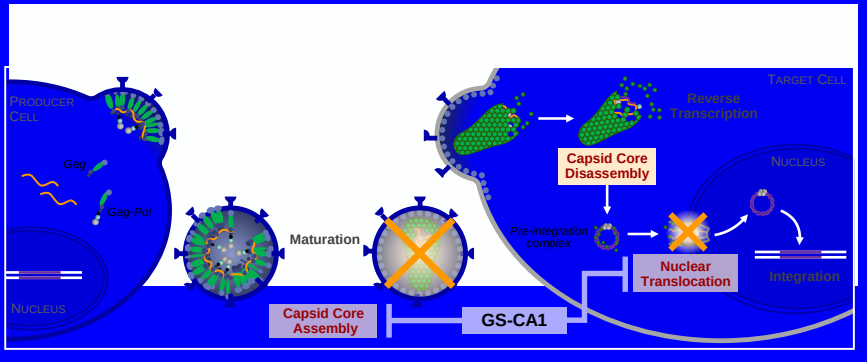
HIV Maturation Inhibitors (MI)



BMS-955176/GSK3532795: +virologic suppression, halted due to GI toxicity

Morales-Ramirez IAS 2017 #MOAB0103

HIV Capsid Inhibitor

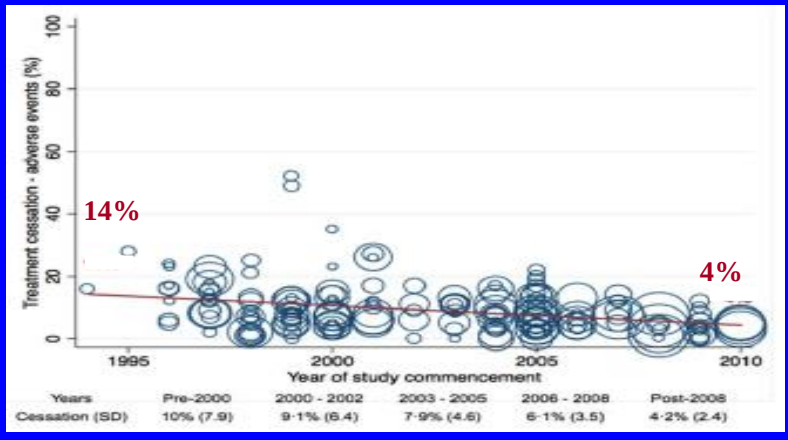


Tse CROI 2017 #38

Safety and Tolerability

ART Trials: Discontinuations for Toxicity

114 studies through 2012, 1-3 years of f/u: ITT analyses



Carr PLoS One 2014;9:e97482

Discontinuations for Adverse Events

Study (reference)	Study arm (N)	Regimen	% d/c for adverse events at 48-96 weeks
ACTG 5257 Lennox Ann Intern Med 2014	**603**	**2 NRTI + RAL**	**<1%**
SPRING-2 Raffi Lancet Infect Dis 2013	**411**	**2 NRTI + DTG**	**2%**
GS-US-292-0104/0111 Wohl JAIDS 2016	**866** **867**	**TAF/FTC/EVG/c** **TDF/FTC/EVG/c**	**1%** **2%**
GS-US-380-1489 Gallant Lancet 2017;390:2063	**316** **315**	**TAF/FTC/BIC** **ABC/3TC/DTG**	**0%** **1%**

Safety and Tolerability: Newer Approaches

- **Lower doses:**
  - ENCORE 1 (2 NRTI + EFV 400 mg vs. 600 mg)

    Double-blind randomized, study of initial ART (N=630) → demonstrated non-inferiority Puls Lancet 2014;383:1474
  - WRHI 052 Venter IAS 2018 #TUAB0107LB

    Switch study of pts on LPV/r >6 months, VL <50, no hx of other PI use (N=300)
    - Randomized to continue LPV/r or switch to DRV/r 400/100 qd
    - VL <50 at wk 48 (ITT) 95.4% (LPV) vs. 96.7% (DRV)
      Δ +1.2% (95% CI: -3.7, +6.2%)
    - Conclusions:
      - DRV/r 400/100 non-inferior + "significantly cheaper"
  - Other studies in progress: ATV 300 mg

Safety and Tolerability: Newer Approaches

- **Newer drugs:**
  - tenofovir alafenamide (TAF)
  - TAF vs. TDF: Similar virologic efficacy
    - 1733 pts on [TAF or TDF]/FTC/EVG/c Sax Lancet 2015;385:2606
  - Switch TDF→TAF improved renal/bone markers
    - 1443 pts on TDF with GFR ≥50 cc/min Mills Lancet ID 2016;16:43
    - 663 pts on TDF with GFR ≥50 cc/min Gallant Lancet HIV 2016;3:e158
    - 242 pts on TDF (65%) or not (35%) with eGFR 30-69 Pozniak JAIDS 2016;71:530

Newer Approaches: 2-Drug Regimens

- PI/r + 3TC (or FTC)
  - GARDEL (LPV/r): Cahn Lancet Infect Dis 2014;14:572
  - OLE (switch; LPV/r): Arribas Lancet Infect Dis 2015;15:785
  - SALT (switch; ATV/r): Perez-Molina Lancet Infect Dis 2015;15:775
  - DUAL (switch; DRV/r): Pulido Clin Infect Dis 2017;65;2112
  - ANDES (DRV/r): Sued IAS 2017 #MOAB0106LB
- PI/r + integrase inhibitor
  - Second-Line (LPV/r + RAL) Boyd Lancet 2013;381:2091
  - NEAT-001 (DRV/r + RAL) Raffi Lancet 2014;384:1942
- NNRTI + integrase inhibitor
  - SWORD (switch; RPV + DTG) Libre Lancet 2018;391:839
  - ETRAL (switch; ETR + RAL) Katlama IAS 2017 #MOPEB0314
  - FLAIR (CAB + RPV) (in progress)

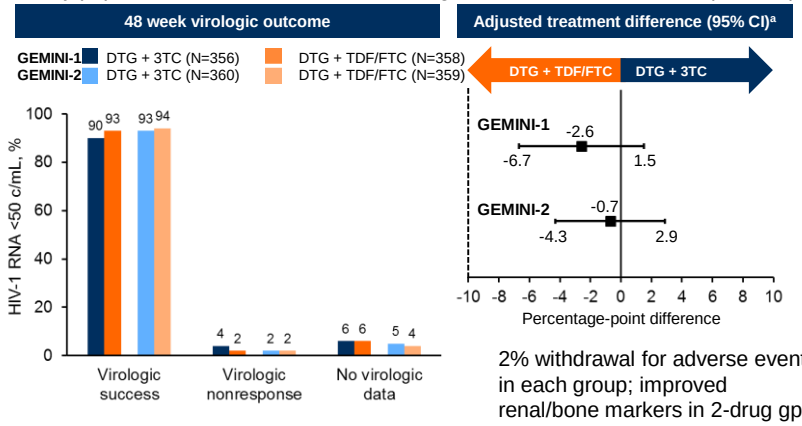
2-Drug Regimen: DTG + 3TC

- PADDLE Study Cahn JIAS 2017;20:1; Figueroa IAS 2017 #MOPEB0287
  - Treatment-naïve individuals with HIV RNA 5-100K (N=20)
  - 2-drug regimen of DTG + 3TC
  - Results: All suppressed VL <50 by week 8
    - 18/20 (90%) remained suppressed through week 96
- ACTG 5353 Taiwo CID 2018;66:1689
  - Treatment-naïve, HIV RNA up to 500K (N=120)
  - 90% <50 copies/ml at week 24 (FDA snapshot analysis)
- GEMINI 1 and 2 Cahn AIDS 2018 #TUAB0106LB
- Switch studies

2-Drug ART: DTG + 3TC vs. DTG + TDF/FTC

Randomized, double-blind, parallel-group, multicenter, non-inferiority (Δ10%) studies

Study population: Rx-naïve, no baseline drug resistance, VL 1000-500K (N=1433)



2% withdrawal for adverse events in each group; improved renal/bone markers in 2-drug gp

Conclusion: DTG + 3TC is non-inferior to DTG + TDF/FTC with respect to proportion <50 at Wk 48 (snapshot, ITT-E population)

Cahn AIDS 2018 #TUAB0106LB

Convenience

ART: Convenience

Newer Approaches

- Less frequent dosing
  - RAL daily formulation Cahn Lancet HIV 2017;4:e486
  - Alburvirtide weekly fusion inh Zhang AIDS Res Ther 2016;13:8
- Newer co-formulations
  - ATV/c and DRV/c
  - TAF/FTC/DRV/c Eron AIDS 2018;32:1431
  - TAF/FTC/BIC Gallant Lancet 2017;390:2063 + Sax Lancet 2017;390:2073
- New Injectable Drugs
  - RPV LA Jackson Clin Pharmacol Ther 2014;96:314
  - Cabotegravir (CAB) Spreen JAIDS 2014;67:481

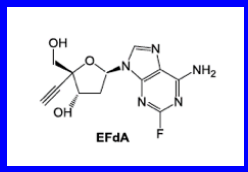
LATTE-2: IM CAB + IM RPV

- Randomized, open-label, phase 2b, non-inferiority study
- Study population: ART-naïve (N=309)
- Study rx: PO CAB + ABC/3TC X 4 wks, then randomized 2:2:1
- Results (HIV RNA <50 at 96 wks)
  - **IM CAB + IM RPV q8 wks – 94%**
  - **IM CAB + IM RPV q4 wks – 87%**
  - **PO CAB + ABC/3TC – 84%**
- Injection site reactions were nearly universal
  - 97%+ were mild or moderate; lasted a median of 3 days
  - 2 pts (<1%) d/c due to ISR
- Conclusions: IM non-inferior (comparable) to PO; well-tolerated

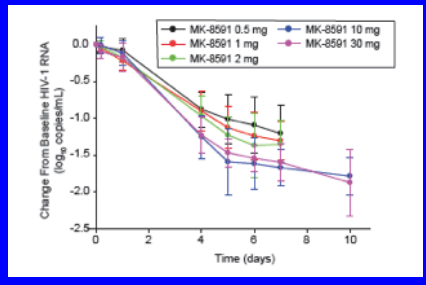
Eron IAS 2017 #MOAX0205LB; Margolis Lancet 2017;390:1499

- Phase 3 studies evaluating IM q8, q4 wks: ATLAS; ATLAS-M

MK-8591 (EFdA)



- 4'-ethynyl-2-fluoro-2'-deoxyadenosine; EFdA
- Non-obligate chain terminator
- Inhibits RT by preventing translocation (NRTTI)
- ½ life 150-160 hours(!)
- Potent antiviral activity (PBMC EC50 = 0.2 nM) with broad coverage (HIV-1, HIV-2, MDR strains)
- Accumulates in LN, vagina, rectum (animals) Grobler CROI 2017 #435
- Low-dose and parenteral formulations with long ½ lives

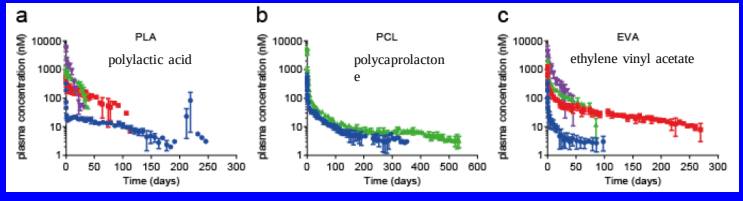


Matthews IAS 2017 #TUPDB0202LB

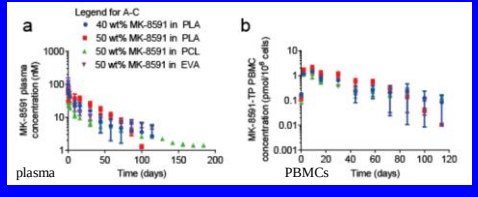
Long-Acting Subdermal Implants: MK-8591 in Animal Studies

Drug-eluting implants, both bioerodible and non-erodible

rats

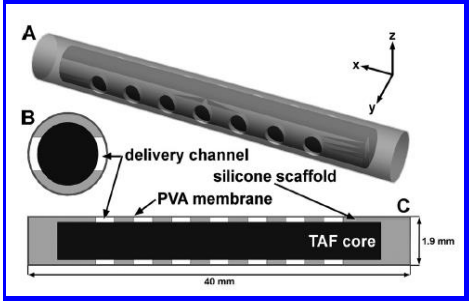


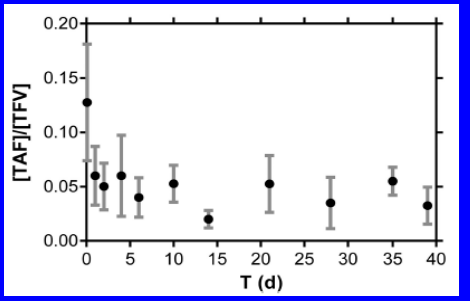
NHP



Barrett AAC 2018 (epub)

Long-Acting Subdermal Implants: Tenofovir Alafenamide (TAF) in Dogs



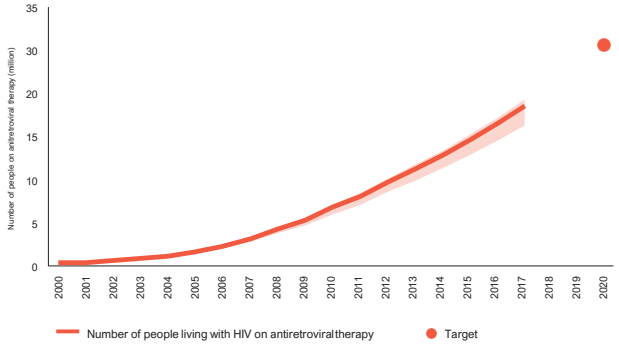


Gunawardana, *AAC* 2015;59:3913

Access and Cost

Aiming for the 2020 treatment target

Number of people living with HIV accessing antiretroviral therapy, global, 2000–2017 and 2020 target



Source: UNAIDS 2018 estimates. Global AIDS Monitoring, 2018.

UNAIDS

ART: Cost

Table 1. Target prices for key first-line combination treatments in low or low-middle income countries

Combination treatment	Estimated price per patient-year	Reference
TDF/3TC/ATV/r	$279	13
TDF/FTC/ELV/COBI	$184	14
ABC/3TC/DTG	$179	14
TDF/FTC/EFV600	$144	13
TDF/3TC/EFV600	$130	13
TDF/3TC/EFV400	$100 to $110	13
TAF/3TC/DTG	$60	14
DTG/3TC	$46	14

Vittoria JIAS 2016;19:20504

Future of ART: Conclusions

- Antiretroviral Therapy
  - Activity — excellent; need MDR-active drugs
  - Safety/tolerability — excellent
  - Convenience — excellent; newer formulations
  - Affordability — improved
  - Accessibility — improved WHO Goal: "30 by 20"

Acknowledgments

- Weill Cornell Medicine
  - Cornell HIV Clinical Trials Unit (CCTU)
  - Division of Infectious Diseases
- AIDS Clinical Trials Group (ACTG)
- HIV Prevention Trials Network (HPTN)
- NIH, NIAID, Division of AIDS
- The participant volunteers!
- David Cooper – mentor and friend!