New drugs pipeline

(credit for all slides: Roy M. Gulick , MD, MPH
Rochelle Belfer Professor in Medicine Chief, Division of Infectious Diseases
Weill Cornell Medicine, New York City)

EATG European AIDS Treatment Group

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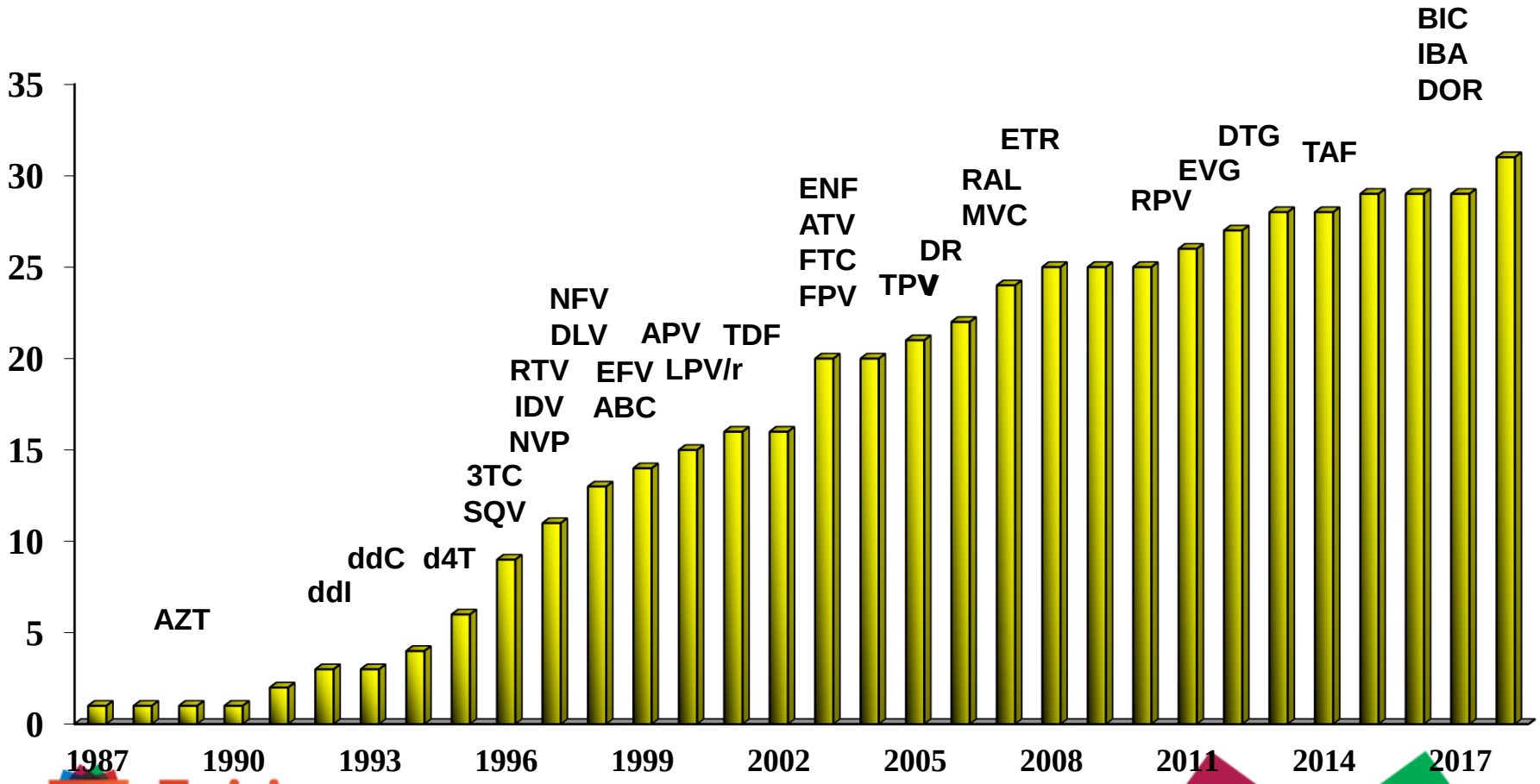
STEP-UP: Skills Training to Empower Patients

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
  - Life Expectancy

Antiretroviral Drug Approval: 1987 - 2018



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When to Start?: Chronic Infection

	AIDS/ symptoms	CD4 <200	CD4 200-350	CD4 350-500	CD4 >500
US DHHS 2018 www.aidsinfo.nih.gov	recommended				
IAS-USA 2018 JAMA 2018;320:379	recommended				
EACS 2018 www.europeanaidsclinicalsociety.org/	recommended				
UK 2016 update www.bhiva.org	recommended				
WHO 2016 http://www.who.int/hiv/pub/guidelines/en/	strong recommendation *PRIORITY*			strong recommendation	

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

	NRTI	NNRTI	PI	II
US DHHS 2018 www.aidsinfo.nih.gov	TAF/FTC TDF/FTC ABC/3TC+	--	--	BIC, DTG, EVG, RAL
IAS-USA 2018 JAMA 2018;320:379	TAF/FTC ABC/3TC+	--	--	BIC, DTG
EACS 2018 www.europeanaidsclinicalsociety.org/	TAF/FTC TDF/FTC ABC/3TC+	RPV*	DRV/c or /r	BIC, DTG, EVG, RAL
UK 2016 update www.bhiva.org	TAF/FTC TDF/FTC	RPV*	ATV/r DRV/r	DTG, EVG, RAL
WHO 2018 http://www.who.int/hiv/pub/guidelines/ARV2018update/en/	TDF/3TC	--	--	DTG

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

ART: What to Start? – Alternative: 2 NRTI + 3rd Drug

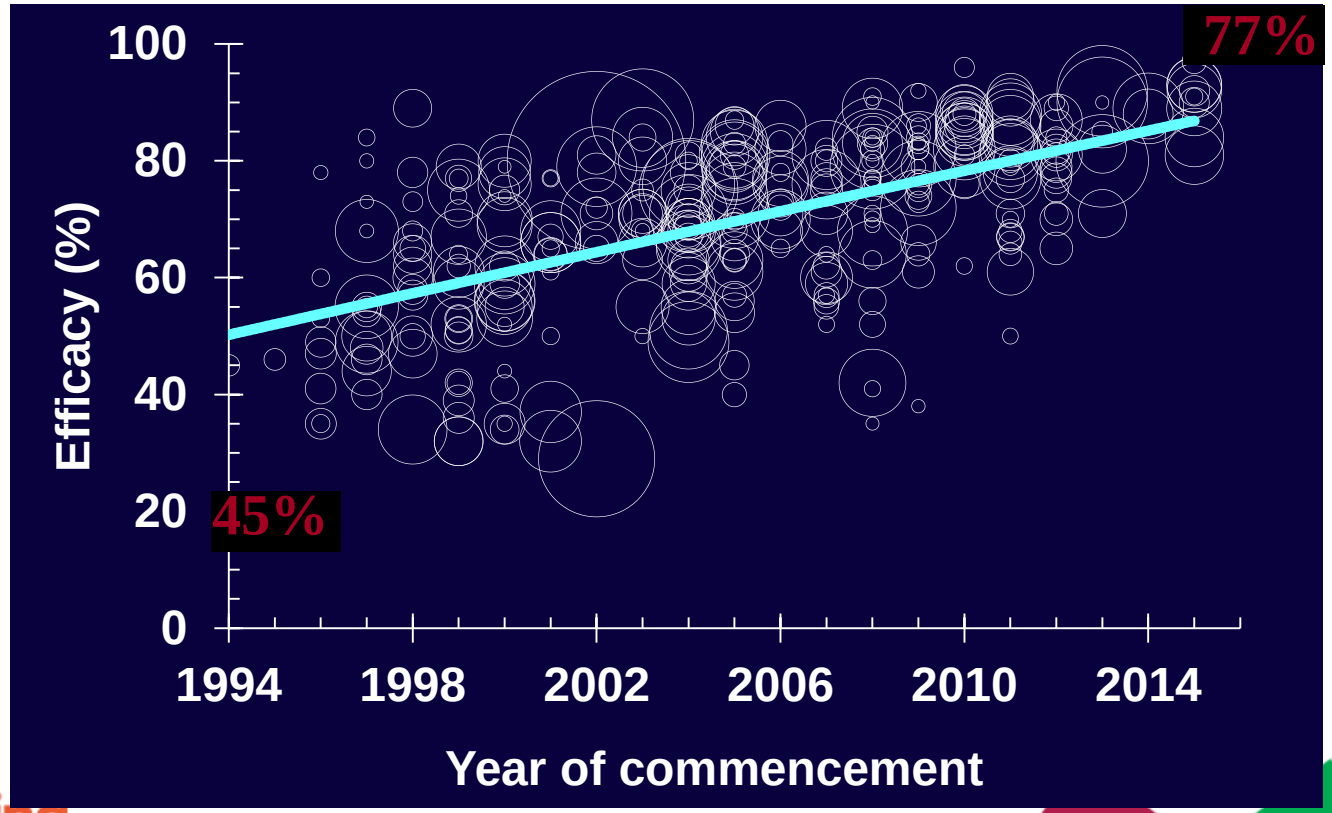
	NRTI	NNRTI	PI	INSTI	other
US DHHS 2018 www.aidsinfo.nih.gov	ABC/ 3TC*	EFV RPV*	ATV/c ATV/r DRV/c		DRV/r + RAL* DRV/r + 3TC DTG + 3TC
IAS-USA 2018 JAMA 2018;320:379	TDF	EFV RPV	DRV/c DRV/r	EVG/c RAL	DRV/c or /r + RAL or DTG or 3TC or FTC
EACS 2018 www.europeanaidsclinicalsociety.org/	ABC/ 3TC	EFV	ATV/c ATV/r	EVG/c	DTG + 3TC DRV/c or /r + RAL
UK 2016 update www.bhiva.org	ABC/ 3TC*	EFV			DRV/r + RAL*
WHO 2018 http://www.who.int/hiv/pub/guidelines/ARV2018update/en/	FTC	EFV 400 or 600		RAL	

* performs less well/not recommended for baseline HIV RNA >100,000, CD4 <200 (except ABC/3TC/DTG)

Antiretroviral Activity

ART Trials: Virologic Responses

354 studies through 2017: ITT analyses
N=77,999



Carr Glasgow 2018 #P051

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%**

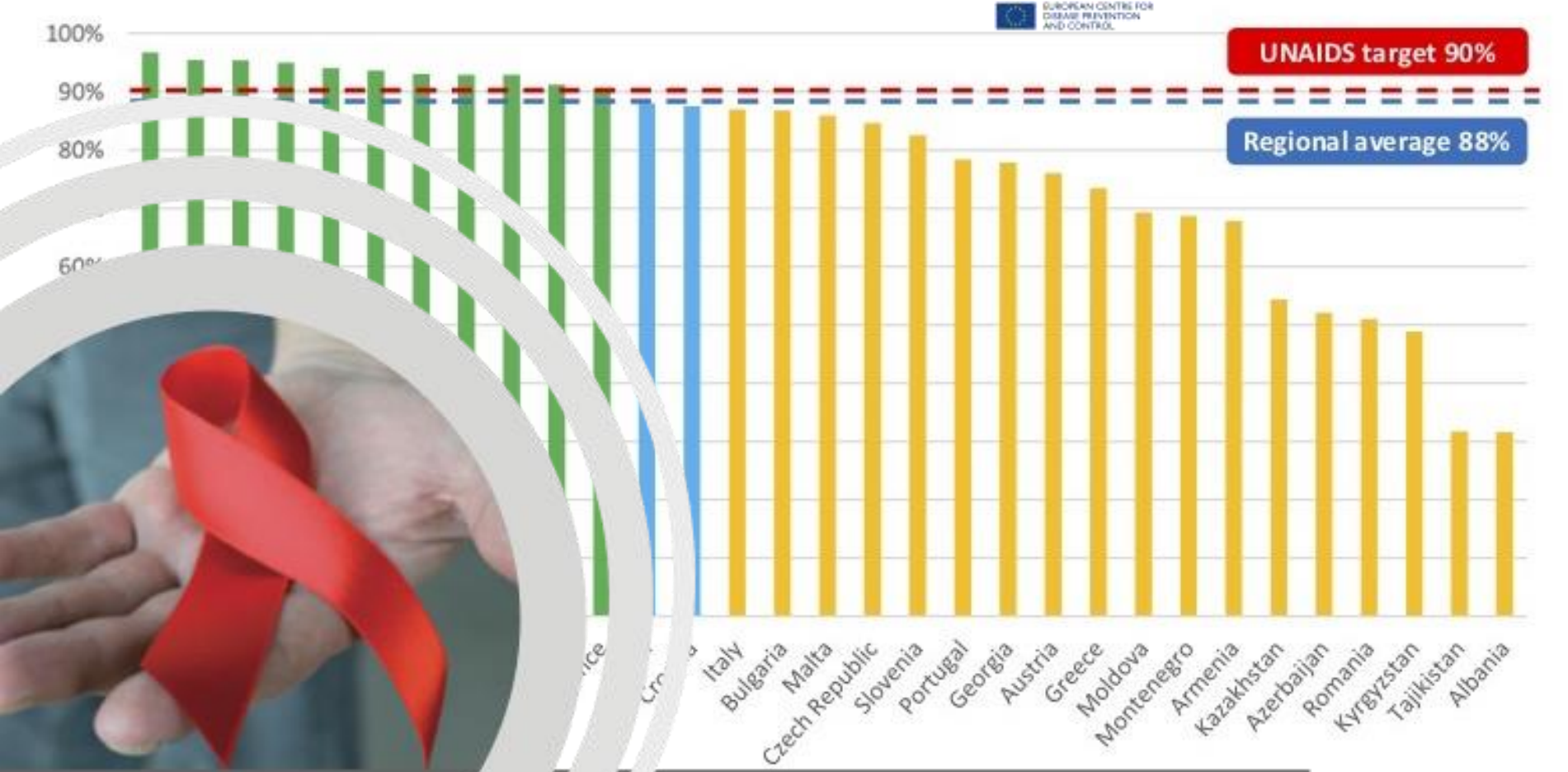
Virologic Responses – Comparative Studies

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

Viral suppression: the continuum of care

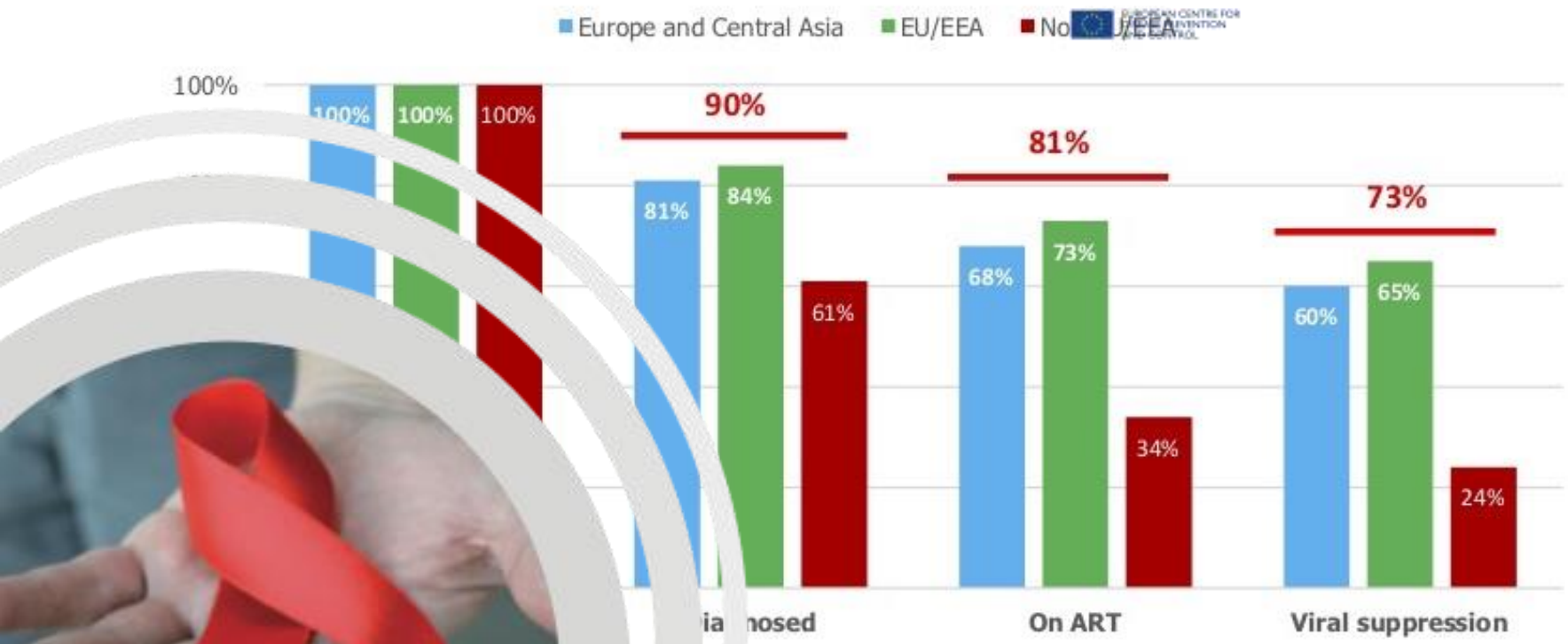
Figure 6. Percentage of people on treatment reaching viral suppression in 31 countries of Europe and Central Asia, 2016[24]



monitoring implementation of the Dublin Declaration on
018

Viral suppression: the continuum of care

Figure 8. Viral suppression among all PLHIV in the 29 countries [illegible]ta on all four stages of the continuum of care, EU/EEA and non-EU/EEA countries, 2016[28]



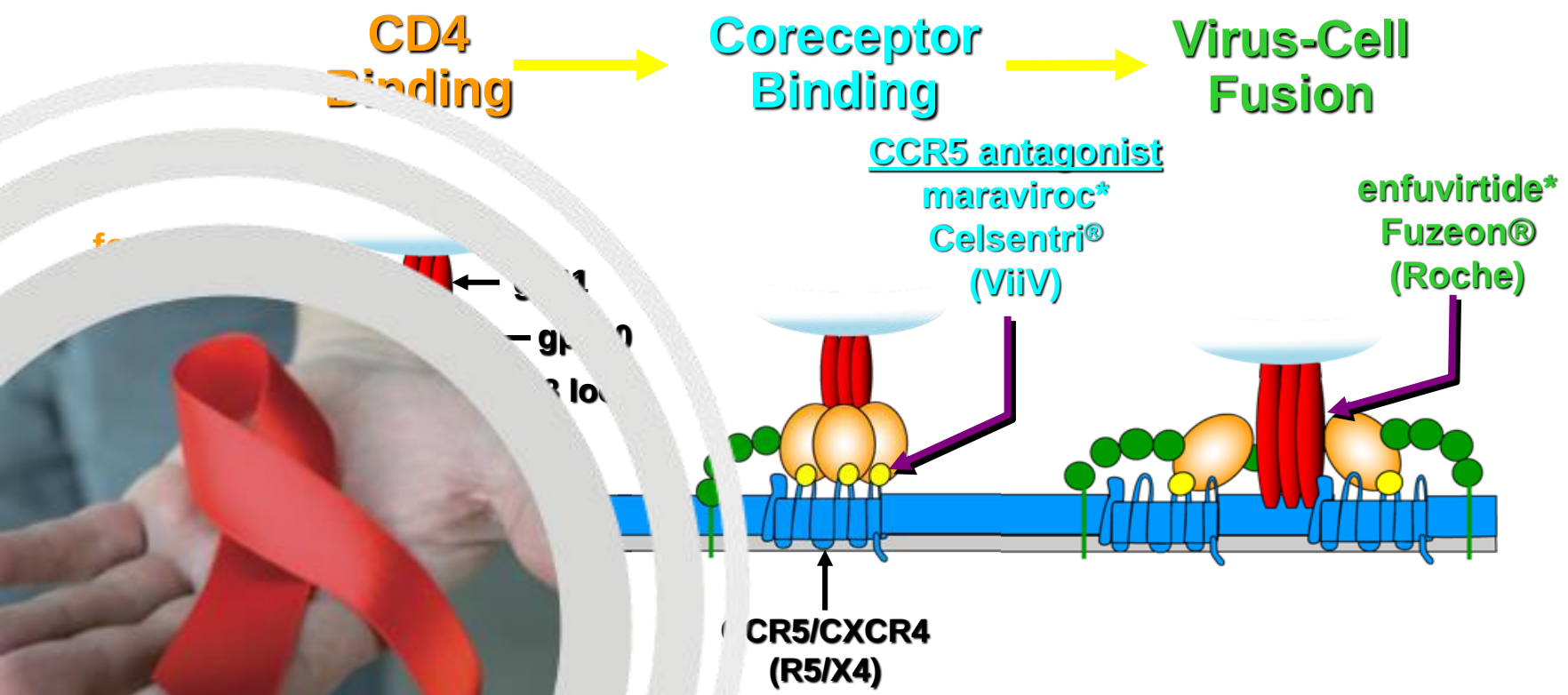
Es a, nland, Iceland, Ireland, Latvia, Liechtenstein, Lithuania, Norway, Poland,

Bo a Herzegovina, the Former Yugoslav Republic of Macedonia, Israel, Kosovo*, kr st Ukraine, Uzbekistan.

onitoring implementation of the Dublin Declaration on 018

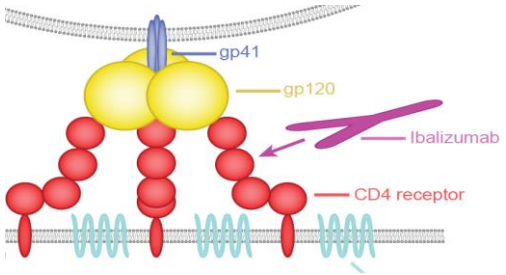
New Drugs

HIV Entry Inhibitors



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

Ibalizumab (IBA): CD4 Post-Attachment Inhibitor

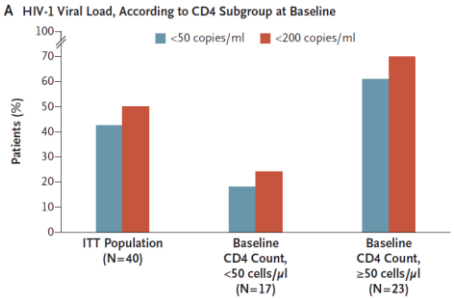


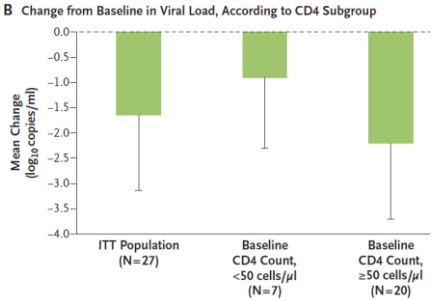
- Monoclonal antibody; parenteral; binds to CD4 receptor
- Phase 3
  - Study pop: VL>1000, ART >6 mos, 3-class resistance, ≥1 sens. drug (N=40)
  - Study treatment: continue ART, add IBA 2000 mg day 7

    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

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Fostemsavir (FTR): Oral Attachment Inhibitor

- Prodrug of **temsavir; i**nhibits CD4 binding by binding to gp120
- PK suggest daily dosing without boosting
- Phase 1 dose-escalation: up to 1.5 log cps/ml ↓; ↓ baseline susceptibility in 12% of pts due to envelope polymorphisms

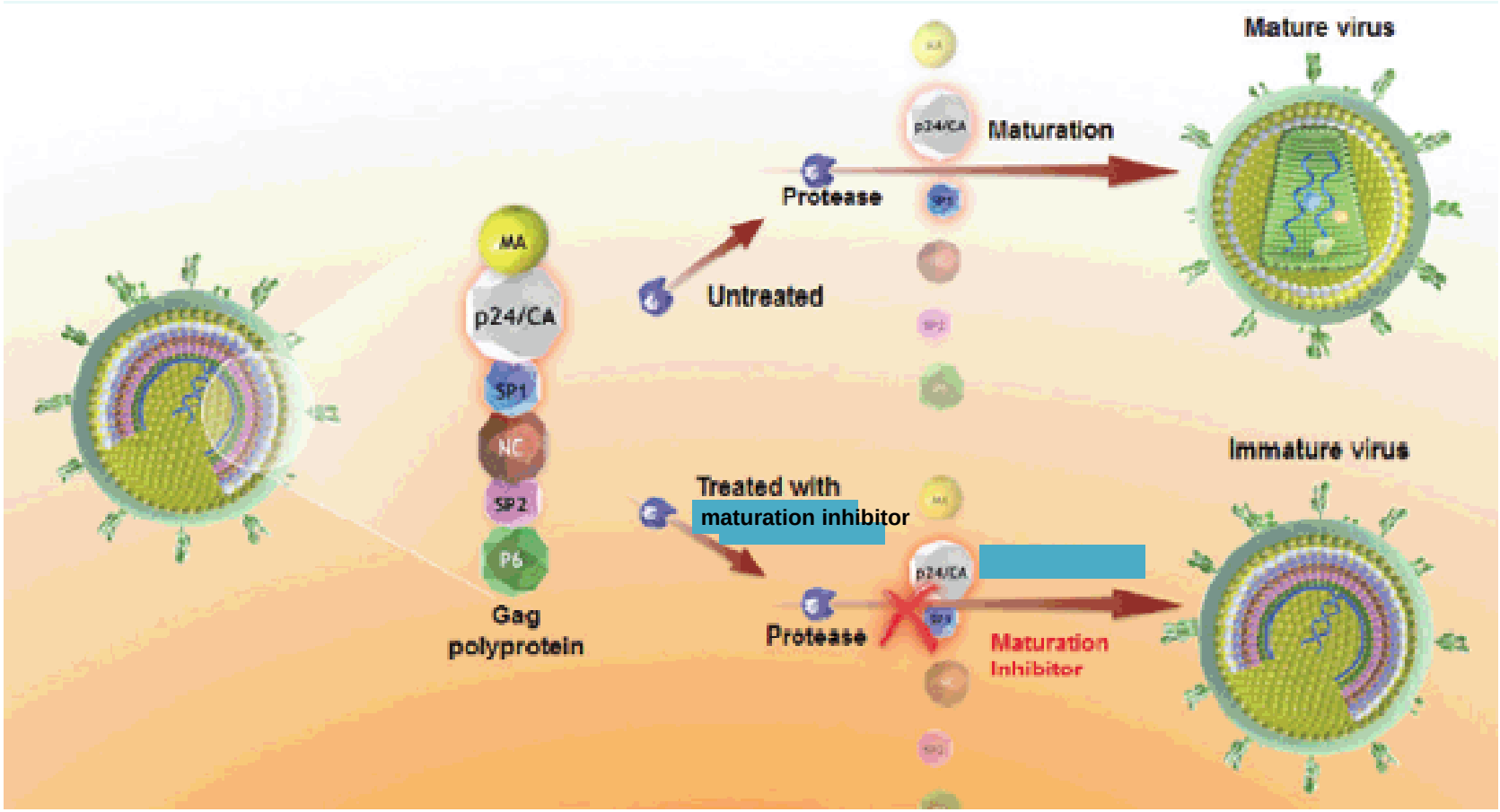
Nettles JID 2012;206:1002

- 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 log cps/ml (placebo) vs. -0.8 (FTR)
  - wk 48: VL <40: 54% (rand) vs. 38% (non-rand) Ackerman Glasgow 2018 #344
- FDA "breakthrough status" July 2015; 2019-2020 filing

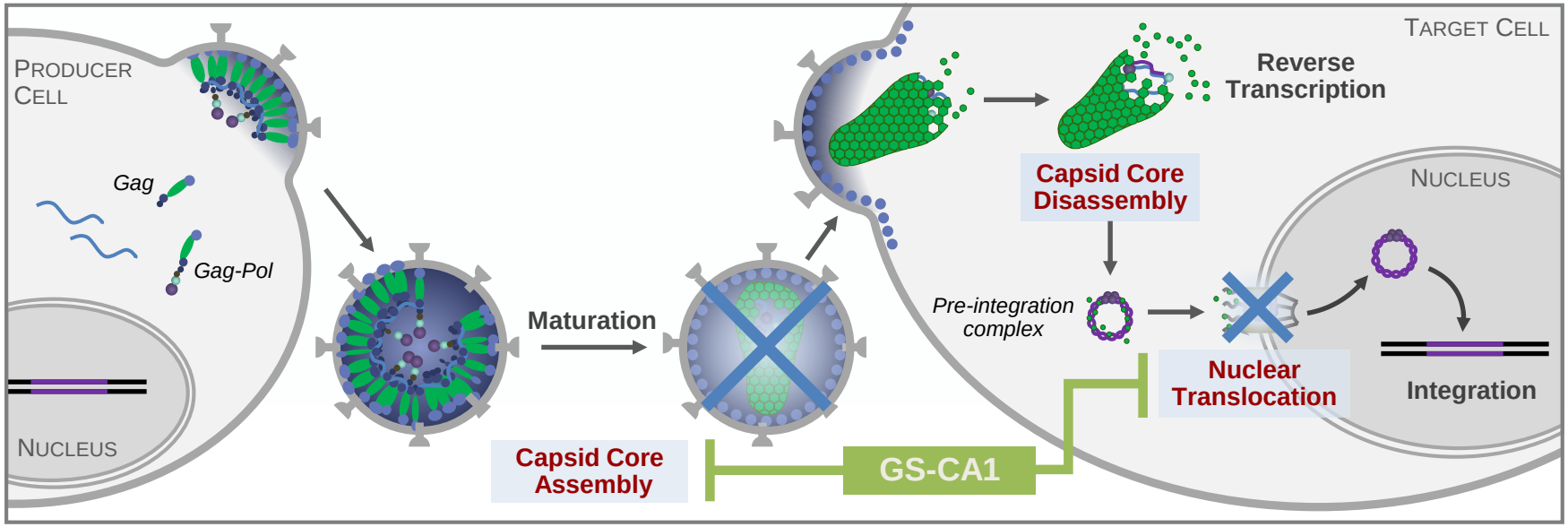
HIV Maturation Inhibitors (MI)



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

Morales-Ramirez IAS 2017 #MOAB0103

HIV Capsid Inhibitor

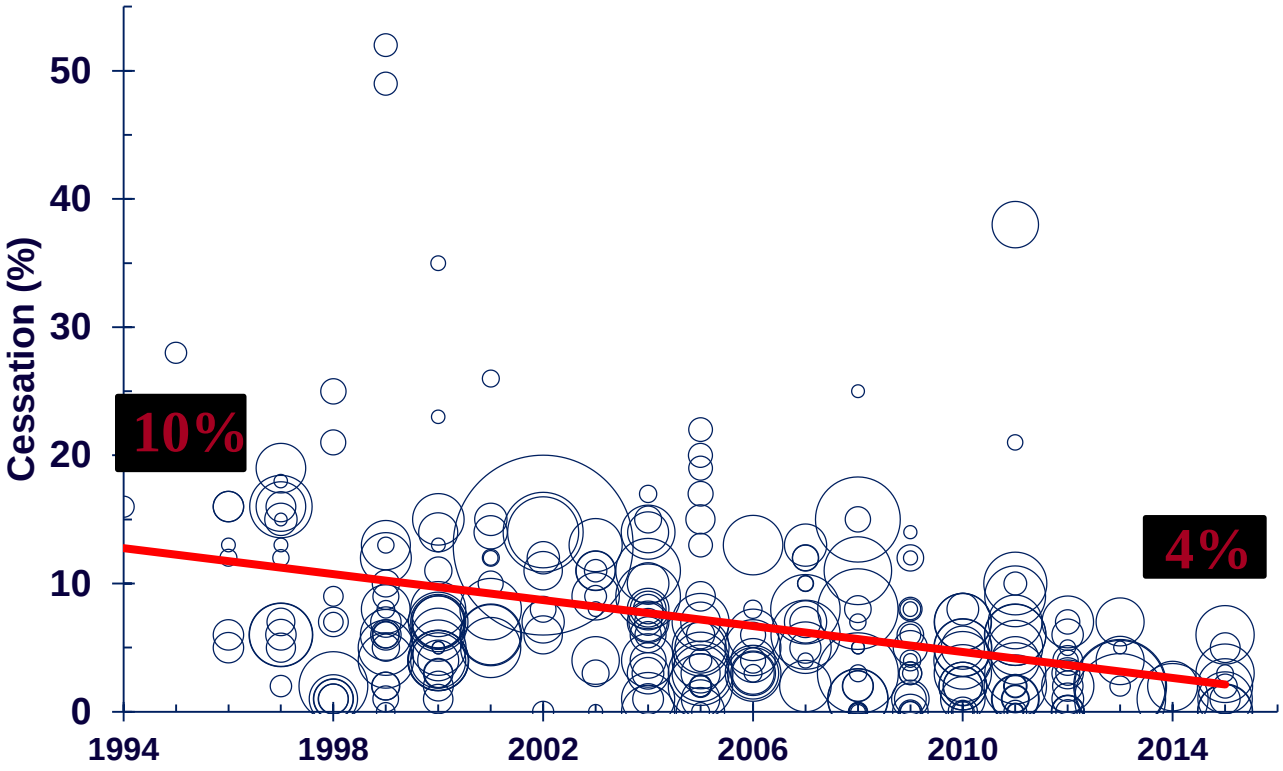


Tse CROI 2017 #38

Safety and Tolerability

ART Trials: Discontinuations for Toxicity

354 studies, through 2017: ITT analyses
N=77,999



Carr PLoS One 2014;9:e97482

Discontinuations for Adverse Events

Study (reference)	Study arm (N)	Regimen	% d/c for adverse events at 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 (EFV 400 mg vs. 600 mg)

double-blind randomized, noninferiority study of initial rx
Puls Lancet 2014;383:1474

  - WRHI 052 Venter IAS 2018 #TUAB0107LB
    - on LPV/r >6 months, VL <50, no hx of other PI use (N=300)
    - Randomized to:
      - continue LPV/r (n=152) or switch to DRV/r 400/100 qd (n=148)
      - Non-inferiority margin Δ -4%
    - 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 for switch and 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;20:1-7; 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
      - 1 had VL 99→246→61 with no RT mutations, then resuppressed
      - 1 had adverse event (suicide) between weeks 24 and 36
- ACTG 5353 Taiwo IAS 2017 #MOAB0107LB
  - 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

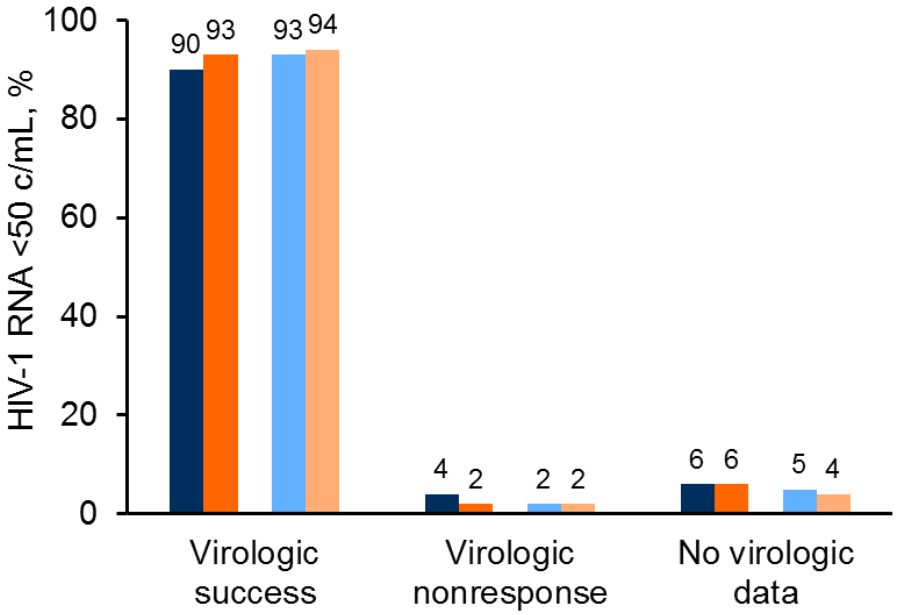
2-Drug ART: DTG + 3TC vs. DTG + TDF/FTC

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

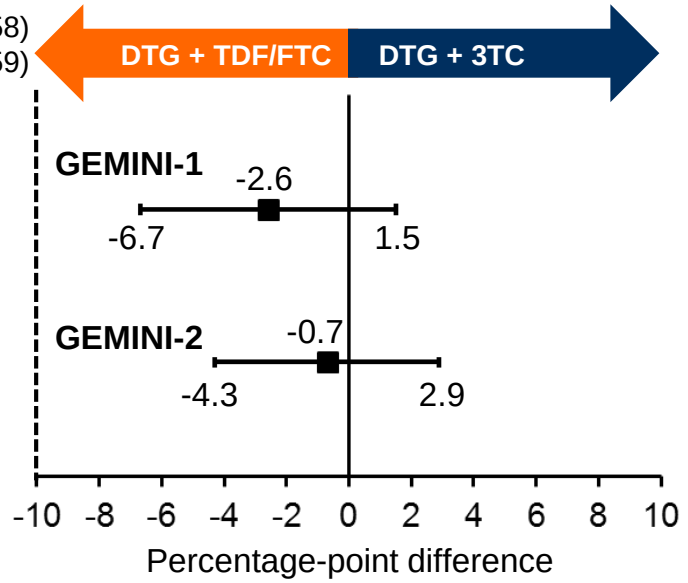
Study population: Rx-naïve, no baseline drug resistance, VL 1000-500K (N=1433)

48 week virologic outcome

GEMINI-1 DTG + 3TC (N=356) DTG + TDF/FTC (N=358)
GEMINI-2 DTG + 3TC (N=360) DTG + TDF/FTC (N=359)



Adjusted treatment difference (95% CI)[a]



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

Cahn AIDS 2018 #TUAB0106LB

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

Convenience

ART: Convenience

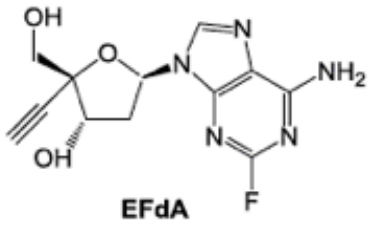
Newer Approaches

- Less frequent
  - RAL daily formulation Cahn Lancet HIV 2017;4:e486
  - Albuvirtide weekly fusion inh Zhang AIDS Res Ther 2016;13:8
- New 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

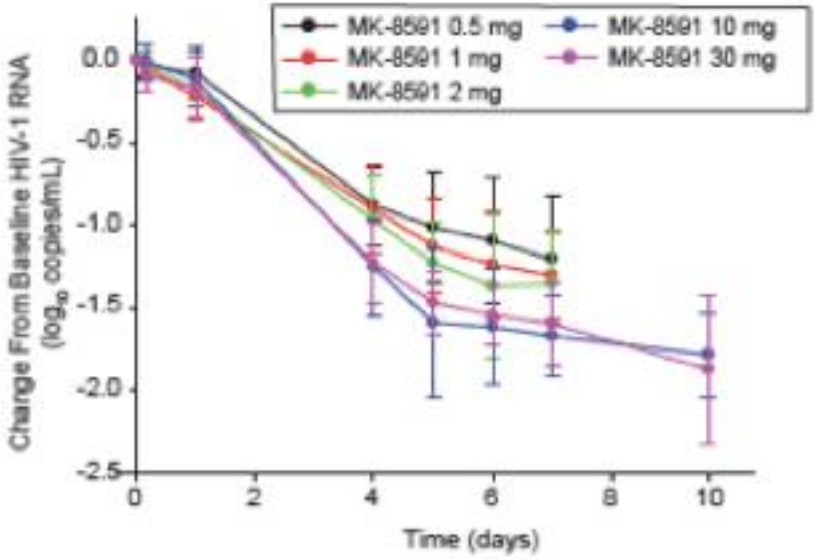
LATTE-2: IM CAB + IM RPV [ViiV/GSK]

- 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) [Merck]

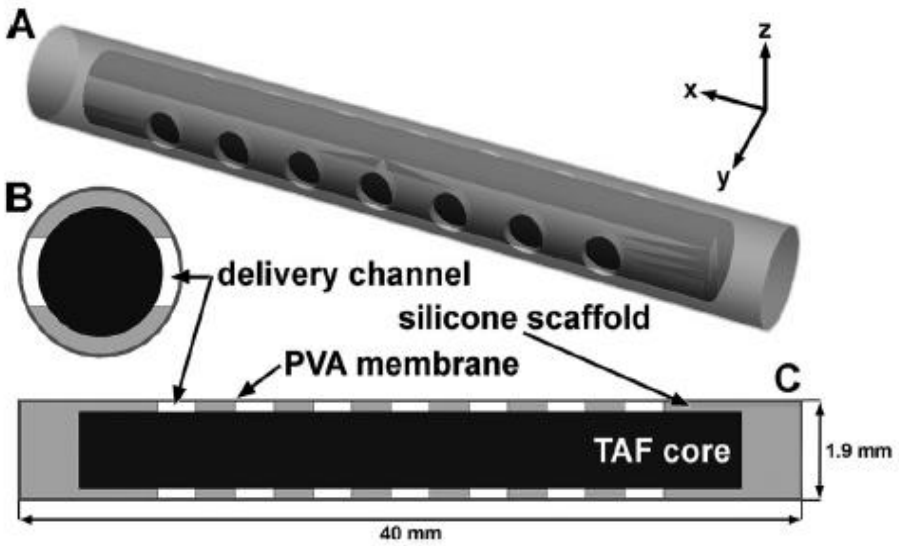


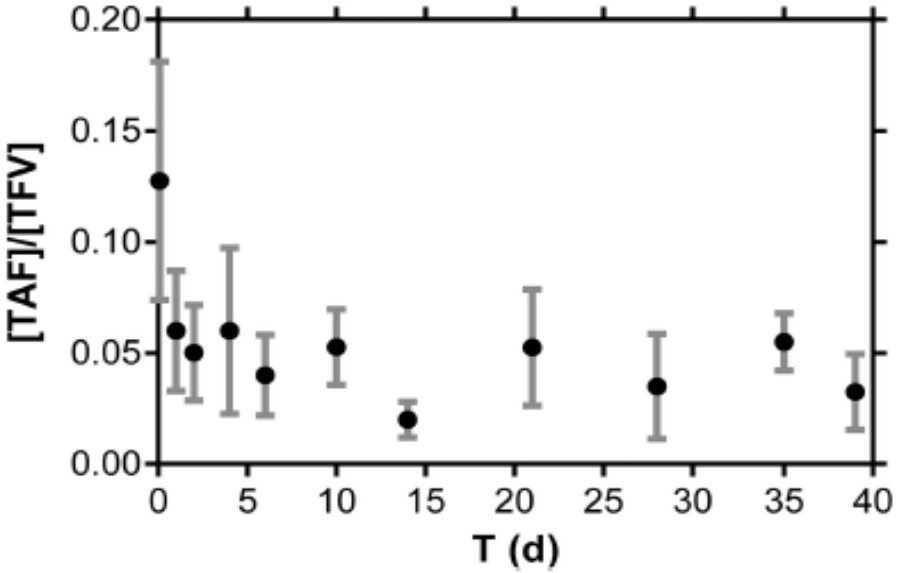
- 4’-ethynyl-2-fluoro-2’-deoxyadenosine; EFdA
- Non-obligate chain terminator
- Inhibits RT by preventing translocation (NRTTI)
- ½ life 150-160 hours(!)
- Potent antiviral activity (PBMC EC50 = 0.2 nM) with broad coverage (HIV-1, HIV-2, MDR strains)
- Accumulates in LN, vagina, rectum (animals) Grobler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



Matthews IAS 2017 #TUPDB0202LB

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





Gunawardana, *AAC* 2015;59:3913

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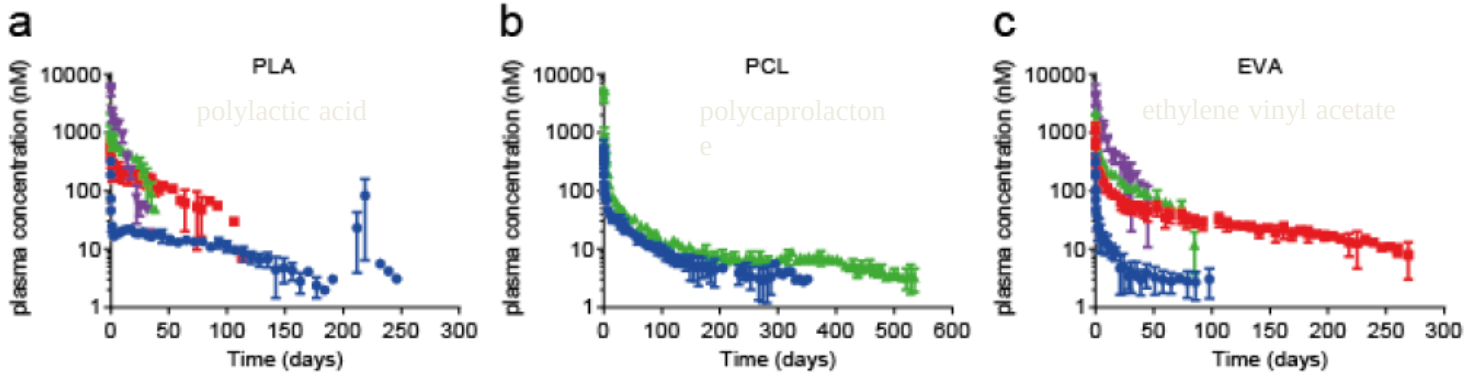
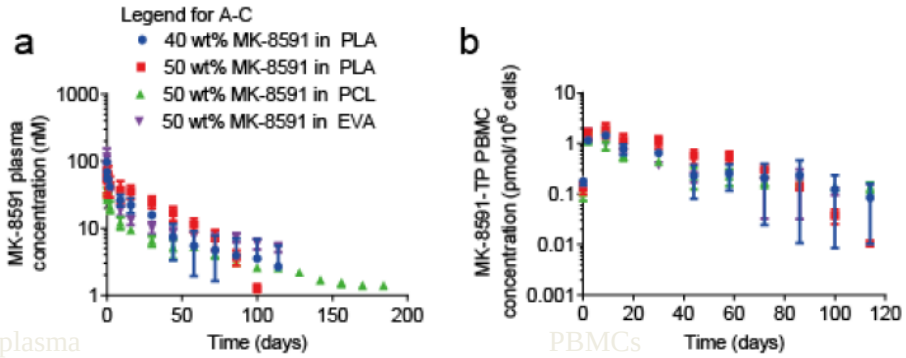
Long-Acting Subdermal Implants: MK-8591 in Animal Studies

Drug-eluting implants, both bioerodible and non-erodible

rats



NHP



Barrett AAC 2018 (epub)

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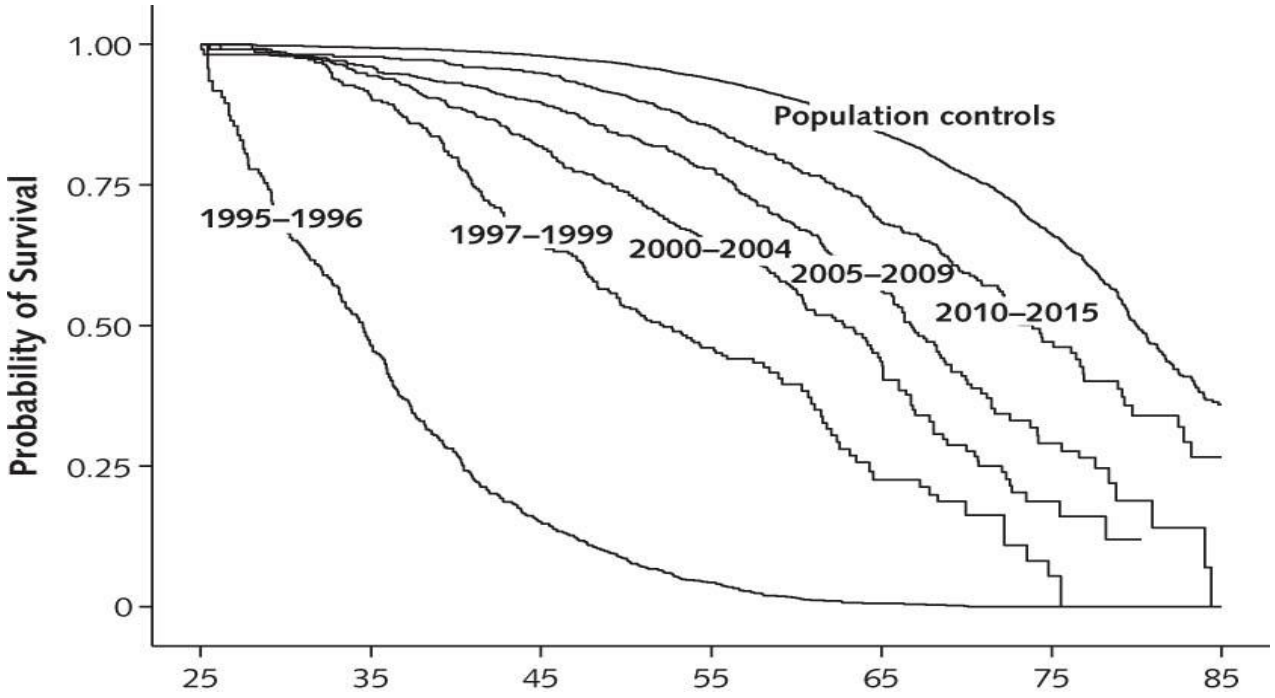
Life Expectancy

LIFE EXPECTANCY: DANISH HIV COHORT SURVIVAL FROM AGE 25 -- UPDATE



Lohse N. *Ann Int Med* 2007;146:87-95
Lohse N. *Ann Int Med* 2016;165:749-750

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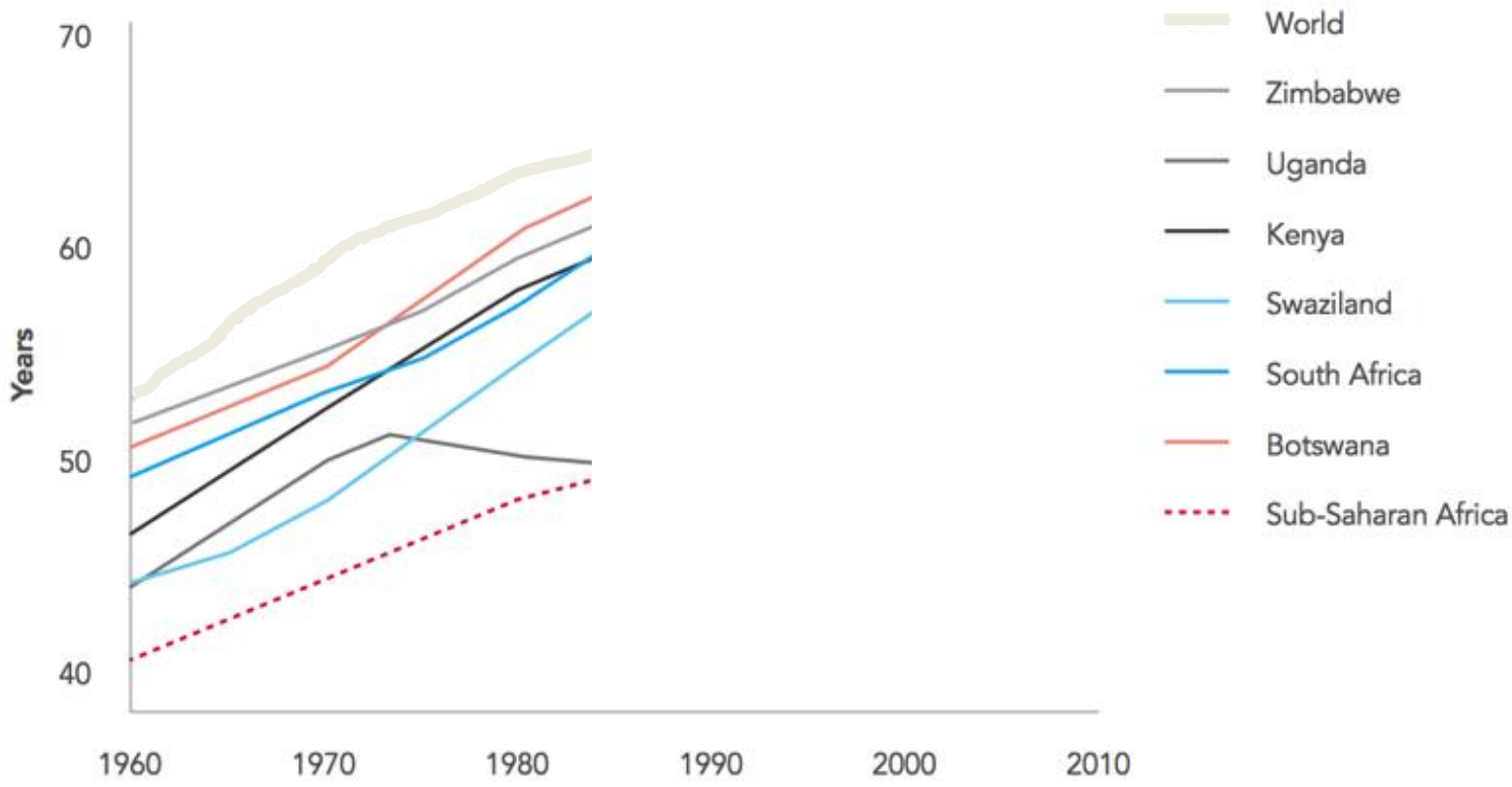
Updated: Life Expectancy



Source: World Bank life expectancy data

Future of ART: What do we need?

- Antiretroviral Therapy
  - Activity
  - Safety/tolerability
  - Convenience
  - Affordability
  - Life Expectancy