Treatment Issues: Maintenance

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Disclosures

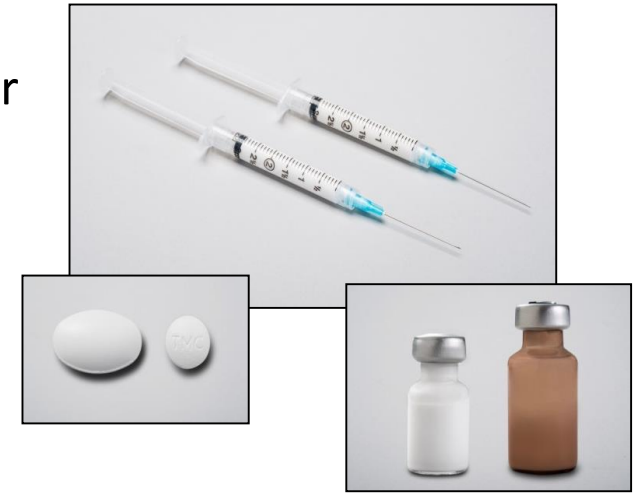
- Tristan Barber has received speaker fees, advisory board honoraria and conference support in the last twelve months from Gilead, Janssen, MSD, Roche and ViiV

Topics

- Dual Therapy: Mouth or Muscle
- Nukes: Love Me, or Leave Me
- New Strategies, New Rules

Dual Therapy: Mouth or Muscle

Background



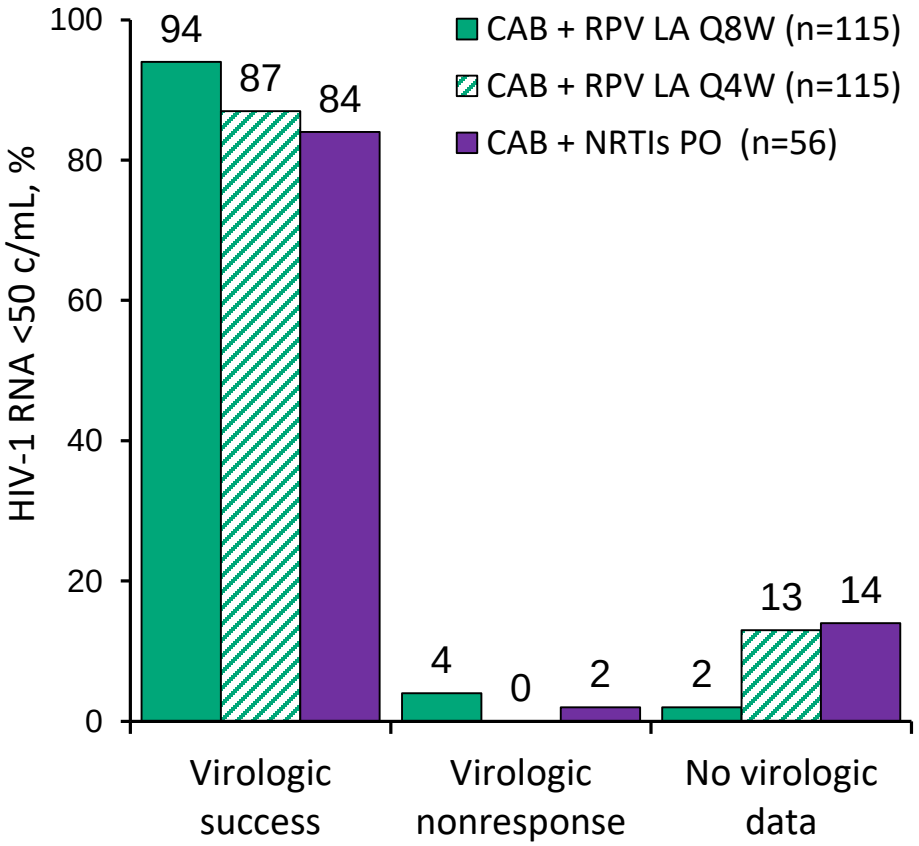
- Cabotegravir (CAB) is an HIV-1 integrase inhibitor
  - Oral 30 mg tablet ($t_{½}$, ~40 hours)
  - IM LA injection 200 mg/mL ($t_{½}$, ~20-40 days)
- Rilpivirine (RPV) is an HIV-1 NNRTI
  - Oral 25 mg tablet ($t_{½}$, ~50 hours)
  - IM LA injection 300 mg/mL ($t_{½}$, ~30-90 days)
- Oral 2-drug CAB + RPV proof of efficacy established through Week 144 in LATTE1
- LATTE-2 Week 48 data supported the decision to evaluate the Q4W CAB LA + RPV LA IM regimen in phase III studies (ongoing)
- Q8W dosing remains under long-term evaluation within LATTE-2

CAB, cabotegravir; IM, intramuscular; LA, long acting; NNRTI, non-nucleoside reverse transcriptase inhibitor; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine; $t_{½}$, half-life.

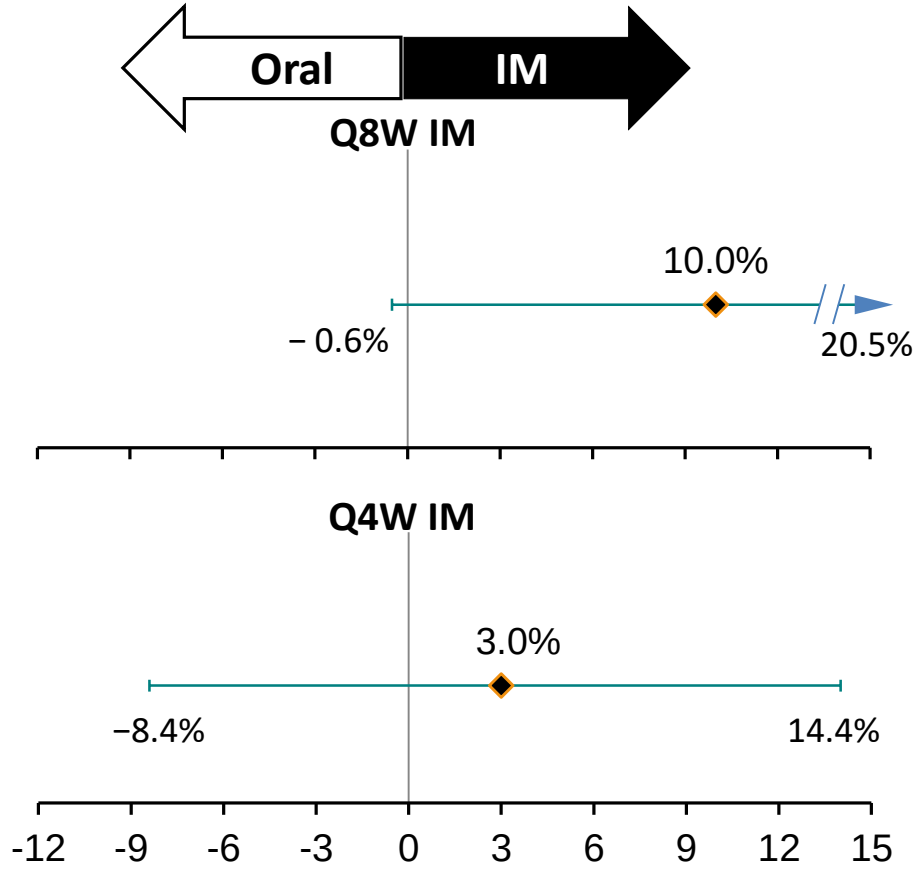
Margolis DA *et al., Lancet Infect Dis.* 2015 Oct;15(10):1145-1155 (CROI 2017)
Eron *et al.*, IAS 2017; Paris, France. Slides MOAX0205LB

Comparable Response Across Arms

Virologic outcomes



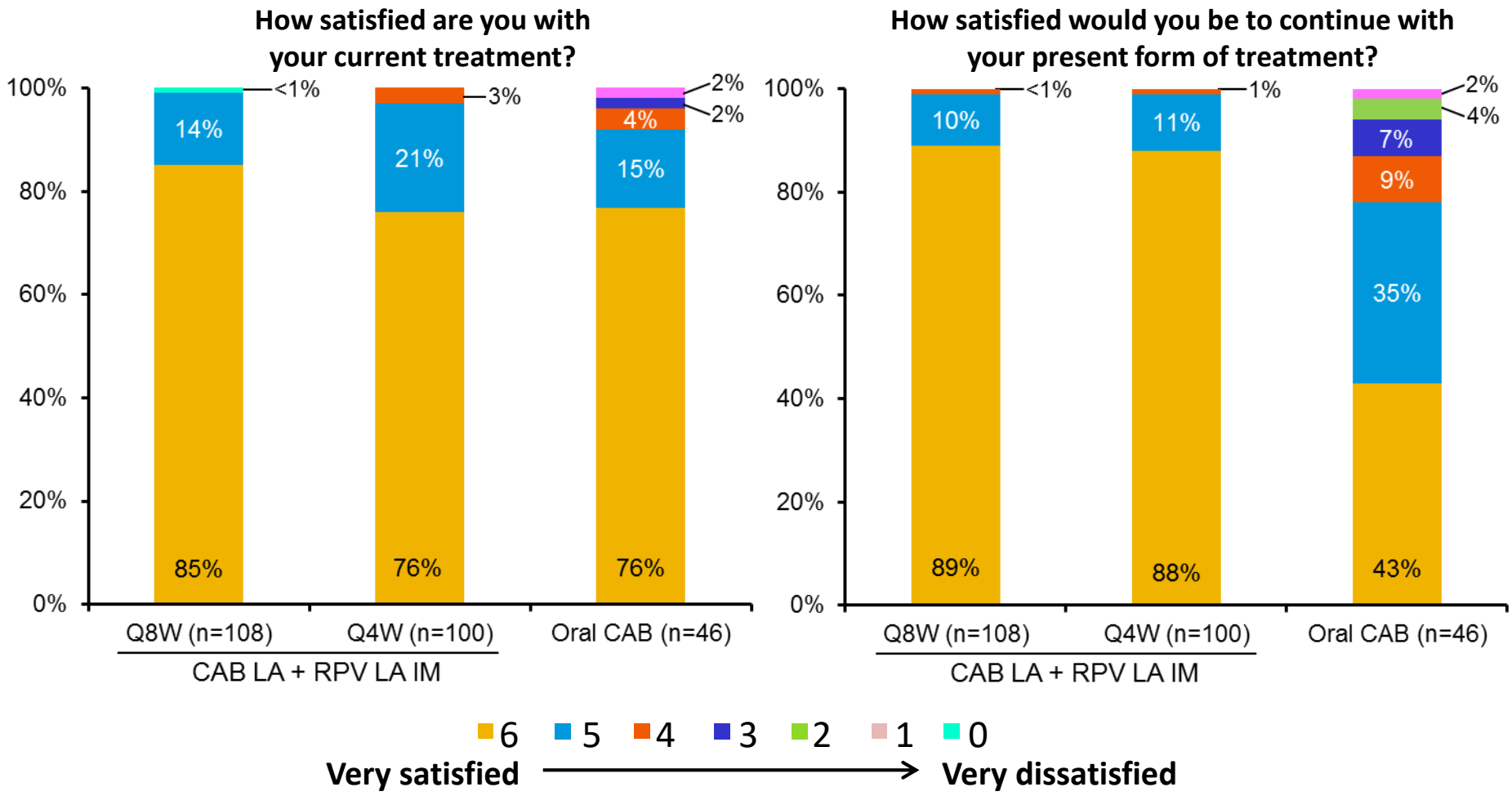
Treatment differences (95% CI)



Week 96 HIV-1 RNA <50 c/mL by Snapshot (ITT-ME)

Eron *et al.*, IAS 2017; Paris, France. Slides MOAX0205LB

Patient-Reported Outcomes at Week 96 Maintenance Treatment[a]



[a]Based on observed case data set of subjects who completed HIV Treatment Satisfaction Questionnaire status version at Week 96

Conclusions - LATTE-2 96-Week Results

- IM CAB LA + RPV LA, dosed every 4 or 8 weeks, successfully maintained HIV-1 viral load <50 c/mL
- 2 participants on LA dosing met PDVF criteria, no participants after Week 48
- Injection tolerability
  - Majority of ISRs were grade 1 to 2 pain, with a median duration of 3 days
  - <1% of participants had an ISR that led to discontinuation
  - High overall patient-reported satisfaction
- Dose selection
  - Q4W dosing selected and under evaluation in 2 pivotal phase III studies
  - Week 96 data demonstrate long-term durability of both Q4W and Q8W dosing options
  - Q8W dosing to be evaluated in upcoming phase III study

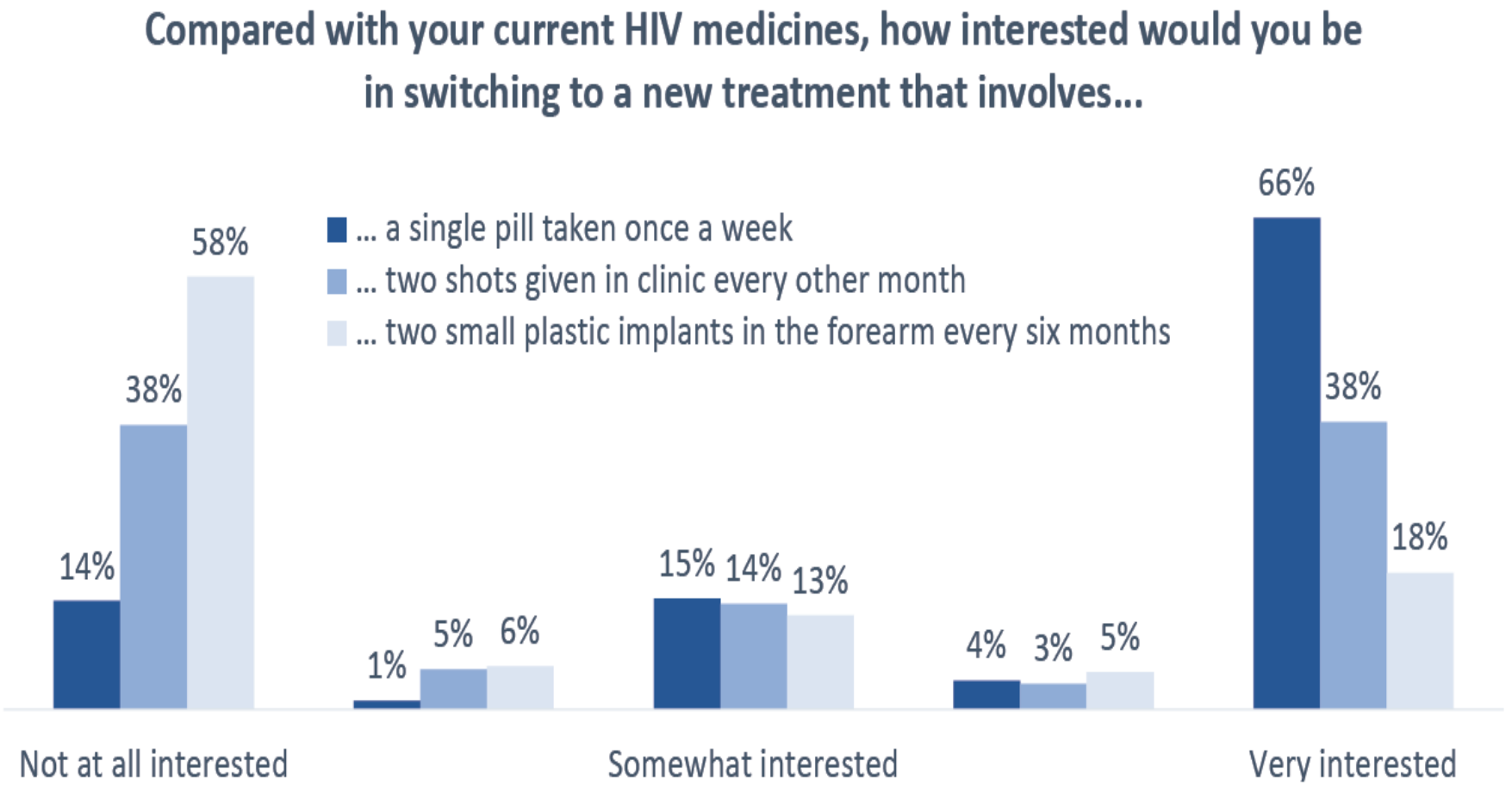
Eron *et al.*, IAS 2017; Paris, France. Slides MOAX0205LB

What do patients think?

- 2017, ID clinics at U. Duke and South Carolina
- 263 treatment experienced patients
- Surveyed about HIV treatment experiences and attitudes

- Asked about characteristics of their current regimen….
- …and interest, on 5-point scales (1=not at all interested; 5=very interested), in switching to either:
  - a single pill once a week
  - two shots in clinic every other month
  - or implanting and removing two small plastic rods about the size of matchsticks in each forearm every six months

WHO WANTS TO SWITCH? GAUGING INTEREST IN POTENTIAL NEW ANTIRETROVIRAL THERAPIES
Ostermann *et al.*, CROI 2018 P503



WHO WANTS TO SWITCH? GAUGING INTEREST IN POTENTIAL NEW ANTIRETROVIRAL THERAPIES

Ostermann *et al.*, CROI 2018 P503

- Survey participants were highly experienced (mean 14.3 years on therapy), predominantly BAME (80.5%), with a mean age of 46.7 years, and 41.4% had received more than high-school education
- In multivariate analysis, clinic, gender, race/ethnicity, time on treatment, taking more than 1 pill a day, and administration restrictions, were not associated with interest in switching to novel regimens
- Higher education was associated with greater interest in switching to injection and implants ($p<.01$)
- Younger age was associated with greater interest in switching to injection ($p=.02$)
- Understanding drivers of preference heterogeneity for new treatment modalities may help to inform their development and predict uptake

Nukes: Love Me, or Leave Me

Question

- Which ART class has shown the worst outcomes when used as part of dual therapy?

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A. NRTI
B. NNRTI
C. PI
D. CCR5
E. INI

Question

- Which ART class has shown the worst outcomes when used as part of dual therapy?

A. NRTI
B. **NNRTI**
C. PI
D. **CCR5**
E. INI

NRTI – Love Me, or Leave Me

- Are two-drug regimens including an NRTI the same as those without?

Naive

Study	Drugs	No. pts	Undetectable viral load at week 48 (%)	Comments
ACTG-5142	LPV/r+EFV	250	83	More drug resistance in the dual arm
PROGRESS	LPV/r+RAL	101	83.2	Non-inferior
CCTG-589	LPV/r+RAL	26	83.2	More rapid viral suppression in the dual arm
SPARTAN	TAZ/r+RAL	63	75 (week 24)	High rate of hyperbilirubinemia
RADAR	DRV/r+RAL	40	62.5	Lower efficacy
NEAT	DRV/r+RAL	398	88.2	Lower response with high viral load +/- low CD4 counts. More resistance in the dual than triple arm
Pfizer-1078	MVC+TAZ/r	60	73.3	Lower efficacy
VEMAN	MVC+LPV/r	25	100	Greater CD4 gain
Pulido	MVC+TAZ/r	32	87.5	
MODERN	MVC+DRV/r	396	77.3	Lower efficacy

Soriano V *et al. Expert Opin Drug Saf.* 2017 Aug;16(8):923-932

Naive

Study	Drugs	No. pts	Undetectable viral load at week 48 (%)	Comments
KALEAD	LPV/r+TDF	72	52.8	Lower efficacy
GARDEL	LPV/r+3TC	214	88.3	Non-inferior to triple therapy
PADDLE	DTG+3TC	20	90	

Soriano V *et al. Expert Opin Drug Saf.* 2017 Aug;16(8):923-932

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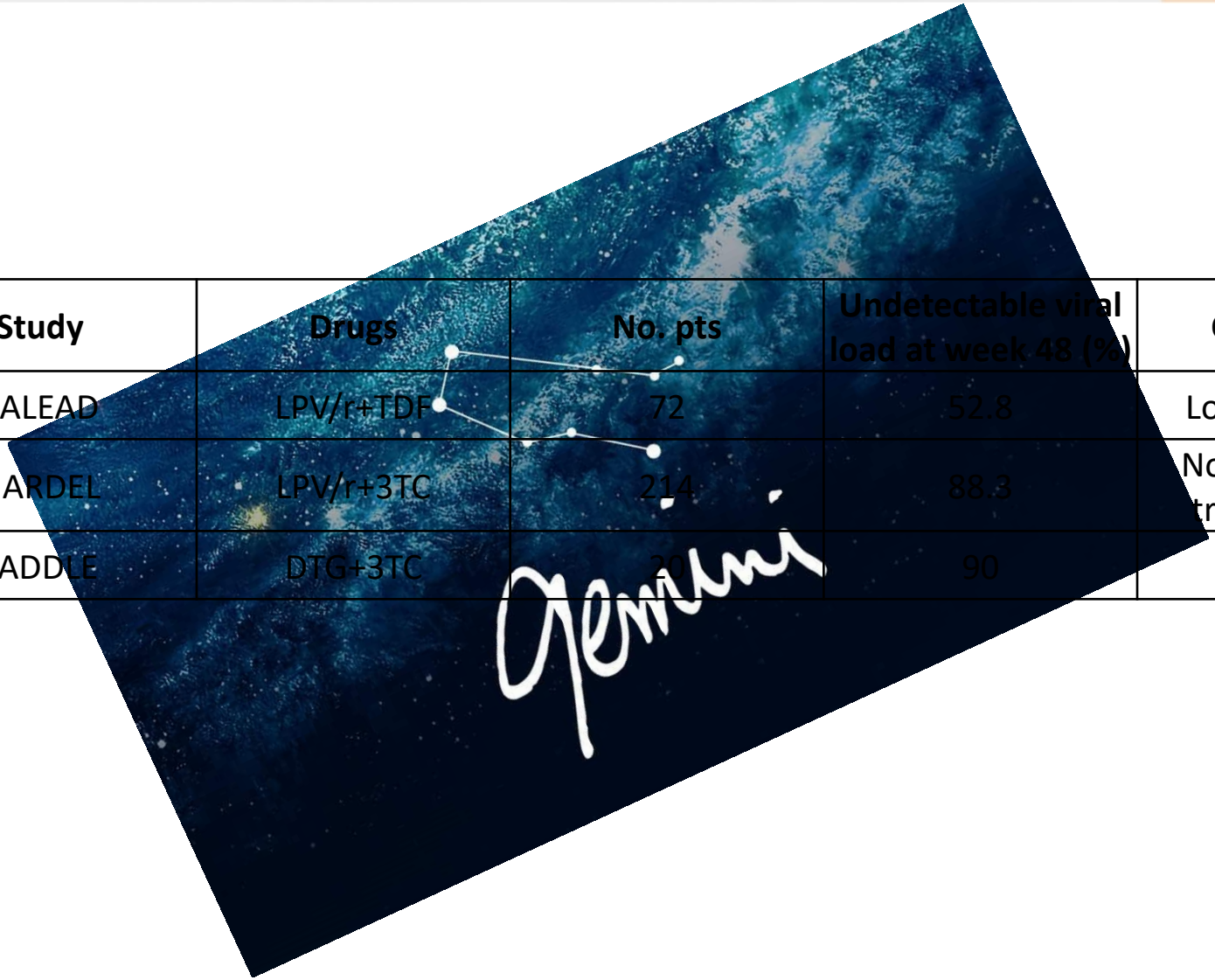


Soriano V *et al. Expert Opin Drug Saf.* 2017 Aug;16(8):923-932

Maintenance

Study	Drugs	Number of Patients	Undetectable viral load at week 48 (%)	Comments
COOL	TDF+EFV	71	81.7	Lower efficacy
KITE	LPV/r+RAL	39	94.9	Non-inferior
SPARE	DRV/r+RAL	28	85.7	Non-inferior
DatAIDS	TAZ+RAL	185	65.4	Lower efficacy
Marinaro *et al.*	TAZ+RAL	102	81.4	Lower efficacy
HARNESS	TAZ/r+RAL	72	69.4	Lower efficacy
PROBE	DRV/r+RPV	30	96.7	Non-inferior
MARCH	MVC+PI/r	157	84.1	Lower efficacy
GUSTA	MVC+DRV/r	62	72.6	Lower efficacy
Calza *et al.*	RAL+ETV	38	81.6	Improved kidney, bone, and lipid parameters
LATTE	CAB+RPV	160	76	
TivEdo	DTG+RPV	50	90	
SWORD 1 & 2	DTG+RPV	513	95	Non-inferior. Improvement in bone markers

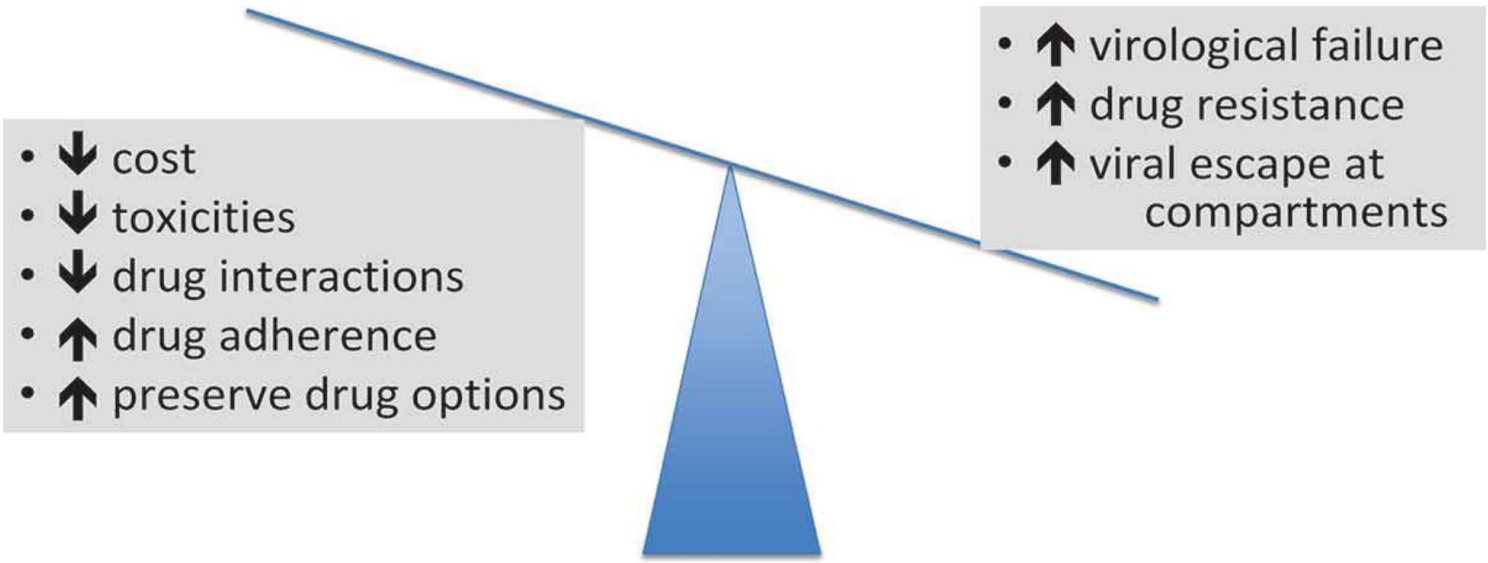
Soriano V *et al. Expert Opin Drug Saf.* 2017 Aug;16(8):923-932

Study	Drugs	Number of Patients	Undetectable viral load at week 48 (%)	Comments
ATLAS-M	TAZ+3TC	133	89.5	Non-inferior
SALT	TAZ+3TC	140	78.6	Non-inferior
OLE	LPV/r+3TC	118	91.5	Non-inferior
DUAL	DRV/r+3TC	126	89%	Non-inferior
LAMIDOL	DTG+3TC	104	97	Improve in bone biomarkers

Soriano V *et al. Expert Opin Drug Saf.* 2017 Aug;16(8):923-932

Study	Dru	detectable viral d at week 48 (%)	Comments
ATLAS-M	TAZ+3	89.5	Non-inferior
SALT	TAZ+3	78.6	Non-inferior
OLE	LPV/r+	91.5	Non-inferior
DUAL	DRV/r-	89%	Non-inferior
LAMIDOL	DTG+	97	Improve in bone biomarkers

Soriano V *et al. Expert Opin Drug Saf.* 2017 Aug;16(8):923-932



Soriano V *et al. Expert Opin Drug Saf.* 2017 Aug;16(8):923-932

Conclusion

- Evidence so far better for maintenance

- DTG + RPV seems good
- DTG + 3TC more data awaited

- MVC based 2DR less effective
- BPI + RAL or 3TC effective but limited by DDI and metabolic sfx

Soriano V *et al. Expert Opin Drug Saf.* 2017 Aug;16(8):923-932

New Strategies, New Rules

New Strategies, New Rules

- Inflammation and blipping
  - Do the rules of triple therapy easily translate to newer strategies?

Viral Escape

- One of the risks of exposure to suboptimal antiretroviral therapy is viral escape

- In a recent study, deep-sequencing of HIV-DNA performed in blood and inguinal lymph nodes from three HIV-positive individuals at different time points during the first 6 months of antiretroviral therapy; evolution of viral sequences was demonstrated

- Persistent HIV-1 replication maintains the tissue reservoir during therapy

Lorenzo-Redondo R *et al., Nature.* 2016 Feb 4;530(7588):51-56

Viral Escape

- Ongoing HIV replication even without selection of drug-resistance mutations may occur in HIV patients under successful ART

- The presence of HIV in sanctuary sites where drug pressure is not enough to completely block virus replication accounts for this phenomenon

Lorenzo-Redondo R *et al., Nature.* 2016 Feb 4;530(7588):51-56

Viral Escape

- The persistence of HIV replication in sanctuary sites despite undetectable viremia in plasma largely explains persistent systemic inflammation and immune activation
  - may account for increased risk of cardiovascular disease and lymphoma seen in PLWH suppressed in plasma

- These phenomena could be more pronounced using dual therapies
  - important to examine longitudinally parameters other than plasma HIV-RNA, including biomarkers of specific organ damage (i.e. cardiovascular, kidney, brain, etc.)

Martinez-Picado J *et al., Curr Opin HIV AIDS.* 2016 Jul;11(4):417-23
Totonchy J *et al., Curr Opin Virol.* 2016 Oct;20:71-77

Viral Escape

- Triple drug therapies are the best way to maximize the chances of adequate tissue penetrance and distribution of antiretroviral drugs to fully suppress HIV replication

- A longer follow-up of patients switched to dual therapies is warranted to ensure that viral escape and selection of drug resistance are ultimately not promoted

Summary

Summary

- Injectable, implants, and longer acting agents may be good for some, but not for all

- 2DR may be good for maintenance but the evidence for naïve (induction) remains to be seen
  - DTG + RPV
  - BPI + NRTI
  - (DTG + 3TC)

- The rules that applied to 3DR regarding inflammation, chronic comorbidities, and viral blipping may not translate easily to 2DR
  - further research needed

Thank You!

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Treatment options in ART-naive PLWH

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Disclosures

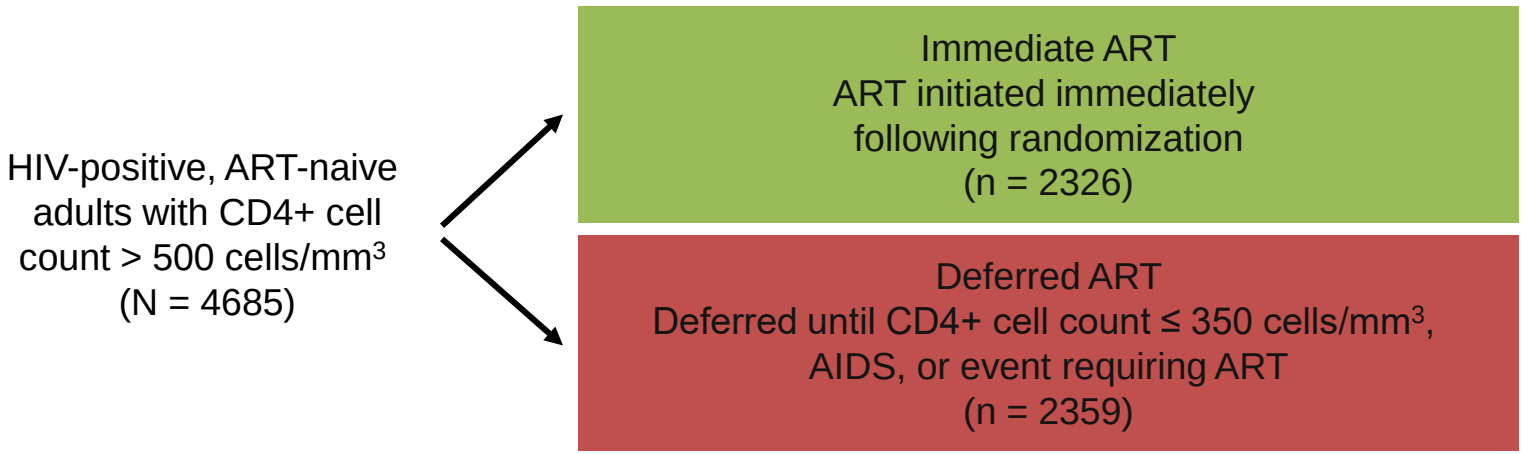
- **Christoph D. Spinner** received honoraria for lectures and/or consultancies from Abbott, AbbVie, Astellas, BMS, Gilead, Janssen, MSD, Pfizer, ViiV.

- Research grants from DZIF, Gilead, Janssen, ViiV.

START: When to start ART in naive PLWH?

- International, randomized trial

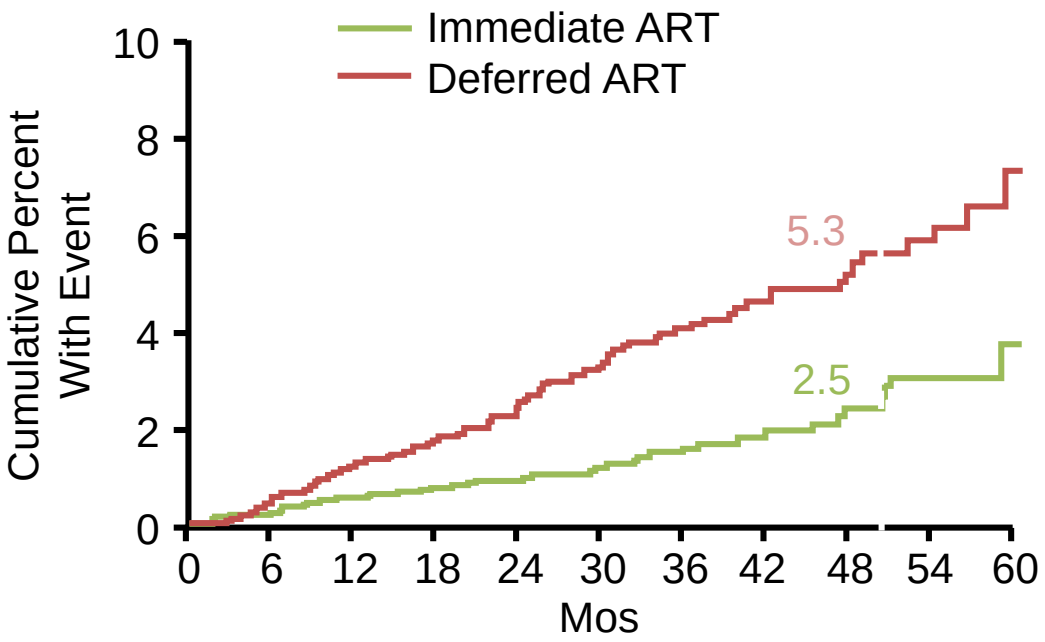
Study closed by DSMB following interim analysis



- Primary composite endpoint (target = 213)
  - Serious AIDS or death from AIDS
  - Serious non-AIDS events and death not attributable to AIDS
    - CVD, ESRD, decompensated liver disease, non-AIDS–defining cancers

INSIGHT START Study Group *et al., N Engl J Med.* 2015 Aug 27;373(9):795-807
Lundgren J, *et al.,* IAS 2015. Abstract MOSY0302.

START: Reduced mortality and morbidity with immediate ART-initiation



- 57% reduced risk of serious events or death with immediate ART
- 68% of primary endpoints occurred in pts with CD4+ cell counts > 500 cells/mm^3
- 72% reduced risk of serious AIDS events with immediate ART
- Reduced risk of cancers with immediate ART

Primary Endpoint	Immediate ART	Deferred ART
No. with event (%)	42 (1.8)	96 (4.1)
Rate/100 PY	0.60	1.38
HR (immediate/deferred)	0.43 (95% CI: 0.30-0.62; *P* < .001)	

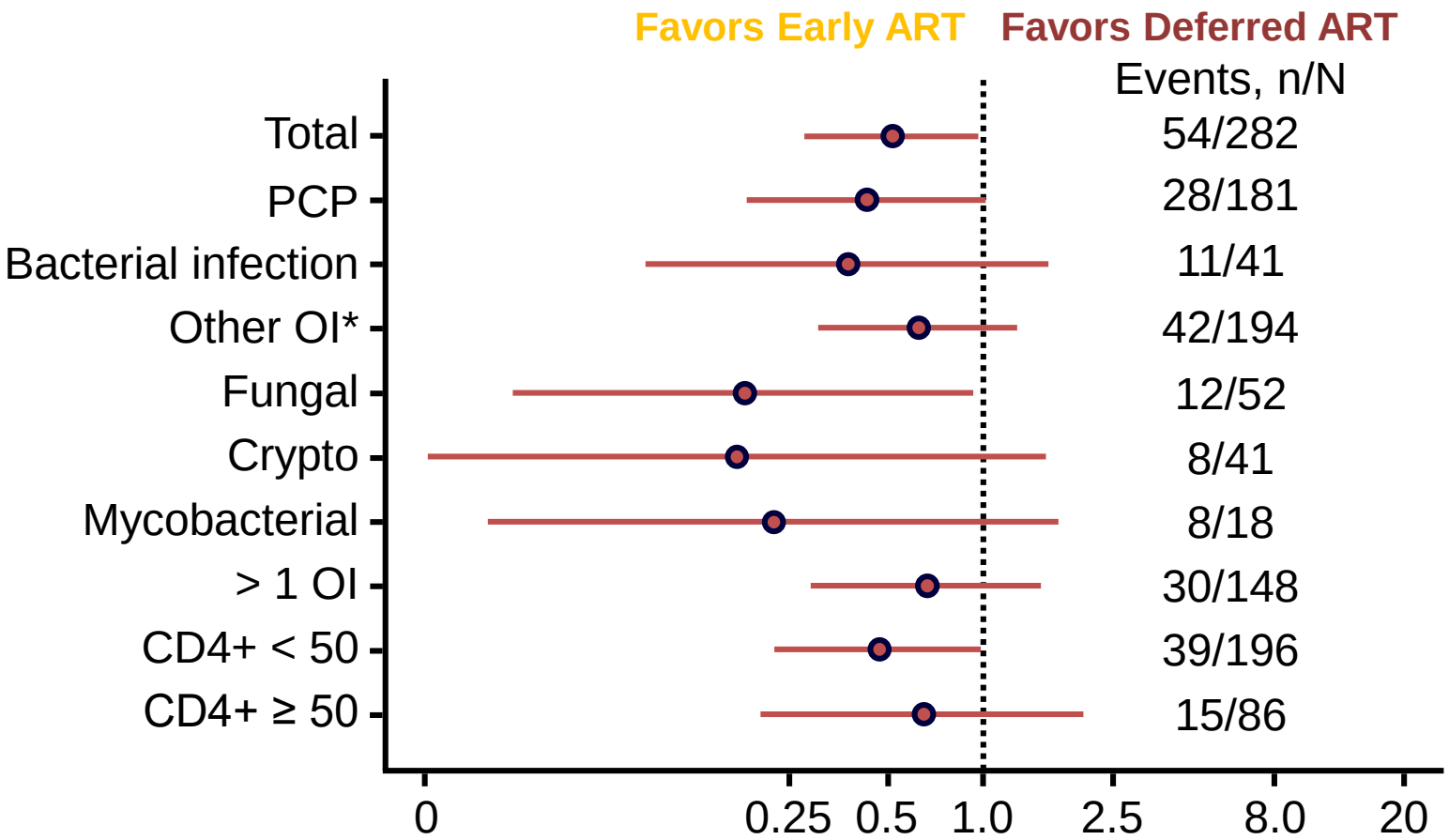
INSIGHT START Study Group *et al., N Engl J Med.* 2015 Aug 27;373(9):795-807
Lundgren J, *et al.,* IAS 2015. Abstract MOSY0302.

ART recommendation in early HIV infection

- ART recommended for early HIV infection[1,2] and should be offered on day of diagnosis where feasible[3]
  - DHHS, IAS-USA, and WHO guidance recommend ART for all HIV-infected pts worldwide, regardless of CD4+ cell count
- ART recommended for pregnant women with early HIV infection[1]
  - To prevent perinatal transmission
- ART can start before drug resistance test results are available[1]
  - (DRV/RTV or DRV/COBI or DTG) + (TAF/FTC or TDF/FTC) recommended to prevent resistance in this setting

1. DHHS Guidelines. October 2017.
2. Günthard HF, *et al. JAMA.* 2016 Jul 12;316(2):191-210.
3. WHO. July 2017.

ACTG 5164: Immediate *vs.* Deferred ART in Pts With Acute Opportunistic Infections



*Includes 13 pts with toxoplasmosis

Zolopa AR, *et al., PLoS One.* 2009;4(5):e5575.

ART guidelines update: 1st line ART-recommendation

Class	EACS[1]	DHHS[2]	IAS-USA[3]
INSTI	▪ **DTG/ABC/3TC** ▪ DTG + (TAF or TDF)/FTC ▪ **EVG/COBI/(TAF or TDF)/FTC** ▪ RAL + (TAF or TDF)/FTC	▪ **DTG/ABC/3TC** ▪ DTG + (TAF or TDF)/FTC ▪ **EVG/COBI/(TAF or TDF)/FTC** ▪ RAL + (TAF or TDF)/FTC	▪ **DTG/ABC/3TC** ▪ DTG + TAF/FTC ▪ **EVG/COBI/TAF/FTC** ▪ RAL + TAF/FTC
PI	▪ **DRV/COBI/TAF/FTC** DRV/r + (TAF or TDF)/FTC		
NNRTI	▪ **RPV/(TAF or TDF)/FTC**		

- Recommendations may differ based on baseline HIV-1 RNA, CD4+ cell count, CrCl, eGFR, HLA-B*5701 status, HBsAg status, and osteoporosis status
- With FDA approval of 1200-mg RAL,[4] all options now available QD (except in pregnancy)
  - Guidelines released in 2016, before approval of QD 1200-mg RAL
  - QD 1200 mg RAL has DDIs with calcium carbonate antacids, rifampin[3]

1. EACS Guidelines. October 2017 V9. 2. DHHS Guidelines. October 2017.
3. Günthard HF, *et al., JAMA.* 2016 Jul 12;316(2):191-210. 4. Raltegravir [package insert].

INSTI Studies of 1st line ART

Trial	INSTI Regimen	Comparator	Weeks	Outcome *vs.* Comparator
SINGLE[1]	**DTG** + ABC/3TC	EFV/TDF/FTC	144	Favors INSTI
FLAMINGO[2]	**DTG** + 2 NRTIs	DRV + RTV + 2 NRTIs	96	Favors INSTI
SPRING-2[3,4]	**DTG** + 2 NRTIs	RAL + 2 NRTIs	96	Noninferior
ARIA[5,6]	**DTG**/ABC/3TC	ATV + RTV + FTC/TDF	48	Favors INSTI*
WAVES[7]	**EVG**/COBI/FTC/TDF	ATV + RTV + FTC/TDF	48	Favors INSTI*
Study 103[8]	**EVG**/COBI/FTC/TDF	ATV + RTV + FTC/TDF	144	Noninferior*
Studies 104/111[9,10]	**EVG**/COBI/FTC/**TAF**	EVG/COBI/FTC/TDF	144	Favors INSTI with TAF
ACTG 5257[11]	**RAL** + FTC/TDF	ATV + RTV + FTC/TDF DRV + RTV + FTC/TDF	96	Favors INSTI†
STARTMRK[12]	**RAL** + FTC/TDF	EFV + FTC/TDF	240	Favors INSTI*
GS-380-1489[13]	**BIC** + FTC/TAF	ABC/3TC/DTG	48	Noninferior
GS-380-1490[14]	**BIC** + FTC/TAF	DTG + F/TAF	48	Noninferior

- No resistance selected for in any INSTI + 2 NRTI regimen in SINGLE,[1] FLAMINGO,[2] SPRING-2,[3,4] and ARIA[5,6] and WAVES[7] and BIC [13, 14].

*Fewer discontinuations for AEs. †Composite endpoint of time to virologic failure or discontinuations for AEs.

STR *vs.* MDR

Advantages	Disadvantages
▪ Simplicity ▪ Convenience ▪ Fewer copays ▪ Reduces selective nonadherence to components of regimen	▪ Inability to adjust dosages of components if needed due to drug–drug interactions or tolerability issues, e.g. renal insufficiency ▪ Not available for all ART regimens ▪ Not available for all NRTI pairings

TDF *vs.* TAF: comparable efficacy in ART studies

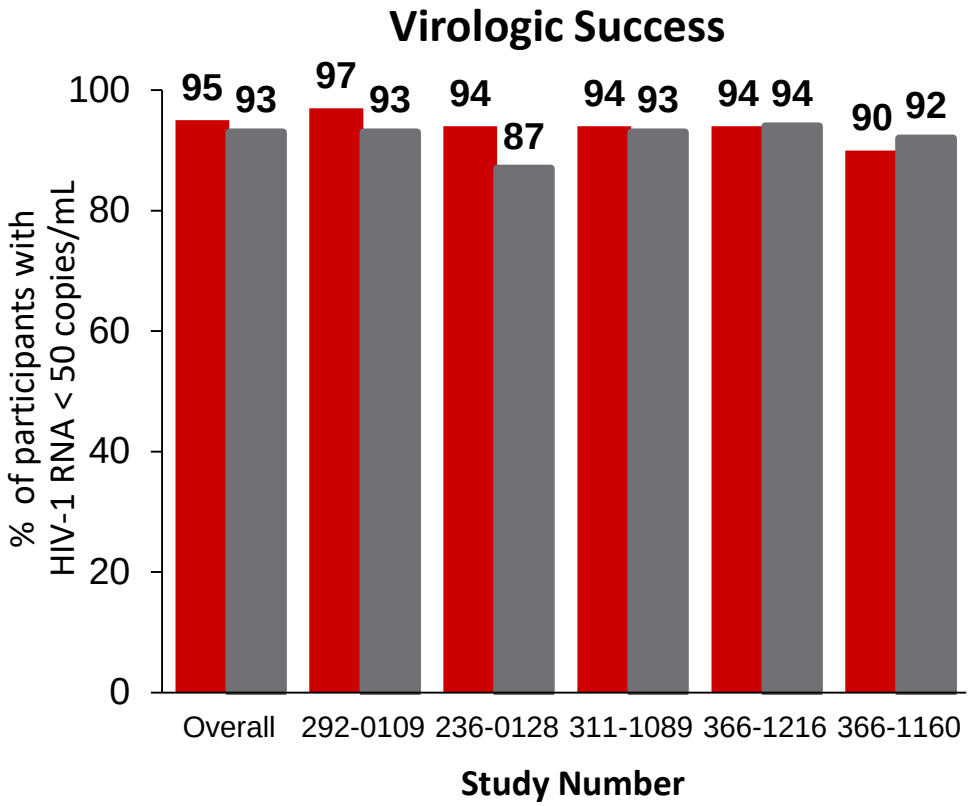
- TAF noninferior to TDF as initial therapy in GS-104/111
  - Week 48 virologic success: 92% with EVG/COBI/FTC/TAF *vs.* 90% with EVG/COBI/FTC/TDF (difference: 2%; 95% CI: -0.7% to 4.7)

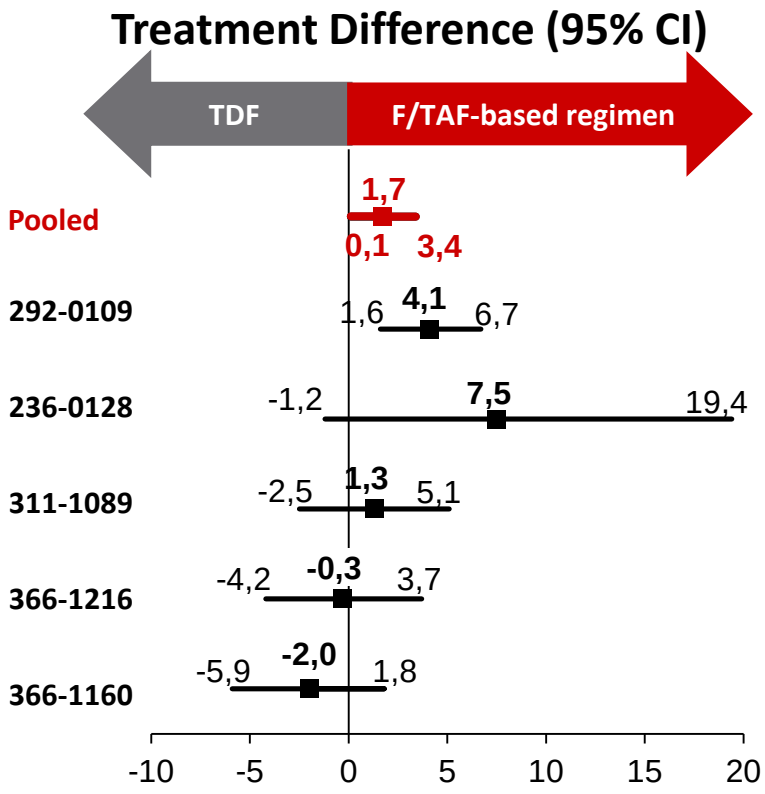
Study	Pt Population	Treatment
GS-104/111[1]	**Treatment naive** (N = 1733)	EVG/COBI/FTC/TAF *vs.* EVG/COBI/FTC/TDF
GS-109[2]	Virologically suppressed on TDF-based regimen (N = 1436)	Switch to EVG/COBI/FTC/TAF *vs.* remain on TDF-based regimen
GS-1089[3]	Virologically suppressed on FTC/TDF + third ARV (N = 663)	Switch to FTC/TAF + continue third ARV *vs.* remain on FTC/TDF + third ARV
GS-112[4]	Virologically suppressed on varied regimens; stable $eGFR_{CG}$ 30-69 mL/min (N = 242)	Switch to EVG/COBI/FTC/TAF

1. Sax PE *et al., Lancet.* 2015 Jun 27;385(9987):2606-15. 2. Mills A *et al., Lancet Infect Dis.* 2016 Jan;16(1):43-52. 3. Gallant JE *et al., Lancet HIV.* 2016 Apr;3(4):e158-65. 4. Pozniak A *et al., J Acquir Immune Defic Syndr.* 2016 Apr 15;71(5):530-7.

TAF *vs.* TDF: Pooled efficacy analysis

- Week 48 data from five studies were pooled. Outcomes were assessed by subgroups including age, sex, race, baseline eGFR, and baseline medical history.



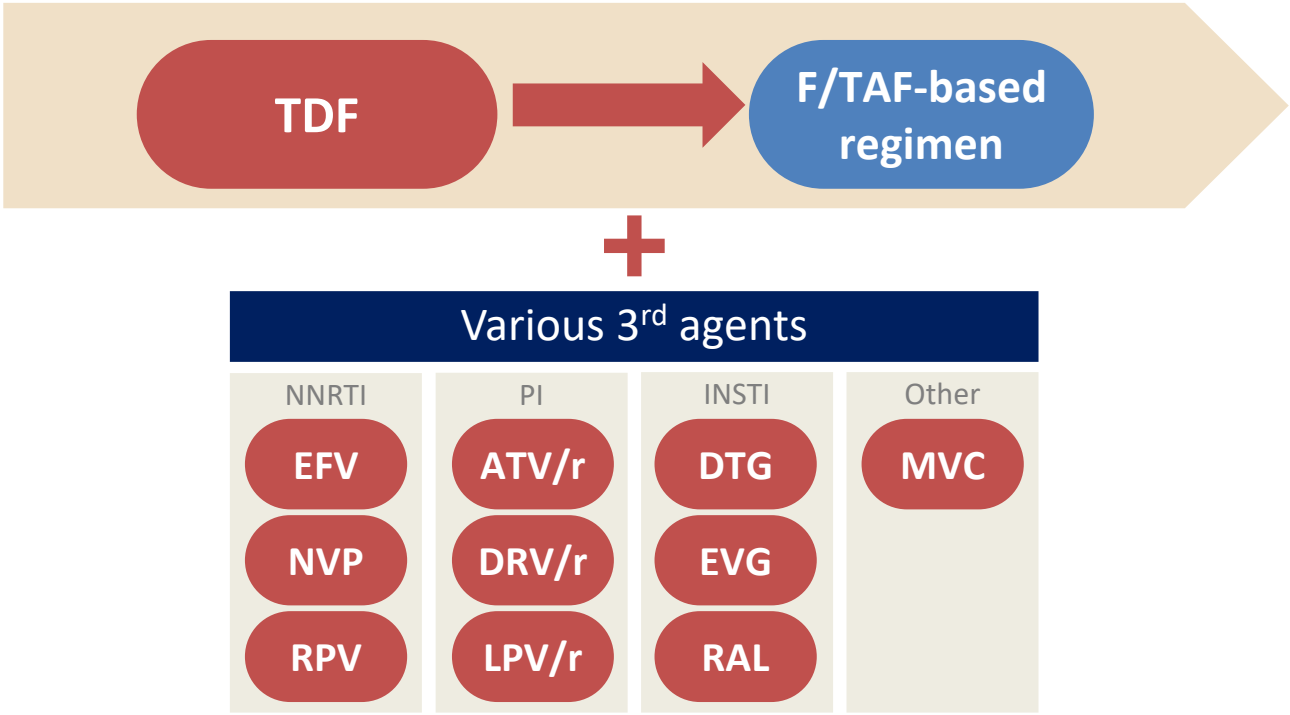


Pooled data showed high rates of virologic suppression

Overall 95% *vs.* 93%; difference of 1.7% (95% CI: 0.1, 3.4)

Rockstroh J *et al.,* IAS 2017, Paris, France. Poster #MOPEB0289

TAF *vs.* TDF: Bone and Renal Safety by 3rd agent



- Improvements in BMD and renal safety parameters were independent of 3rd agent, $p < 0.001$ for all treatment differences at week 48

For BMD, P-values were from the ANOVA model including study and treatment as fixed effects.
For renal safety parameters, P-values were from the van Eltaren test including study as a stratification factor.

Rockstroh J *et al.,* IAS 2017, Paris, France. Poster #MOPEB0289

Novel and upcoming injectable options

- Phase II/III studies of long-acting ARVs

Agent	MoA	Phase	Implications
3BNC117[1,2]	Anti-CD4 receptor mAb	II	▪ Studies ongoing in treatment-experienced and naive pts
TMC278 LA[3]	LA injectable RPV (IM)	II	▪ Potential as long-acting injectable (Q8W)
UB-421[4]	Anti-CD4 receptor mAb	II	▪ Studied as possible ART alternative for maintenance therapy in suppressed pts
VRC01[5,6]	Anti-CD4 receptor mAb	II	▪ Phase II PrEP and treatment trials ongoing
CAB[7]	INSTI	III	▪ Studies in ART-naive pts in combination with TMC278LA

Adopted from CCO.com

1. Caskey M *et al., Nature.* 2015 Jun 25;522(7557):487-91. 2. ClinicalTrials.gov. NCT03041012. 3. Bekker LG *et al.,* CROI 2017. Abstract 421LB. 4. Wang CY *et al.,* CROI 2017. Abstract 450LB. 5. ClinicalTrials.gov. NCT02716675. 6. ClinicalTrials.gov. NCT02568215. 7. Margolis DA *et al., Lancet.* 2017 Sep 23;390(10101):1499-1510.

Novel and upcoming options

- **NNRTI (Phase III)**
  - DOR/3TC/TDF: noninferior to DRV/r+FTC/TDF in ART-naive pts [1]
- **Attachment inhibitors (Phase III)**
  - TMB-301: anti-CD4-mAb in highly treatment experienced, failing pts [2]
  - Fostemsavir (gp120 binding): highly treatment experienced pts [3]
- **Others**
  - PRO140: humanized IgG4 CCR5-mABb as switch/failure strategy in CCR5-tropic pts (Phase III) [4-6]
  - Elsulfavirine: NNRTI prodrug of VM1500A for initial ART (Phase IIb) [7]
  - MK8591: NRTTI (Phase IIb) for treatment and prevention with long half-life [8-9]
  - Vaccines (Phase II/IIII): numerous options in development

Adopted from CCO.com

1. Molina JM *et al.,* CROI 2017. Abstract 45LB 2. Lewis S *et al.,* CROI 2017. Abstract 449LB 3. Kozal M *et al.,* EACS 2017. Abstract PS8/5. 4. Lalezari J *et al.,* CROI 2017. Abstract 437. 5. ClinicalTrials.gov. NCT02859961. 6. ClinicalTrials.gov. NCT02483078. 7. Murphy R *et al.,* CROI 2017. Abstract 452LB. 8. ClinicalTrials.gov. NCT03272347. 9. Matthews RP *et al.,* IAS 2017. Abstract TUPD0202LB.

CONCLUSIONS

- Early ARV priority for all patients except Tb and cryptococcosis
- Increasing INSTI recommendation for first-line use
- TAF is noninferior to TDF but offers a more favorable safety profile, remarkably concerning kidney and bone metabolism
- Several novel strategies and drugs in development, including parenteral options