Two as Good as Three? Dual Therapy

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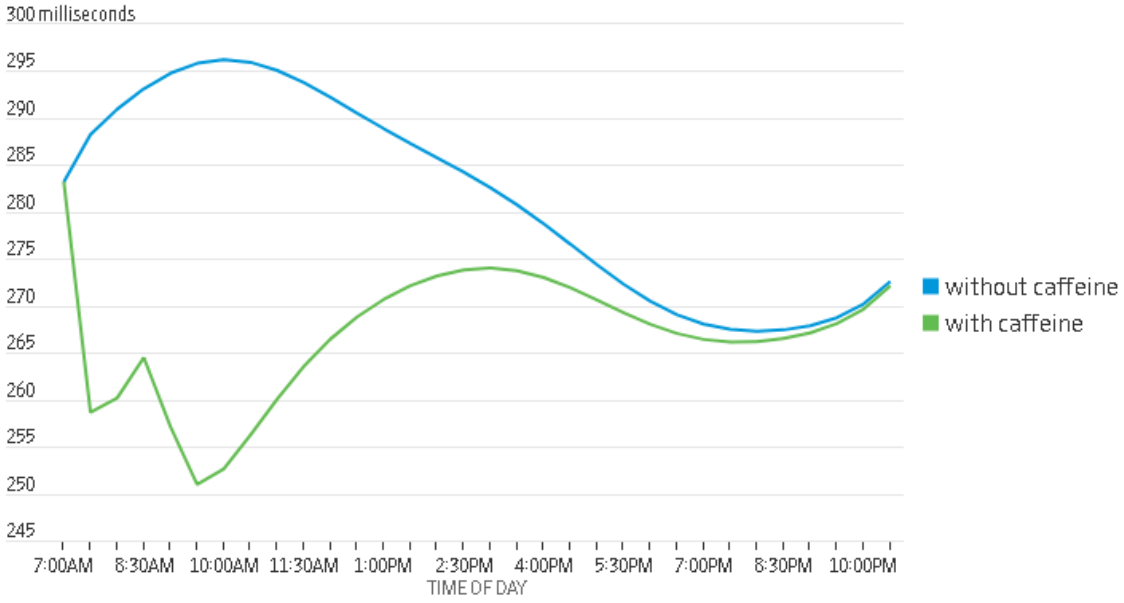
September 14, 2018

Benefits of Coffee!!

Coffee Boost

A well-rested person will react to a visual stimulus in about a quarter of a second. Here are mean response times after five hours of sleep, without caffeine and with 100 mg, equivalent to 8 ounces of weak coffee, at 7 a.m. and 9 a.m., the optimal dose for this scenario according to an algorithm designed by the U.S. Army.



Source: Jaques Reifman, U.S. Army Medical Research and Materiel Command

Outline

- Why Consider
- Studies of Dual Therapy – Initial vs Maintenance, combinations
- Cautions
- Future Direction

Why?
(The Holy Grail of Medical Care)

- Simplification
- Avoid toxicity
- Improve tolerability, convenience and adherence
- Manage potential drug–drug or drug–food interactions
- Pregnancy
- BMD
- Renal
- CV- lipids
- Resistance
- Cost savings:
  - $ 500 million over 5 years*

Not a new Concept
("nuc sparing")

DHHS Guidelines.

*CID 2016;62(6):784-91

DHHS, IAS-USA Guidelines: Recommended Regimens for First-line ART

Class	DHHS[1]	IAS-USA[2]
INSTI	▪ **BIC/TAF/FTC** ▪ **DTG/ABC/3TC** ▪ DTG + (TAF or TDF)/FTC ▪ **EVG/COBI/(TAF or TDF)/FTC** ▪ RAL + (TAF or TDF)/FTC	▪ **BIC/TAF/FTC** ▪ **DTG/ABC/3TC** ▪ DTG + TAF/FTC

Bold text identifies STR.

- Recommendations may differ based on baseline HIV-1 RNA, CD4+ cell count, CrCl, eGFR, HLA-B*5701 status, HBsAg status, osteoporosis status, and pregnancy status
- Data are lacking for women of child-bearing age not using contraception
- IAS-USA now lists EVG/COBI/TAF/FTC and RAL + TAF/FTC as alternative regimens (lower resistance barriers and, more drug interactions and higher pill burden[2]

1. DHHS Guidelines. May 2018. 2. Saag MS, et al. JAMA. 2018;320:379-396.

DHHS Guidelines: Initial ART Recommendations
"Certain Clinical Situations"

Recommended Initial Regimens in Certain Clinical Situations
These regimens are effective and tolerable, but have some disadvantages when compared with the regimens listed above, or have less supporting data from randomized clinical trials. However, in certain clinical situations, one of these regimens may be preferred (see Table 7 for examples).
Regimens to Consider when ABC, TAF, and TDF Cannot be Used:[d] • DRV/r + RAL (BID) **(CI)—if HIV RNA <100,000 copies/mL and CD4 >200 cells/mm^3** • LPV/r + 3TC[a] (BID)[e] **(CI)**

DHHS guidelines. March 27, 2018.

DHHS: Key Concerns With Selected Triple-Therapy Regimens Containing ABC, TAF, or TDF

Component	Key DDIs	May Be Suboptimal for Pts With:			Use Standard Dose When CrCI:
		Hyperlipidemia	CVD	Osteoporosis	
NRTI Backbone					
ABC/3TC			X		≥ 50 mL/min
FTC/TAF					≥ 30 mL/min
FTC/TDF				X	≥ 50 mL/min
Additional Agents					
Boosted PIs	Lipid-lowering agents, PPIs, steroids	X			
DTG	Antacids				
EVG/COBI	Lipid-lowering agents, steroids	X			
RAL	Antacids				
RPV	PPIs, dexamethasone				

- **DTG + RPV reasonable option when NRTIs not desirable/when no expected resistance components**
- **PI/RTV + 3TC may be reasonable option when TDF, TAF, or ABC is contraindicated or not desirable**

DHHS Guidelines.

Dual Therapy: Potential Boosted PI Regimens for Initial/Maintenance Therapy

Study	Treatment Setting	N	Regimen	Results
NEAT001[1]	**Initial**	805	DRV/RTV + RAL	Similar efficacy as DRV/RTV + FTC/TDF; **poor efficacy in pts with high HIV-1 RNA, low CD4+ cell counts**
GARDEL[2]	**Initial**	426	LPV/RTV + 3TC	**Similar** efficacy as LPV/RTV + 2 NRTIs
MODERN[3]	**Initial**	813	DRV/RTV + **MVC**	**Inferior** efficacy vs DRV/RTV + FTC/TDF
SPARTAN[4]	**Initial**	94	ATV + RAL	**Similar** virologic suppression, **higher VF and hyperbilirubinemia rates** vs ATV/RTV + FTC/TDF
ANDES[5]	**Initial**	145	DRV/RTV + 3TC	**Similar** efficacy as DRV/RTV + 3TC/TDF
OLE[6]	**Switch**	250	LPV/RTV + 3TC	Similar efficacy as continued standard ART
KITE[7]	**Switch**	60	LPV/RTV + RAL	**Small** study; encouraging efficacy
SALT[8]	**Switch**	286	ATV/RTV + 3TC	Similar efficacy as ATV/RTV + 2 NRTIs
ATLAS-M[9]	**Switch**	266	ATV/RTV + 3TC	**Improved** efficacy vs ATV/RTV + 2 NRTIs
DUAL-GESIDA[10]	**Switch**	257	DRV/RTV + 3TC	Similar efficacy as DRV/RTV + 2 NRTIs

Slide credit: clinicaloptions.com

Selected Studies of Boosted PI–Based Initial Dual Therapy

Study	N	Regimen	Results
NEAT001[1]	805	DRV/RTV + **RAL**	▪ Similar efficacy vs DRV/RTV + FTC/TDF ▪ **Poor efficacy in pts with high HIV-1 RNA, low CD4+ cell counts**
GARDEL[2]	426	LPV/RTV + 3TC	▪ Similar efficacy vs LPV/RTV + 2 NRTIs
SPARTAN[3]	94	ATV + **RAL**	▪ Similar virologic suppression, **higher VF and hyperbilirubinemia rates** vs ATV/RTV + FTC/TDF
ANDES[4] *Interim analysis.	145	DRV/RTV + 3TC	▪ Similar efficacy vs DRV/RTV + 3TC/TDF* ▪ **Efficacy maintained when BL HIV-1 RNA > 100,000 copies/mL**

1. Raffi F, et al. Lancet. 2014;384:1942-1951. 2. Cahn P, et al. EACS 2015. Abstract PS10/4.
3. Kozal MJ, et al. HIV Clin Trials. 2012;13:119-130. 4. Sued O, et al. IAS 2017. Abstract MOAB0106LB.

Selected Dual-Therapy Regimens Under Investigation for Initial/Maintenance Therapy

Regimen	Treatment Setting	Studies
DTG + 3TC	**Maintenance**	▪ ASPIRE* (randomized phase III)[1] ▪ ANRS 167 LAMIDOL* (single-arm phase II)[2]
	Initial	▪ **GEMINI 1 & 2 (randomized phase III)[3,4]** ▪ PADDLE* (single-arm phase IV)[5,6] ▪ ACTG A5353* (single-arm phase II)[7]
DTG + **DRV**/RTV	**Maintenance**	▪ DUALIS (randomized phase III)[8]
DRV/RTV + 3TC	**Maintenance**	▪ DUAL-GESIDA* (randomized phase IV)[9]
	Initial	▪ ANDES* (randomized phase IV)[10]
ATV/RTV + 3TC	**Maintenance**	▪ SALT* (randomized phase IV)[11] ▪ ATLAS-M* (randomized phase IV)[12]
LA CAB + RPV	**Maintenance**	▪ ATLAS, FLAIR, ATLAS-2M (randomized phase III)[13-15] ▪ LATTE-2* (randomized phase IIb)[16]

*Available data.

Slide credit: clinicaloptions.com

ANDES: DRV/RTV + 3TC vs DRV/RTV + 3TC/TDF in Treatment-Naive Patients at Wk 48

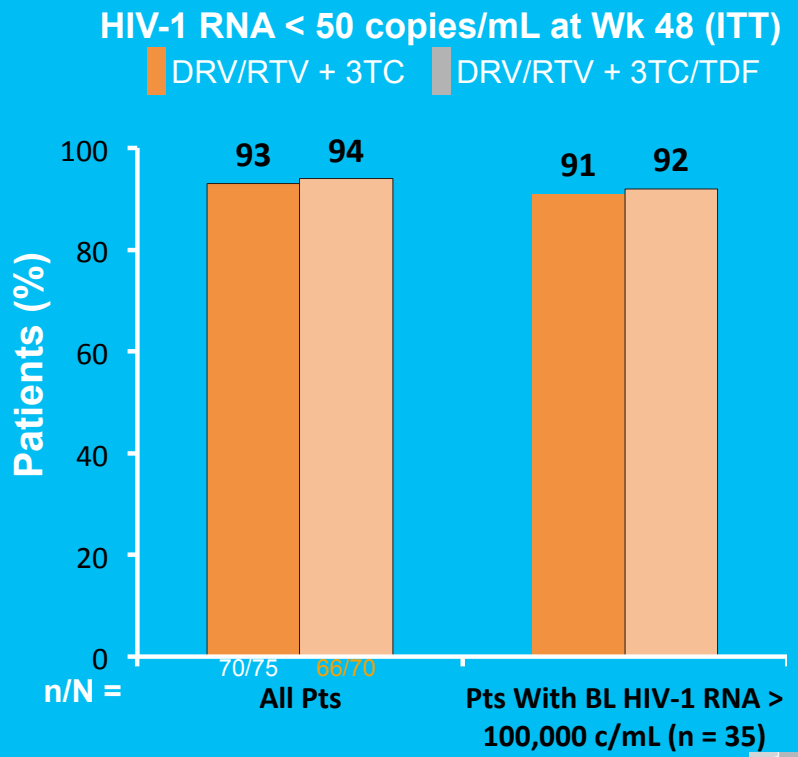
- Randomized, open-label phase IV study in Argentina

Primary Endpoint Wk 48

ART-naive patients with HIV-1 RNA > 1000 c/mL, no NRTI or PI resistance, and **HBsAg negative** (N = **145**)

- DRV/RTV + 3TC QD (n = **75**)
- DRV/RTV + 3TC/TDF QD (n = **70**)

Dosing: DRV/RTV, 800/100 mg; 3TC, 300 mg; 3TC/TDF, 300/300 mg.



Figueroa MI, et al. CROI 2018. Abstract 489.

Slide credit: clinicaloptions.com

Selected Studies of Boosted PI Maintenance Dual Therapy

Study	N	Regimen	Results
SALT[1]	286	ATV/RTV + 3TC	▪ Similar efficacy, less frequent d/c for AEs vs ATV/RTV + 2 NRTIs
ATLAS-M[2]	266	ATV/RTV + 3TC	▪ Improved efficacy, similar safety profile vs ATV/RTV + 2 NRTIs
DUAL-GESIDA[3]	257	DRV/RTV + 3TC	▪ Similar efficacy and tolerability vs DRV/RTV + 2 NRTIs

1. Perez-Molina JA, et al. Lancet Infect Dis. 2015;15:775-784.
2. Di Giambenedetto S, et al. J Antimicrob Chemother. 2017;72:1163-1171.
3. Pulido F, et al. HIV Glasgow 2016. Abstract O331.

Dual Therapy: bPI Naïve Studies Meta-analysis

ART-naive patients					
Sued et al. [8]	2017	ANDES	NCT02770508	3TC + DRV/RTV	Viral load < 400 copies/ml after 24 weeks 94.7% (n = 71/75) of patients with dual ART 97.1% (n = 68/70) of patients with triple ART
Cai et al. [7]	2017			3TC + LPV/RTV	Viral load < 50 copies/ml after 48 weeks 92% (n = 92/100) of patients with dual ART 89.8% (n = 88/98) of patients with triple ART p = 0.629
Cahn et al. [6]	2014	GARDEL	NCT01237444	3TC + LPV/RTV	Viral load < 50 copies/ml after 48 weeks 88.3% (n = 189/198) of patients with dual ART 83.7% (n = 169/175) of patients with triple ART p = 0.171
Andrade et al. [5]	2011	LOREDA		3TC + LPV/RTV	Viral load < 48 copies/ml after 48 weeks 66.7% (n = 26/39) of patients (Intention-to-treat-analysis) 81.3% (n = 26/32) of patients with (as-treated-analysis)
Pinola et al. [13]	2008	Kalead	NCT00234910	LPV/r + TDF	Viral load < 50 copies/ml after 72 weeks 51.4% (n = 37/ 72) of patients with dual ART (intention-to-treat) 52.5% (n = 42/80) of patients with triple ART (intention-to-treat) 87.2% (n = 36/42) of patients with dual ART (As-treated-analysis) 93.0% (n = 42/45) of patients with triple ART (as-treated-analysis)

Infection June 2018 online https://doi.org/10.1007/s15010-018-1171-z

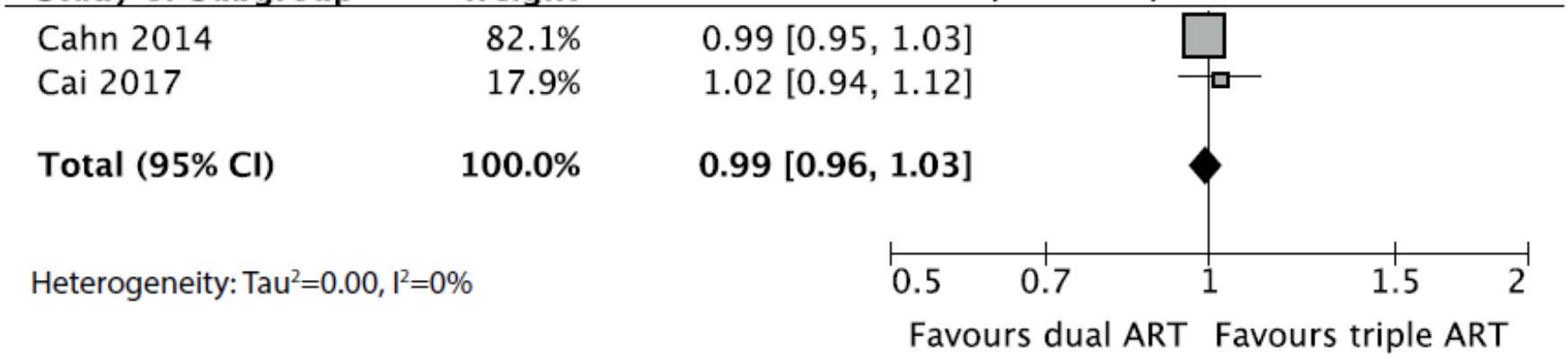
Dual Therapy: bPI Switch Studies Meta-analysis

Switch therapy in ART-experienced patients					
Pulido et al. [12]	2017	DUAL-GESIDA 8014-RIS-EST45	NCT02159599	3TC DRV/RTV	Viral load < 50 copies/ml 48 weeks 88.9% (n = 112/126) of patients with dual ART 92.7% (n = 114/123) of patients with triple ART
Di Giambenedetto et al. [14]	2017	ATLAS-M	NCT01599364	3TC + ATV/RTV	Viral load < 50 copies/ml after 48 weeks 89.5% (n = 119/133) of patients with dual ART 79.7% (n = 106/133) of patients with triple ART
Arribas et al. [9]	2016	OLE	NCT01471821	3TC + LPV/RTV	Viral load < 50 copies/ml after 48 weeks 87.8% (n = 108/123) of patients with dual ART 86.6% (n = 110/127) of patients with triple ART p = 0.92
Perez-Molina et al. [11]	2015	SALT	NCT01307488	3TC + ATV/RTV	Viral load < 50 copies/ml after 48 weeks 83% (n = 111/133) of patients with dual ART 78% (n = 105/135) of patients with triple ART

Infection June 2018 online https://doi.org/10.1007/s15010-018-1171-z

Dual Therapy: bPI Naïve
Studies Meta-analysis Results

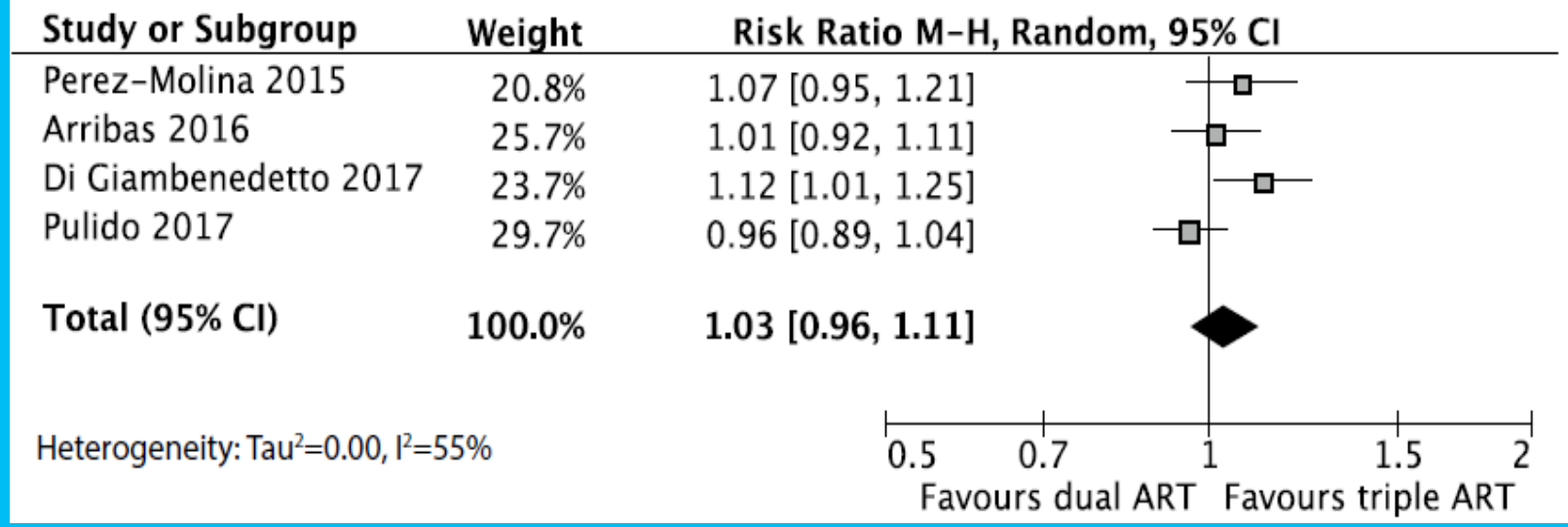
Treatment-naive patients only



Infection June 2018 online https://doi.org/10.1007/s15010-018-1171-z

Dual Therapy: bPI Switch Studies Meta-analysis Results

Switch-therapy only



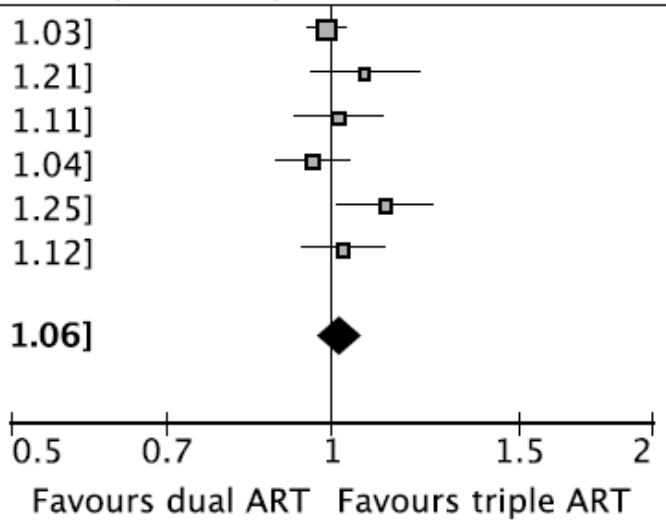
Infection June 2018 online https://doi.org/10.1007/s15010-018-1171-z

Dual Therapy: bPI Dual and Switch Studies Meta-analysis

All trials with 48-week follow-up

Study or Subgroup	Weight	Risk Ratio M-H, Random, 95% CI
Cahn 2014	29.0%	0.99 [0.95, 1.03]
Perez-Molina 2015	10.7%	1.07 [0.95, 1.21]
Arribas 2016	14.3%	1.01 [0.92, 1.11]
Pulido 2017	17.6%	0.96 [0.89, 1.04]
Di Giambenedetto 2017	12.7%	1.12 [1.01, 1.25]
Cai 2017	15.6%	1.02 [0.94, 1.12]
Total (95% CI)	**100.0%**	**1.02 [0.97, 1.06]**

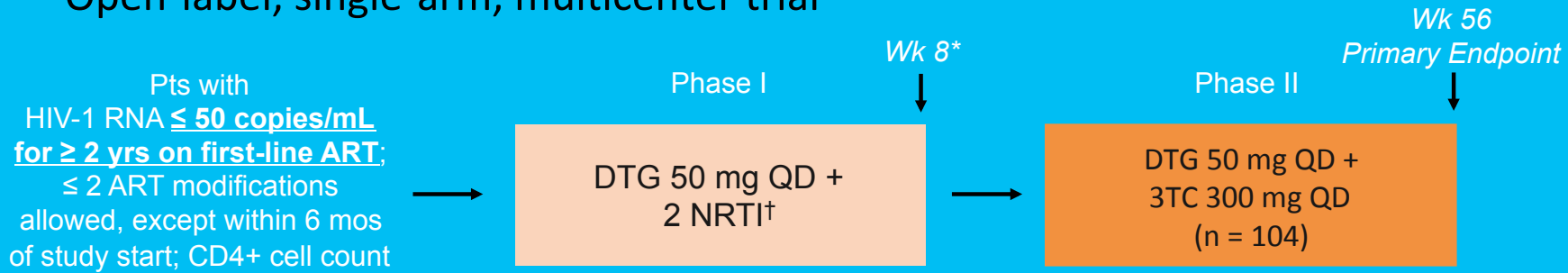
Heterogeneity: $Tau^2=0.00$, $I^2=46\%$



Infection June 2018 online https://doi.org/10.1007/s15010-018-1171-z

ANRS 167 LAMIDOL: Switch to DTG + 3TC in Virologically Suppressed Pts on Triple ART

- Open-label, single-arm, multicenter trial



*Pts with HIV-1 RNA ≤ 50 copies/mL proceeded to phase II.
†In phase I, third agent (NNRTI, boosted PI, or INSTI) in regimen replaced with DTG; baseline NRTI backbone maintained.

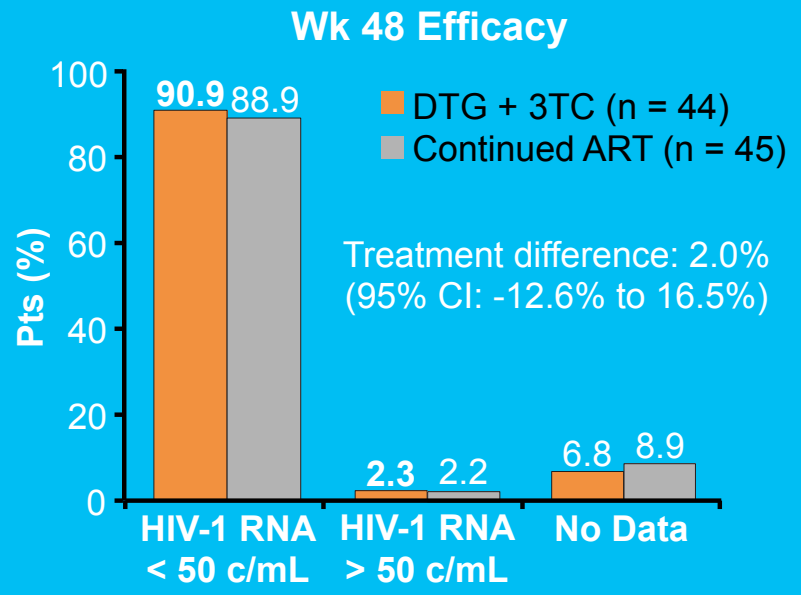
- 97% (n/N = 101/104) of pts maintained therapeutic success through 40 wks (study Wk 48)
- 7 serious AEs, only 2 related to dual therapy

Joly V, et al. CROI 2017. Abstract 458.

Slide credit: clinicaloptions.com

ASPIRE: Switch to DTG + 3TC in Virologically Suppressed Pts on Triple ART

- Randomized, open-label, multicenter phase III trial in which pts who were virologically suppressed on 3-drug ART regimen with no history of VF were randomized to **DTG + 3TC QD** or **continued 3-drug ART** (N = 90)



- Similar lipid changes between regimens
- CrCl changes from baseline, DTG + 3TC vs continued ART:
  - Wk 24: –6 vs 3.6 (*P* < .001)
  - Wk 48: –3.8 vs 0 (*P* = .07)
- Similar rates of SAEs; 1 d/c for AEs (DTG + 3TC arm, grade 2 constipation)

Taiwo BO, et al. EACS 2017. Abstract PE8/5.

Slide credit: clinicaloptions.com

ACTG A5353: DTG + 3TC for ART-Naive Pts

- Single-arm phase II study

ART-naive pts with
HIV-1 RNA ≥ 1000 and < 500,000 copies/mL;
no RT, INSTI, major PI resistance mutations
(N = 120)

→ DTG 50 mg + 3TC 300 mg

Primary Endpoint
Wk 24

Virologic Outcome at Wk 24, n (%)	Baseline HIV-1 RNA, copies/mL		Total (N = 120)
	> 100,000 (n = 37)	≤ 100,000 (n = 83)	
Success*	33 (89)	75 (90)	108 (90)
Nonsuccess	3 (8)	2 (2)	5 (4)
No data	1 (3)	6 (7)	7 (6)

*HIV-1 RNA < 50 copies/mL.

- n = 3 with PDVF; n = 1 with emergent M184V and R263R/K mixture
  - All 3 pts had DTG levels reflective of suboptimal adherence

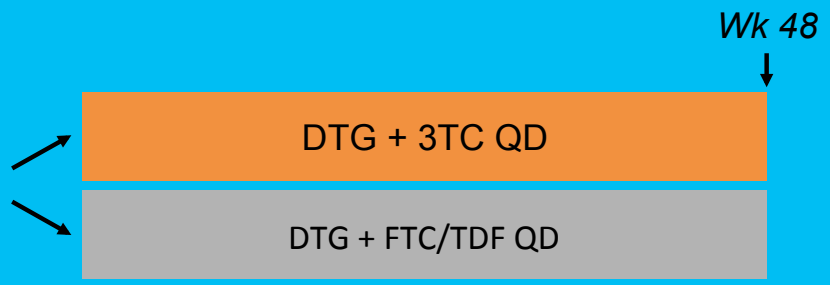
Taiwo BO, et al. IAS 2017. Abstract MOAB0107LB.

Slide credit: clinicaloptions.com

GEMINI 1 & 2: DTG + 3TC for Treatment-Naive Pts

- Ongoing multicenter, randomized, double-blind, active-comparator phase III studies

ART-naive pts with HIV-1 RNA > 1000 to ≤ 500,000 copies/mL, no HBV infection, CrCl ≥ 50 mL/min/1.73 m^2 (planned N = 700 for each trial)



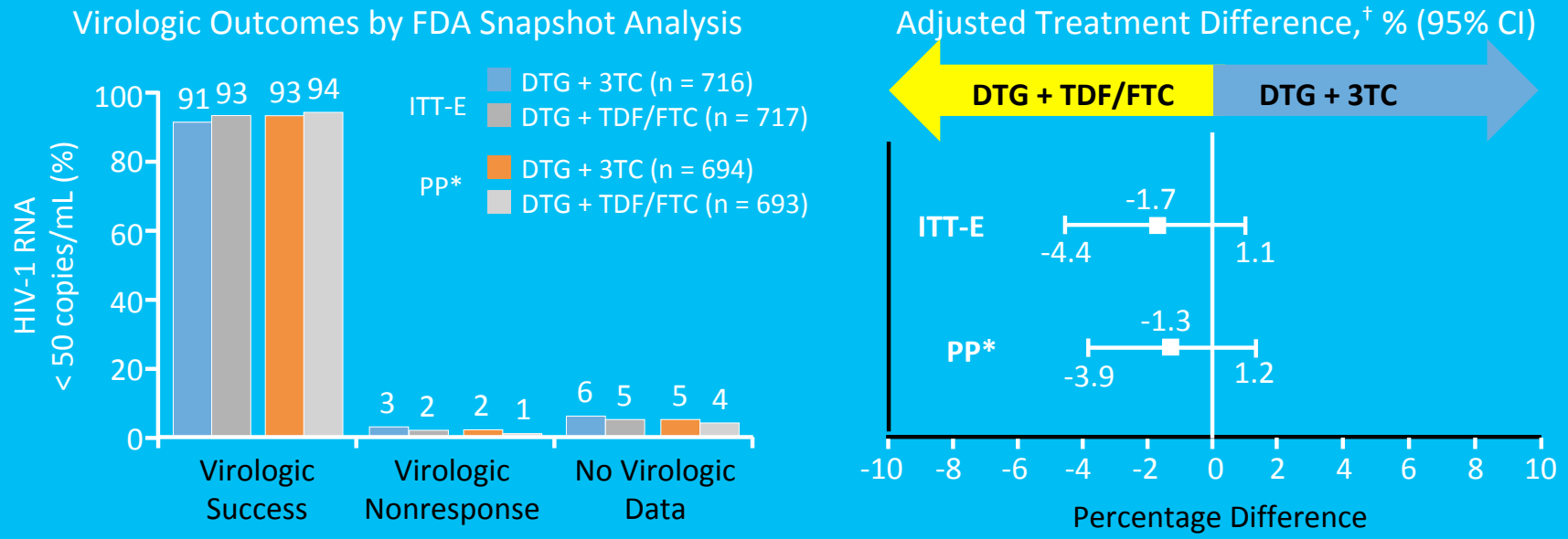
Dosing: DTG 50 mg, 3TC 300 mg, FTC/TDF 200/300 mg.

- Primary endpoint: proportion with HIV-1 RNA < 50 copies/mL at Wk 48

ClinicalTrials.gov. NCT02831673. ClinicalTrials.gov. NCT02831764.

Slide credit: clinicaloptions.com

GEMINI-1 and -2: Virologic Response at Wk 48

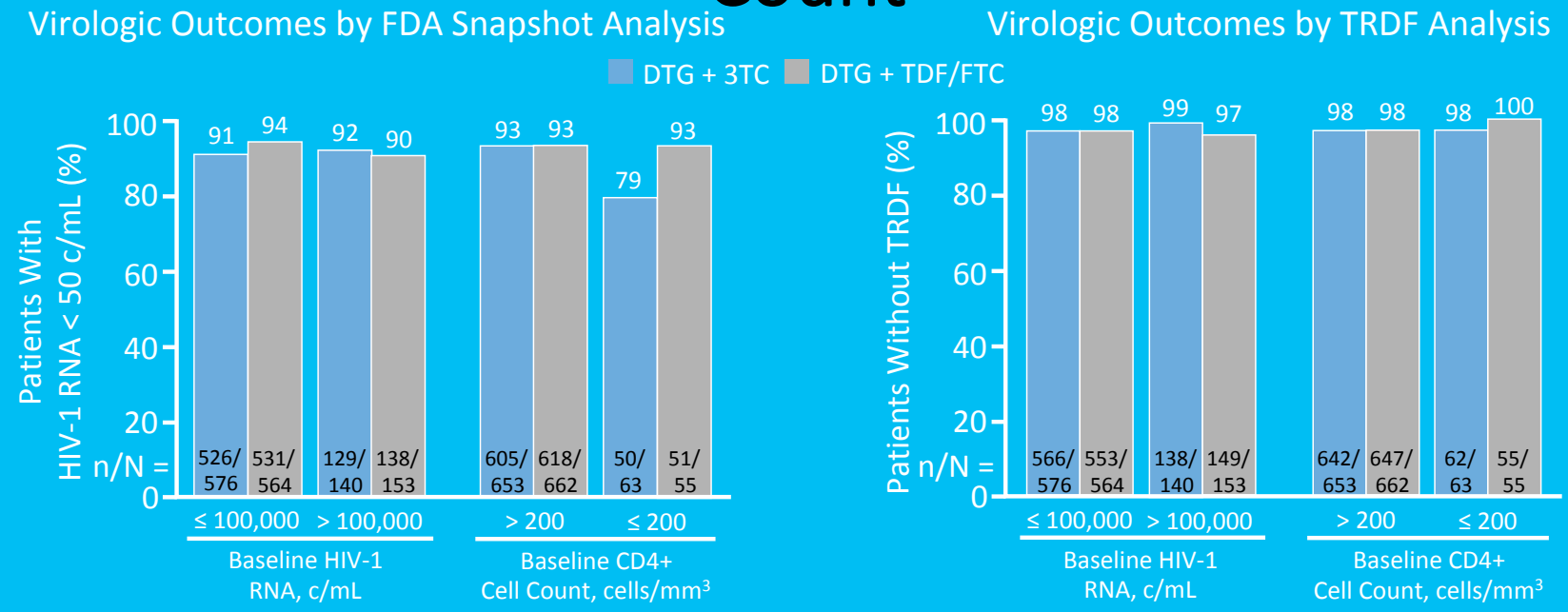


*ITT-E population excluding significant protocol violations.
†Adjusted for HIV-1 RNA (≤ vs > 100,000 copies/mL), CD4+ cell count (≤ vs > 200 cells/mm^3), and study (GEMINI-1 vs GEMINI-2).

Cahn P, et al. AIDS 2018. Abstract TUAB0106LB.

Slide credit: clinicaloptions.com

GEMINI-1 and -2: Virologic Response at Wk 48 by Baseline HIV-1 RNA and CD4+ Cell Count



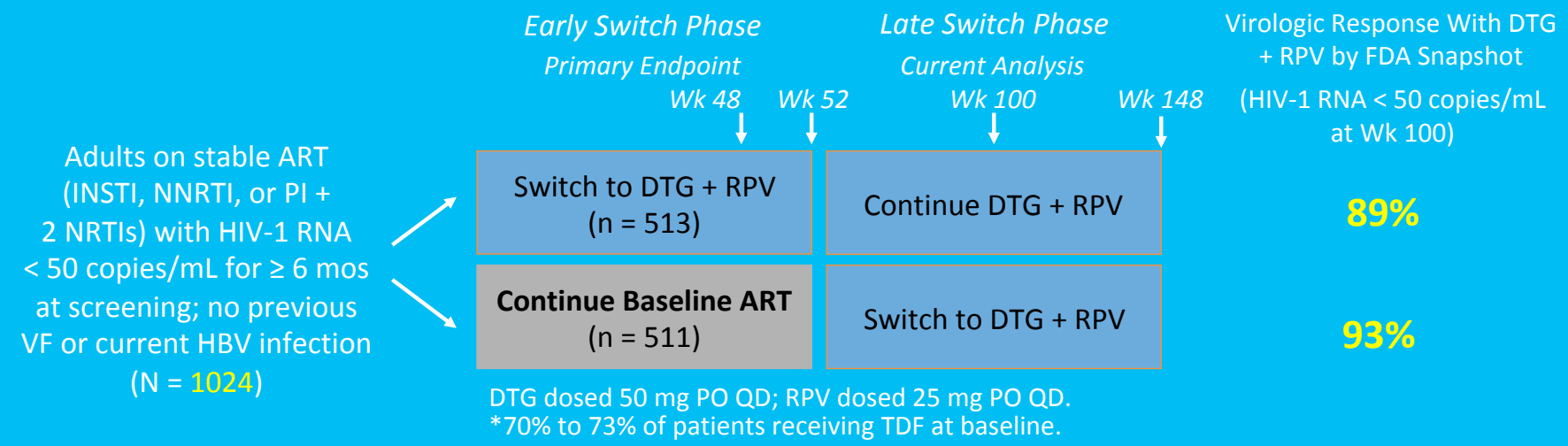
- TRDF includes confirmed virologic withdrawal, withdrawal for lack of efficacy or treatment-related AEs, and participants meeting protocol-defined stopping criteria

Cahn P, et al. AIDS 2018. Abstract TUAB0106LB.

Slide credit: clinicaloptions.com

SWORD-1 and -2: Switch to DTG + RPV vs Continuation in Virologically Suppressed Adults

- Parallel, randomized, open-label, multicenter phase III noninferiority studies[1,2]



DTG dosed 50 mg PO QD; RPV dosed 25 mg PO QD.
*70% to 73% of patients receiving TDF at baseline.

- Primary endpoint: HIV-1 RNA < 50 copies/mL maintained in 95% of patients in each arm at Wk 48; adjusted treatment difference: -0.2% (95% CI: -3.0 to 2.5)[2]

1. Aboud M, et al. AIDS 2018. Abstract THPEB047. 2. Llibre JM, et al. Lancet. 2018;391:839-849.

Slide credit: clinicaloptions.com

SWORD-1 and -2: Bone and Lipid Markers

P Value for Change From BL in Mean Serum Concentration	Early Switch		Late Switch
	Wk 48	Wk 100	Wk 100
Osteocalcin	< .001	< .001	< .001
Bone-specific alkaline phosphatase	< .001	< .001	< .001
Procollagen 1 N-terminal propeptide	< .001	-	.05
Type 1 collagen-C telopeptide	< .001	< .001	.05

- All **bone turnover** markers significantly lower at Wk 100 vs BL except procollagen 1 N-terminal propeptide in early switch arm

- No changes in **lipid levels** (total cholesterol, LDL-C, HDL-C, triglycerides, total cholesterol:HDL-C ratio) or atherogenesis and inflammation biomarkers at Wk 100 vs BL in either group
- Early switch group maintained improvements in markers of **renal tubular function** (urine retinol-binding protein/creatinine ratio and urine β_2-microglobulin/creatinine ratio) observed from BL to Wk 48 through Wk 100

Aboud M, et al. AIDS 2018. Abstract THPEB047.

Slide credit: clinicaloptions.com

SWORD-1 and -2: Resistance

- 10/990 (1%) confirmed virologic withdrawals through Wk 100
  - Treatment-emergent NNRTI resistance **mutations** documented in **3**/10, all from early switch arm*

Time of Failure	Previous Regimen	Mutations at Baseline		Mutations at Confirmed Virologic Withdrawal	
		NNRTI	INSTI	NNRTI	INSTI
Wk 36	EFV/TDF/FTC	None	None	K101K/E	None
Wk 88	DTG/ABC/3TC	None	None	E138E/A	None
	EFV/TDF/FTC	K101E, E138A	G193E	K101E, E138A, M230M/L	Wk 100

*For these 3 patients, HIV-1 RNA at last measurement: < 50 copies/mL, 55 copies/mL, 300 copies/mL, respectively.

Aboud M, et al. AIDS 2018. Abstract THPEB047.

Slide credit: clinicaloptions.com

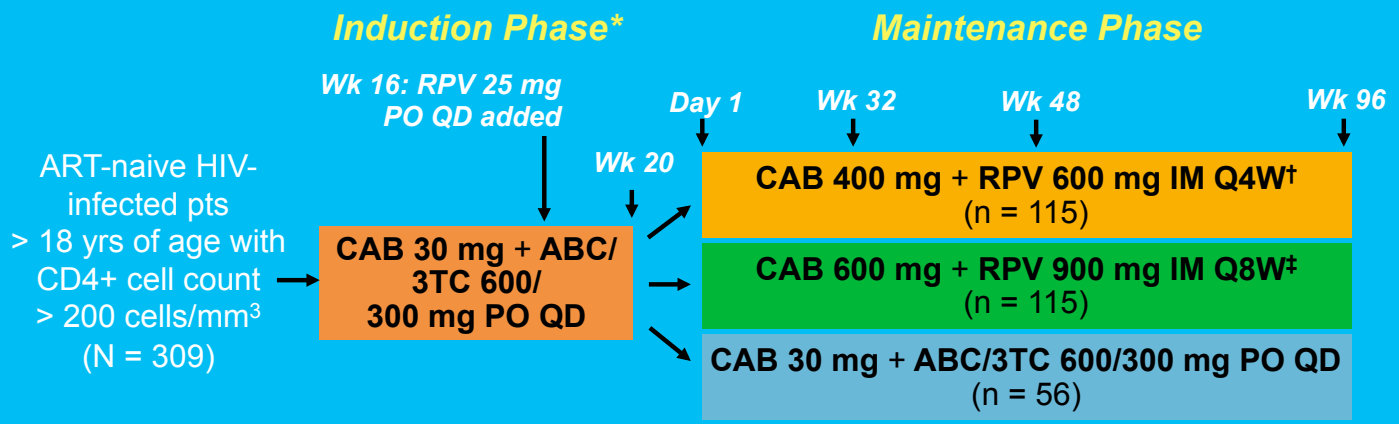
DTG/RPV FDA Approved for Maintenance Therapy

- Once-daily single-tablet regimen of DTG and RPV
  - First 2-drug STR FDA approved for use as a complete regimen in the US

Key US Label Information	
Indication	▪ For pts who have been **virologically suppressed for ≥ 6 mos** ▪ Pts must have **no history of treatment failure and no resistance** to DTG or RPV
Administration requirements	▪ Must be taken **with a meal**
Key DDIs	▪ **Separate dose of DTG/RPV and antacid/polyvalent cation–containing medications** ▪ **Avoid PPIs** (eg, omeprazole, pantoprazole), **dexamethasone**
Dose adjustments	▪ None required for pts with mild/moderate renal impairment; in pts with **CrCl < 30 mL/min**, increase monitoring for AEs

LATTE-2: Cabotegravir IM + Rilpivirine IM: Long-Acting Maintenance ART

- Multicenter, open-label, randomized phase IIb study
  - **Cabotegravir**: INSTI formulated as oral tablet and for long-acting IM injection



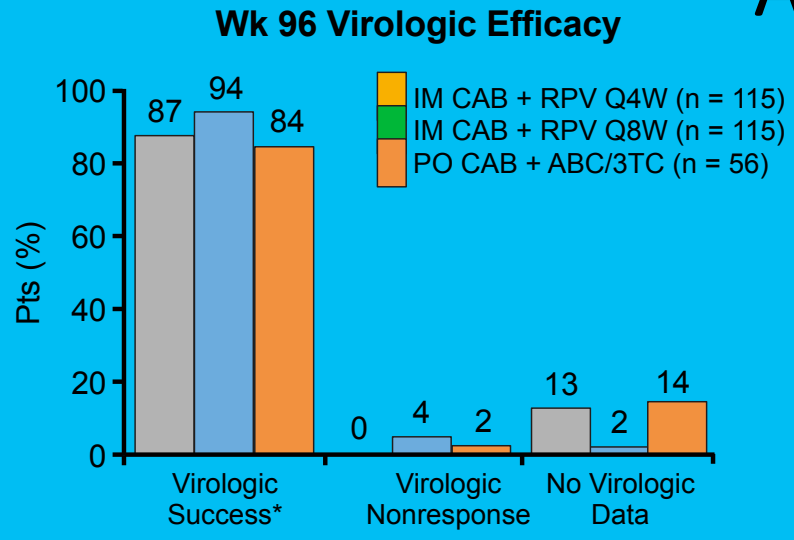
*Pts with HIV-1 RNA < 50 copies/mL from Wks 16-20 continued to maintenance phase. †CAB loading dose at Day 1. ‡CAB loading doses at Day 1 and Wk 4.

- Injections were 2-3 mL, IM (gluteal region), provider administered

Margolis DA, et al. IAC 2016. Abstract THAB0206LB. ClinicalTrials.gov. NCT02120352.

Slide credit: clinicaloptions.com

LATTE-2: 96-Wk Results for Cabotegravir IM + Rilpivirine IM as Long-Acting Maintenance ART



*HIV-1 RNA < 50 copies/mL.

Treatment difference (vs CAB PO):
CAB IM Q4W: 3.0% (95% CI: -8.4% to 14.4%)
CAB IM Q8W: 10.0% (95% CI: -0.6% to 20.5%)

- At 96 wks, ~ 30% pts receiving IM injection experienced ISR
  - 99% of ISRs mild/moderate
  - AEs leading to withdrawal: pooled Q4W/Q8W IM arms, 4%; PO arm, 2%
- PDVF, n = 3 (n = 1 PO arm; n = 2 Q8W arm)
  - 1 pt in Q8W group with K103N, E138G, K238T (NNRTI) and Q148R (INSTI) resistance mutations
  - No additional PDVFs after Wk 48 in any arm
- Phase III maintenance trials ongoing: ATLAS and FLAIR assessing Q4W dose; ATLAS-2M comparing Q4W and Q8W doses[3-5]

Slide credit: clinicaloptions.com

DHHS: Principles of Regimen Switching in Virologically Suppressed Pts

- Review ART history for intolerance or possible virologic failure
- Review all available drug resistance testing results
- If prior resistance uncertain, only consider switch if new regimen likely to maintain suppression of resistant virus
  - Care needed when switching from PI/RTV to another class if full treatment or resistance history is not known
- Consult an expert when switching a pt with resistance to ≥ 1 class
- Within class switches usually maintain virologic suppression if no resistance to drugs in that class are present
- Increase monitoring during first 3 mos after switch

DHHS Guidelines.

DHHS: Guidance for Switching to Dual Therapy in Virologically Suppressed Pts

- DTG + RPV a reasonable option when use of NRTIs not desirable and when no expected resistance to regimen components
- PI/RTV + 3TC may be a reasonable option when use of TDF, TAF, or ABC is contraindicated or not desirable
- Insufficient evidence to recommend: DTG + 3TC, DRV/RTV + RAL
- ***Not recommended***: DTG or PI/RTV **monotherapy**, ATV/RTV + RAL
- bPI +MVC or NNRTI not noninferior or significant increase side effects

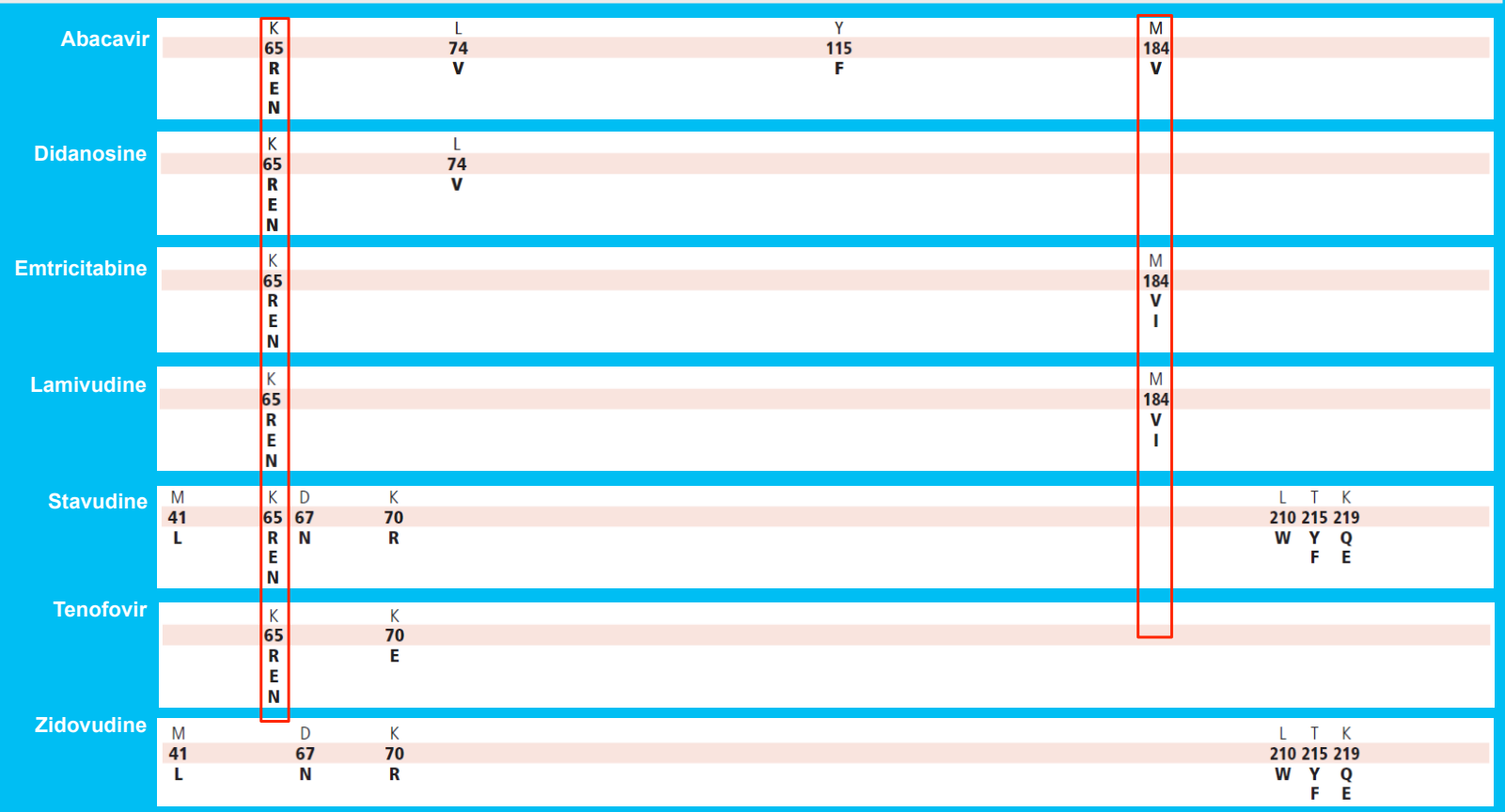
DHHS guidelines. October 2017.

Summary

- DTG/RPV QD STR approved for maintenance therapy in virologically suppressed pts
  - May be particularly relevant for pts for whom NRTI-containing regimens are suboptimal due to comorbidities or DDIs
- Additional regimens under investigation:
  - DTG + 3TC (first-line/maintenance)
  - Boosted PIs + 3TC (first-line/maintenance)
  - DTG + boosted PIs (maintenance)
  - LA CAB + RPV (maintenance)

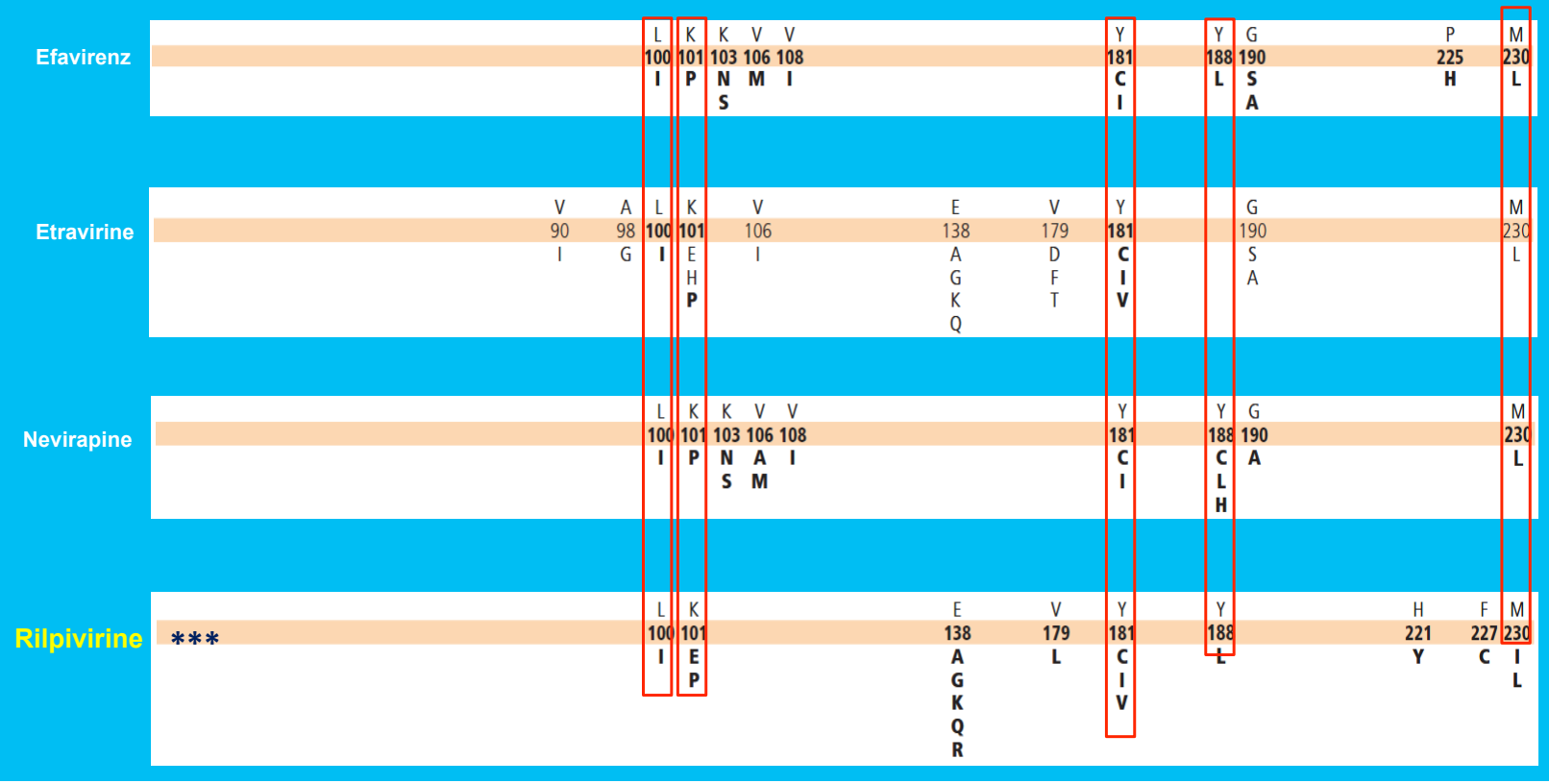
Slide credit: clinicaloptions.com

Mutations in the Reverse Transcriptase Gene Associated With Resistance to Reverse Transcriptase Inhibitors

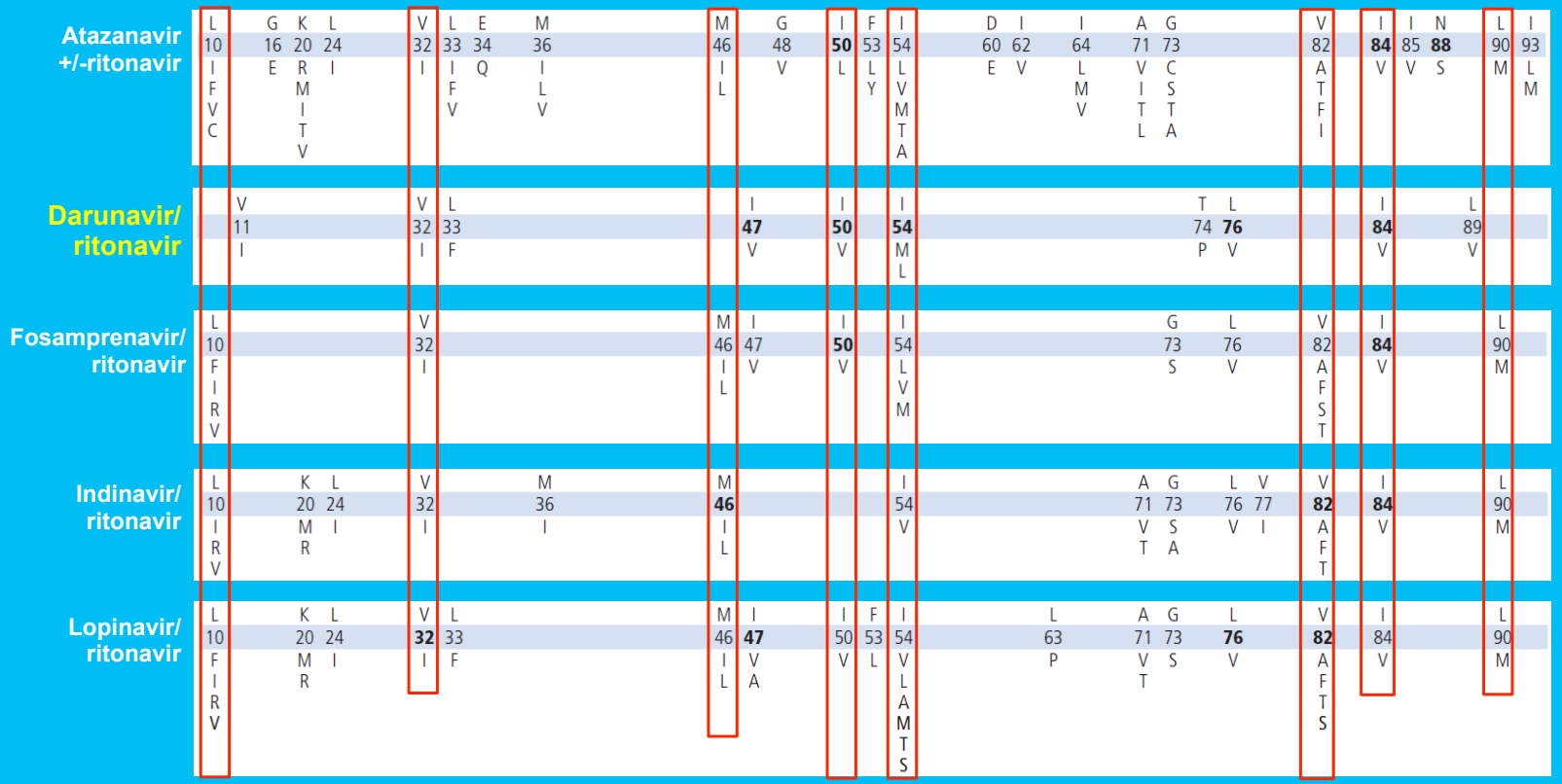


Mutations in the Reverse Transcriptase Gene Associated With Resistance to Reverse Transcriptase Inhibitors (cont'd)

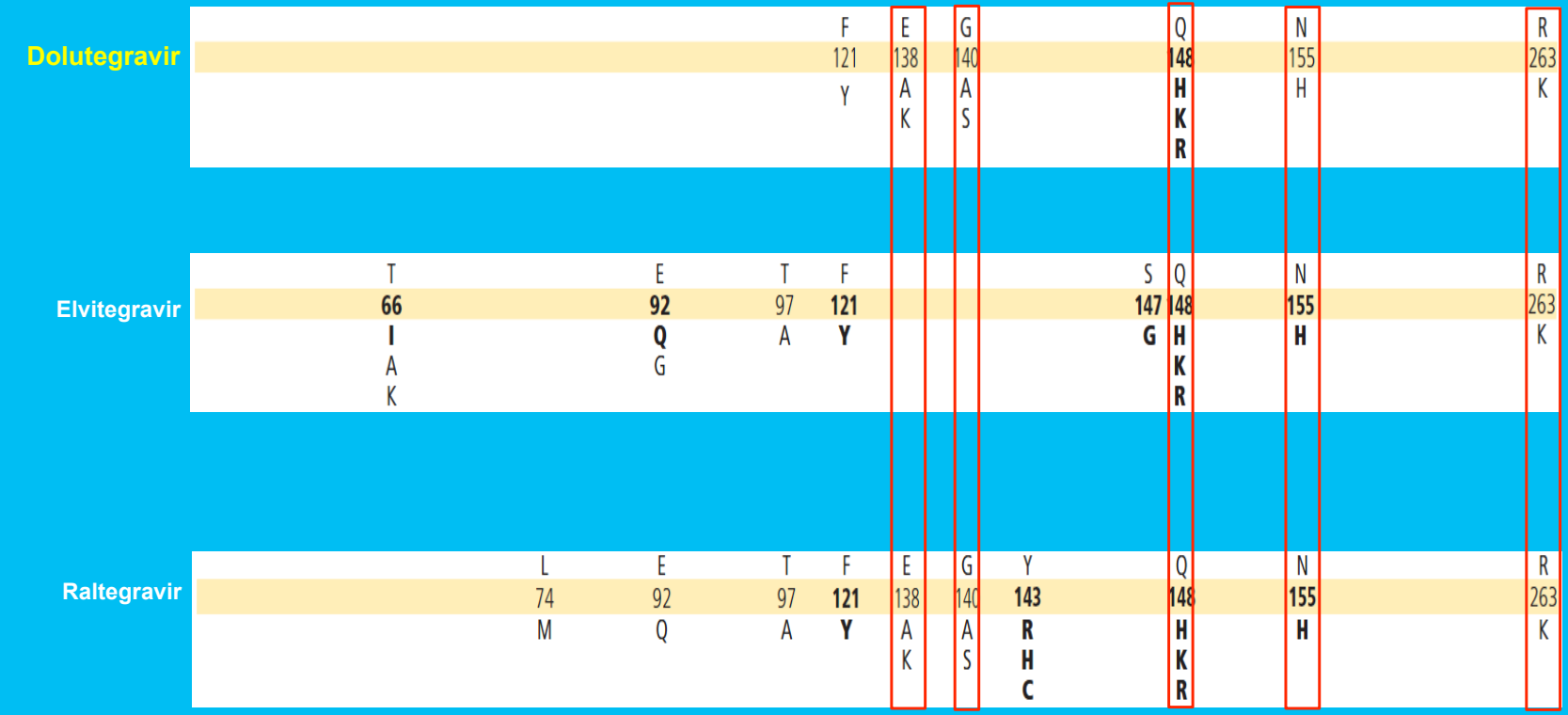
Nonnucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs)



Mutations in the Protease Gene Associated With Resistance to Protease Inhibitors



Mutations in the Integrase Gene Associated With Resistance to Integrase Strand Transfer Inhibitors



HIV Genotyping ARUP

SEE NOTE

Comment:

(NOTE)

Drug Resistance:

NRTI Drug Class

VIDEX, (didanosine, ddI)	None
VIREAD, (tenofovir, TDF)	None
ZERIT, (stavudine, d4T)	None
ZIAGEN, (abacavir, ABC)	None
EMTRIVA, (emtricitabine, FTC)	Resistance
RETROVIR, (zidovudine, ZDV)	None
EPIVIR, (lamivudine, 3TC)	Resistance

NRTI drug resistance mutations identified: M184V

NNRTI Drug Class

SUSTIVA, (efavirenz, EFV)	Resistance***
VIRAMUNE, (nevirapine, NVP)	Resistance***
INTELENCE, (etravirine, ETR)	None
EDURANT, (rilpivirine, RPV)	Possible Resistance***

NNRTI drug resistance mutations identified: K103N, E138K

Date Viral Load Collected	08/29/2018	DATE	Final	Unknown
Raltegravir Resistance	NOT PREDICTED		Final	CCM
Elvitegravir Resistance	PREDICTED		Final	CCM
Dolutegravir Resistance	NOT PREDICTED		Final	CCM

Comment:

(NOTE)

Mutations Detected: T66A,L68V/L,S230N

Performing Lab

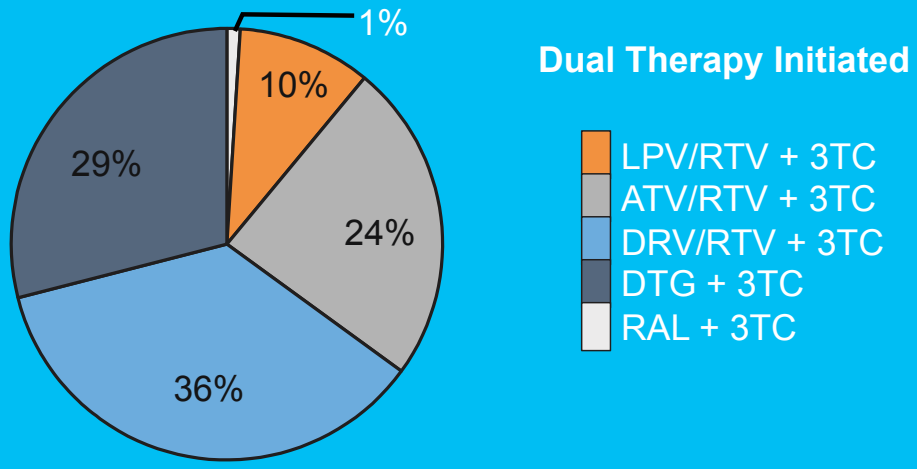
FORTOVASE / INVIRASE, (saquinavir, SQV)	None

PI+ drug resistance mutations identified: None

63 y/o HIV ~ 1997, psychogenic swallowing disorder. Previous regimens: 3TC, FTC, D4T, TDF, tAF, EVT, RTV, DRV, NVP, ETR. Often missed at least 2-3 doses/ week. Presented to our practice for care taking EVTc/FTC/tAF. VL 67000, CD4 141/9%. Genotype obtained and displayed.

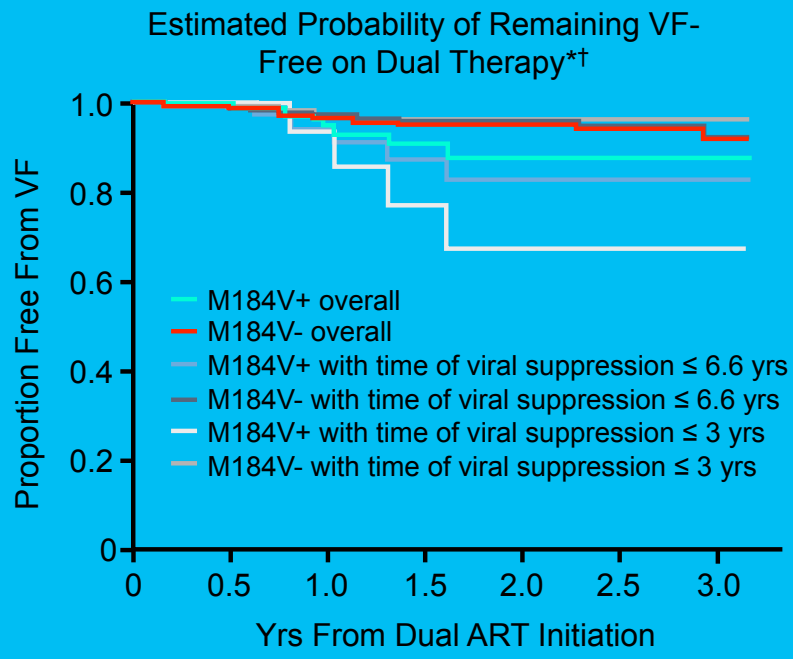
Impact of M184V on Virologic Efficacy of Switch to 3TC-Based Dual ART

- Retrospective observational study comparing efficacy of 3TC-based dual ART for patients with or without M184V history in Antiretroviral Resistance Cohort Analysis database (N = 436)
  - Inclusion criteria:
    HIV RNA ≤ 50 copies/mL,
    switching to dual therapy
    (3TC + either PI/RTV or INSTI),
    ≥ 1 prior genotyping
  - M184V determined in historic genotypic resistance tests and last genotyping
  - Primary endpoint: time to virologic failure in M184V-positive vs M184V-negative patients



Gagliardini R, et al. CROI 2018. Abstract 498.

M184V and Switch to 3TC-Based Dual ART: More Blips But No Greater Risk of Virologic Failure



- No difference in 3-yr probability of remaining free from virologic failure without vs with M184V (*P* = .323)
- Significantly higher 3-yr probability of remaining free from viral blip‡ without vs with M184V (log-rank *P* = .016)
  - M184V: 79.8% (95% CI: 67.8% to 91.8%)
  - No M184V: 90.1% (95% CI: 84.0% to 96.2%)

*VF: 2 HIV-1 RNA findings > 50 c/mL or 1 finding ≥ 200 c/mL. †No VF in 21 pts on DTG + 3TC over median f/u of 10 mos.
‡Viral blip: single HIV-1 RNA finding 51-199 c/mL, not confirmed.

Gagliardini R, et al. CROI 2018. Abstract 498. Reproduced with permission.

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Significance of NNRTI Minority Variants

- Evolution of understanding and newer medications
- Degree of adherence
- Prior experience in class
- Primary infection **vs** experienced

JAIDS 2005;38:37[1], JID 2010;201:672-680[2], JAMA 2011;305:1327-35[3]; AIDS 2012;26:185-92[4]; J Clin Vir 2012;55:107-13[5], CID 2018;66(10): 1588-94

Dolutegravir Resistance S230R

- One is not as good as two! (and far inferior to three)
- Domono Trial (and Sailing)
- Mutations emerged on monotherapy
  modest decreased in RC but with increase in IC_{50}
- Previously believed to require association with major mutation
- No “major” mutations
  - Much to learn but……..

No Monotherapy !

JID 2018;218:688-97, 673-5, 698-706

Think Carefully!

- Strategy not for all patients
- Probably not rapid start combination
- No known background resistance in naïve (transmitted) or switch patients
- Switch to dual only after successful suppression on triple or special circumstances – current recommendations
- Maraviroc should be avoided in dual therapy
- Patient should not have HBV
- Watch for DDI and meal requirements
- If blip or concern of adherence/resistance – follow carefully and counsel

Additional Longer-Acting and mAb Investigational Agents (Phase II/III)

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

1. Caskey M, et al. Nature. 2015;522:487-491. 2. ClinicalTrials.gov. NCT03041012. 3. Bekker L-G, et al. CROI 2017. Abstract 421LB. 4. Wang C-Y, et al. CROI 2017. Abstract 450LB. 5. ClinicalTrials.gov. NCT02716675. 6. ClinicalTrials.gov. NCT02568215.

Future?

- Doravirine – NNRTI – approved STR and stand alone
- Fostemsavir – Attachment Inhibitor
- New combinations
- Monoclonal Antibody Therapy - Ibalizumab

Questions?

Thank you for attending

We hope this has been a worthwhile learning experience for you