Southern African HIV Clinicians Society

3rd Biennial Conference

13 - 16 April 2016
Sandton Convention Centre
Johannesburg

Our Issues, Our Drugs, Our Patients

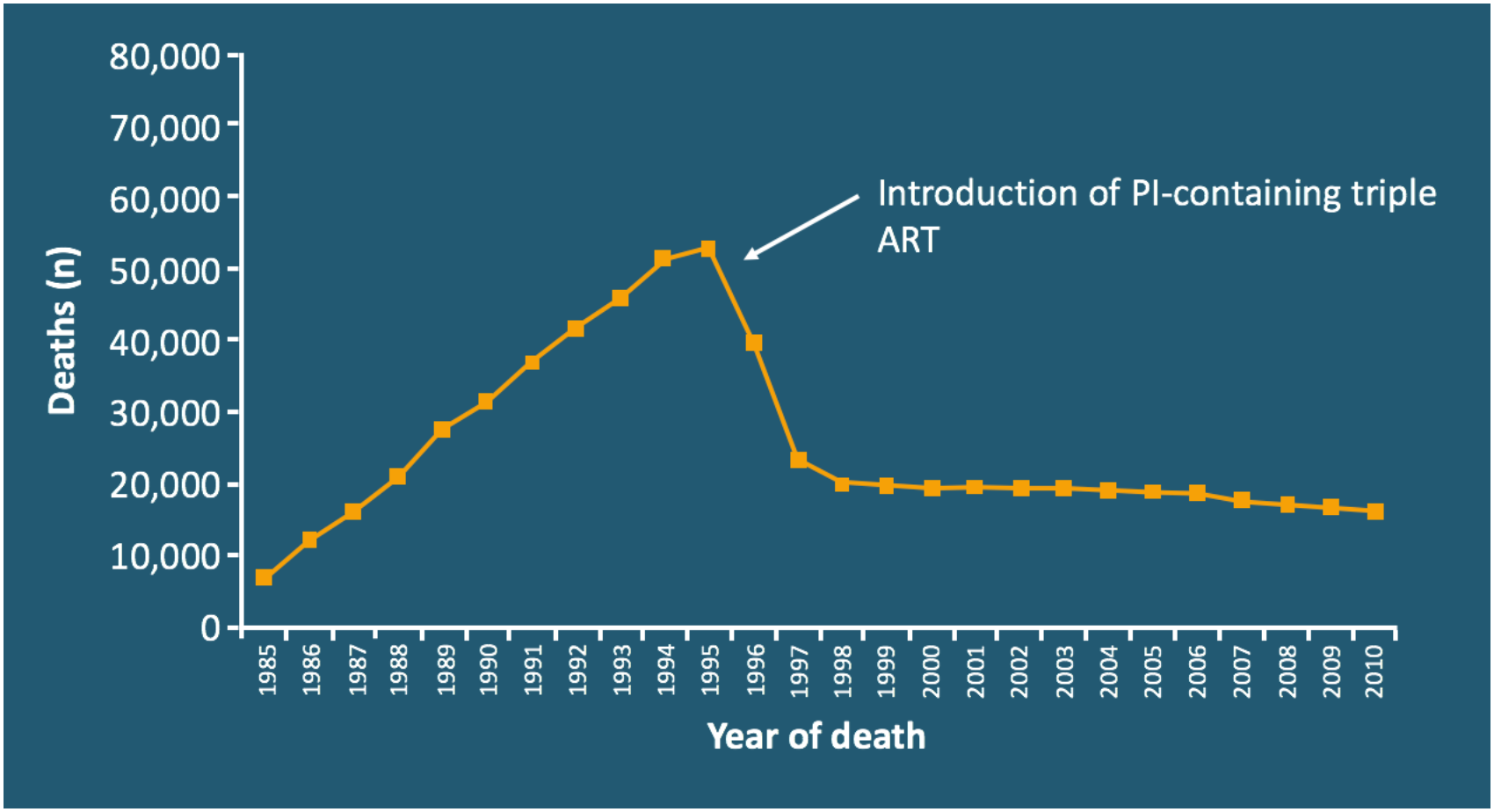
www.sahivsoc.org
www.sahivsoc2016.co.za

Drug toxicities: Safest PIs

Michelle Moorhouse

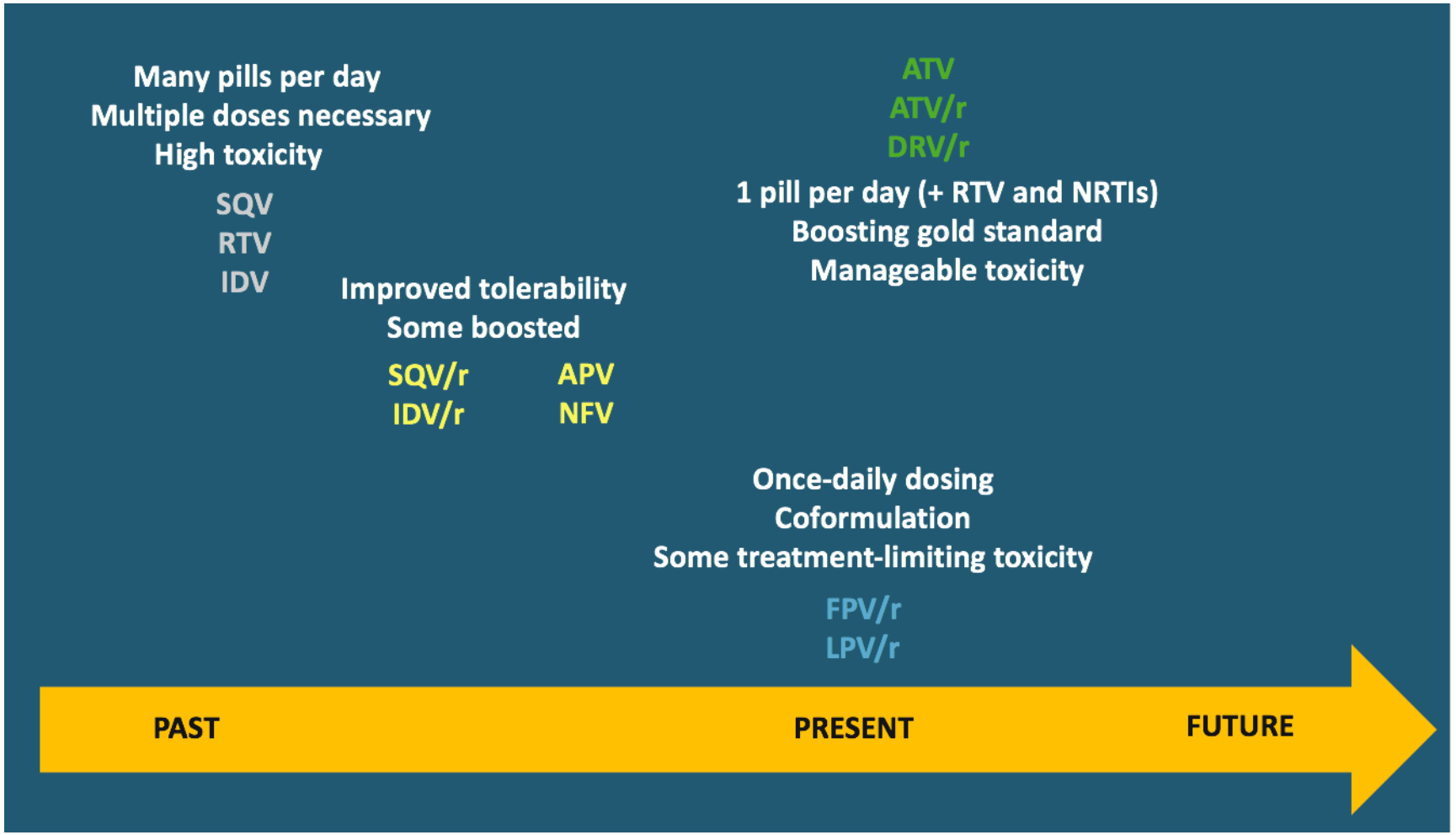
14 Apr 2016

Impact of PIs on AIDS mortality



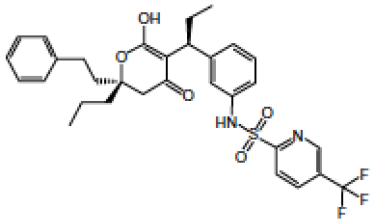
CDC.gov. Epidemiology of HIV infection.

Evolution of PIs

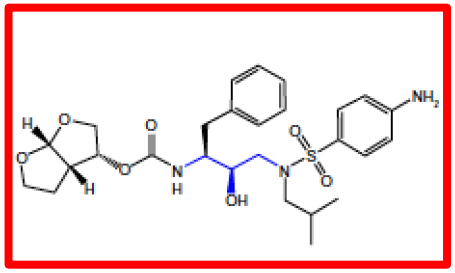


http://www.clinicaloptions.com/HIV/Treatment%20Updates/Boosted%20PIs/Interactive%20Virtual%20Presentation/Slideset.aspx

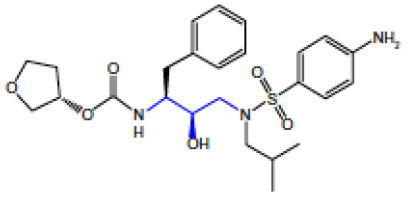
(FDA) Licensed PIs



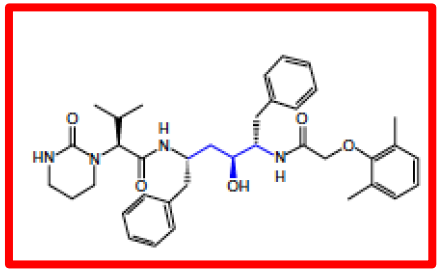
Tipranavir



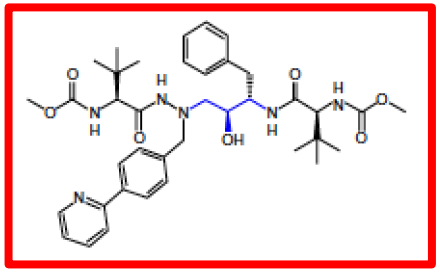
Darunavir



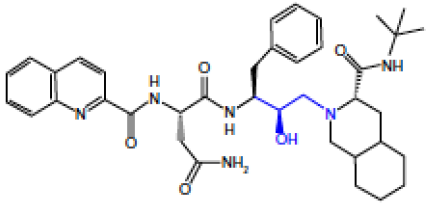
Amprenavir



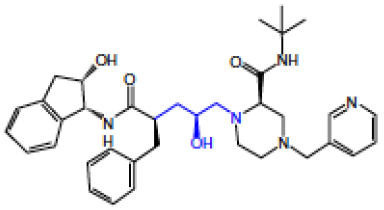
Lopinavir



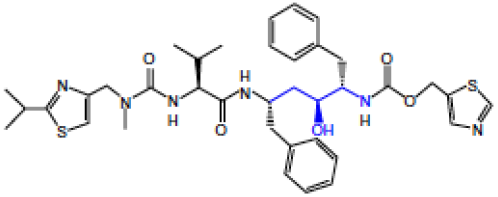
Atazanavir



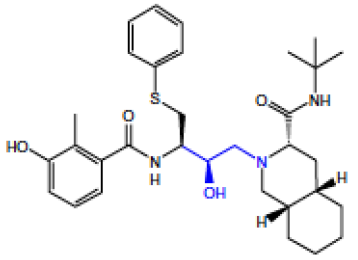
Saquinavir



Indinavir



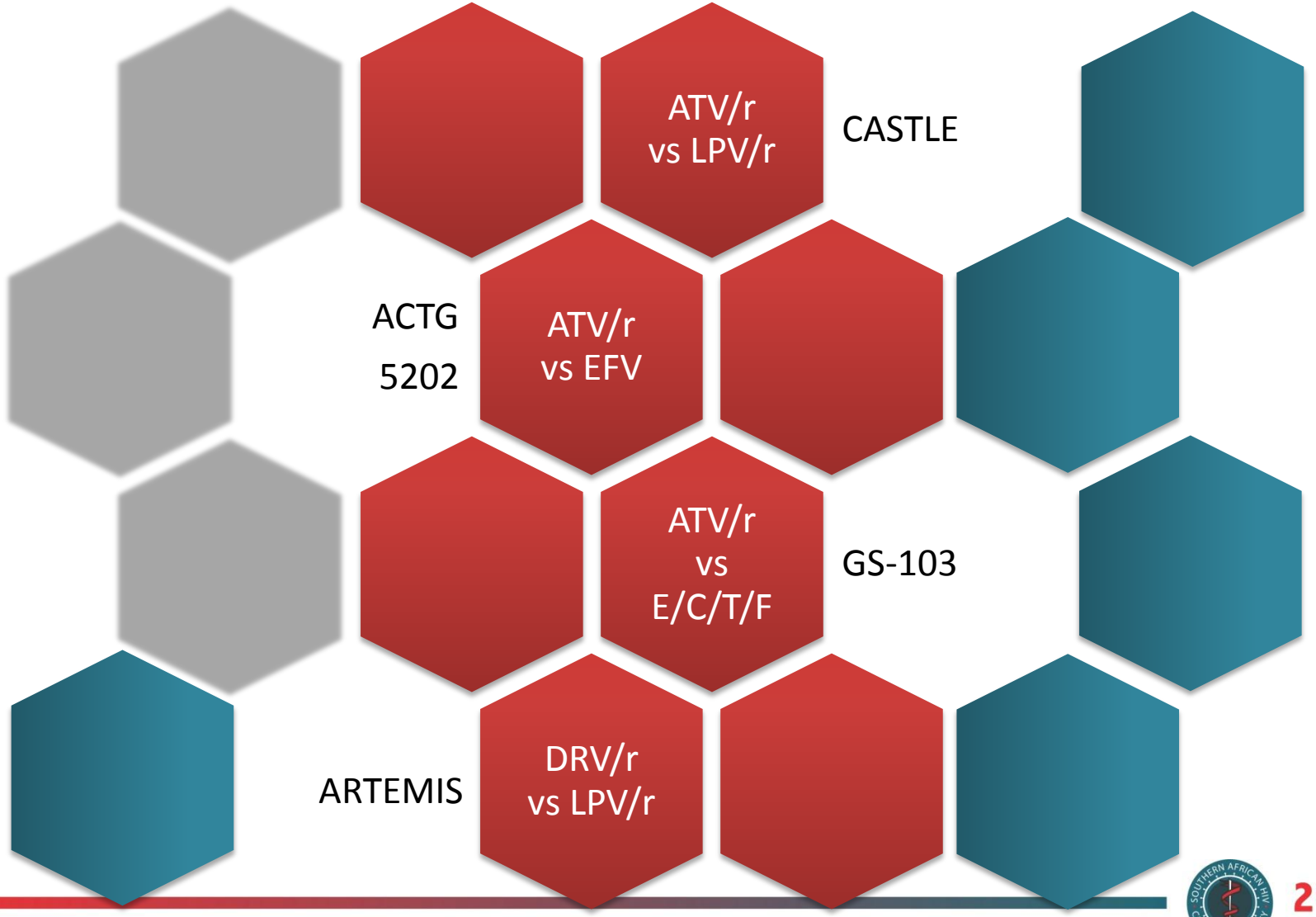
Ritonavir



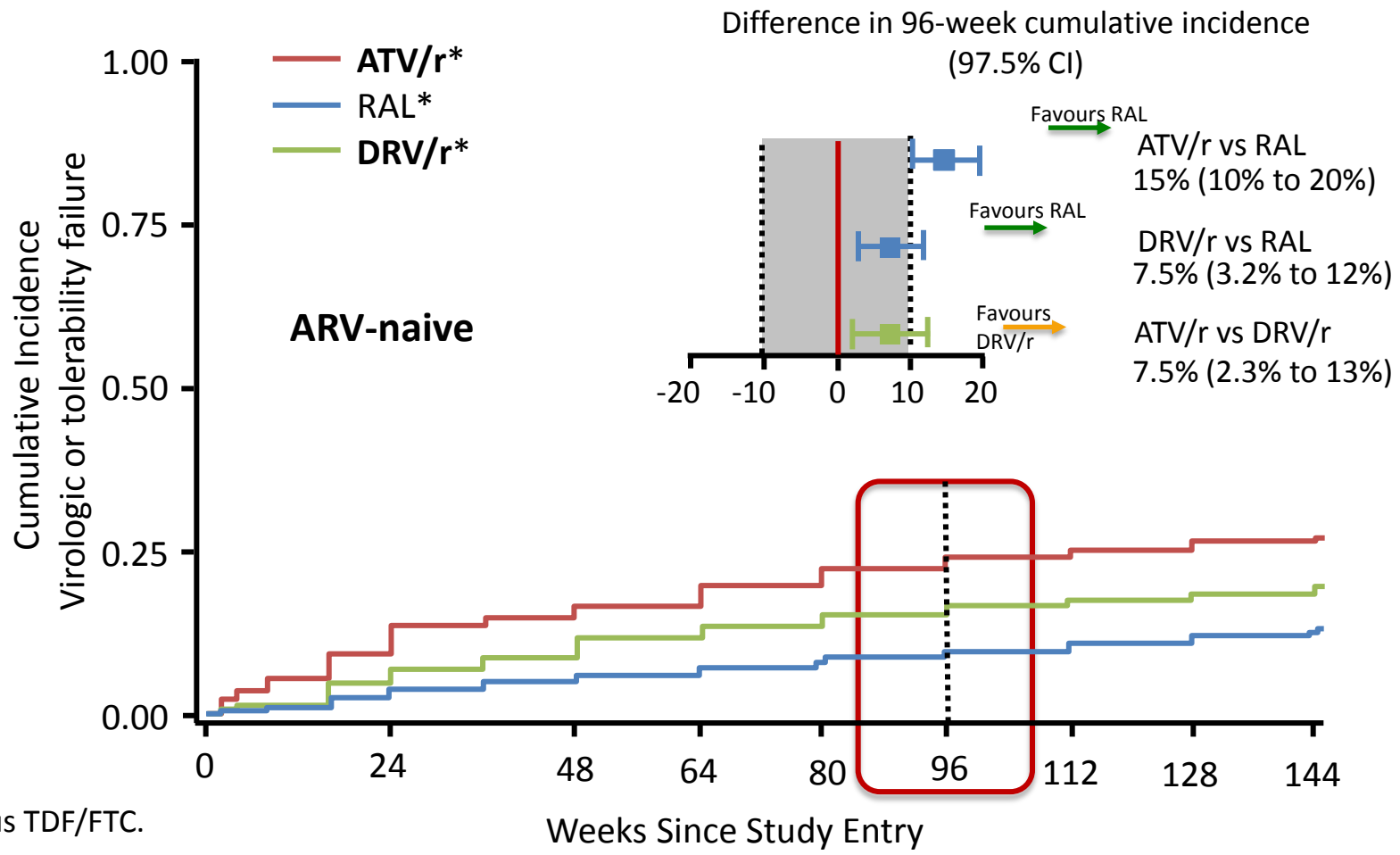
Nelfinavir

Can we talk about safety and ignore efficacy?

PIs work


ATV/r
vs LPV/r
CASTLE
ACTG
5202
ATV/r
vs EFV
ATV/r
vs
E/C/T/F
GS-103
DRV/r
vs LPV/r
ARTEMIS

Then came ACTG 5257



*Plus TDF/FTC.

Lennox JL, et al. Ann Intern Med. 2014;161:461-471.

Comparing preferred and alternative first-line regimens

GUIDELINES	NRTI BACKBONE			NNRTI			INSTI			PI		
	TDF/XTC	ABC/3TC	AZT/3TC	EFV	NVP	RPV	DTG	EVG	RAL	ATV	DRV	LPV
IAS (2014)												
DHHS (2015)												
EACS (2015)												
WHO (2015)												
SA NDoH												
SAHIVCS												

preferred

alternative

not recommended/ special situations

Safety issues with PIs

LPV/r

- GI upset
- Lipids
- Hepatitis
- Dysglycaemia

ATV/r

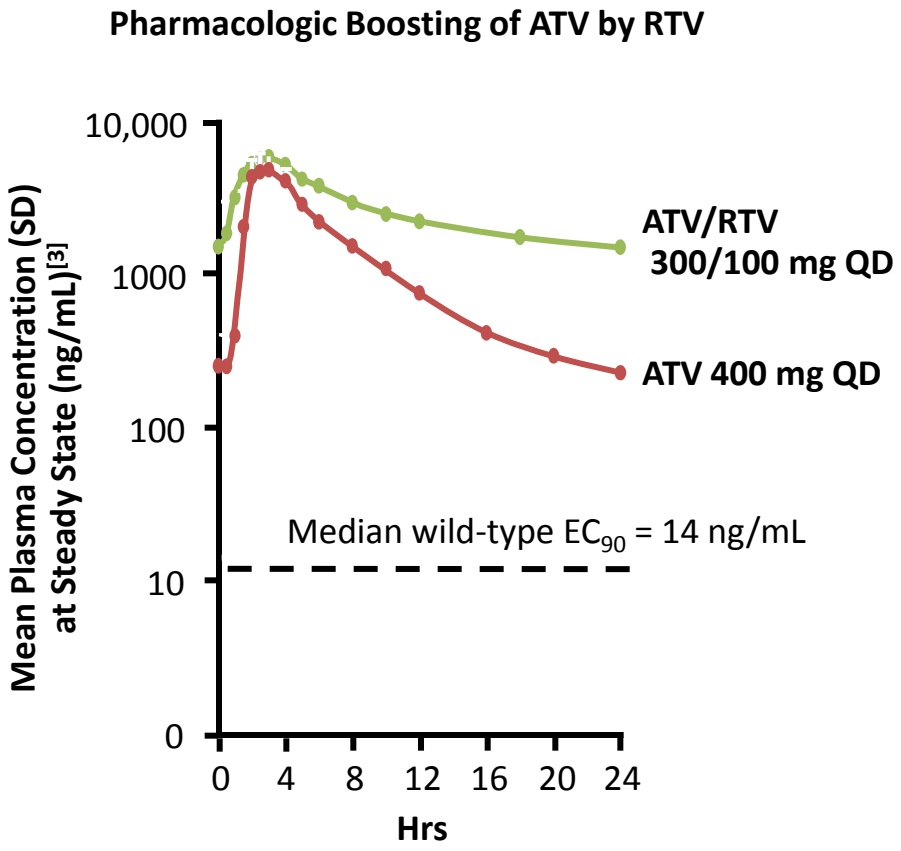
- Jaundice
- Lipids (low potential)
- Renal stones
- Hepatitis

DRV/r

- Rash
- GI upset
- Hepatitis

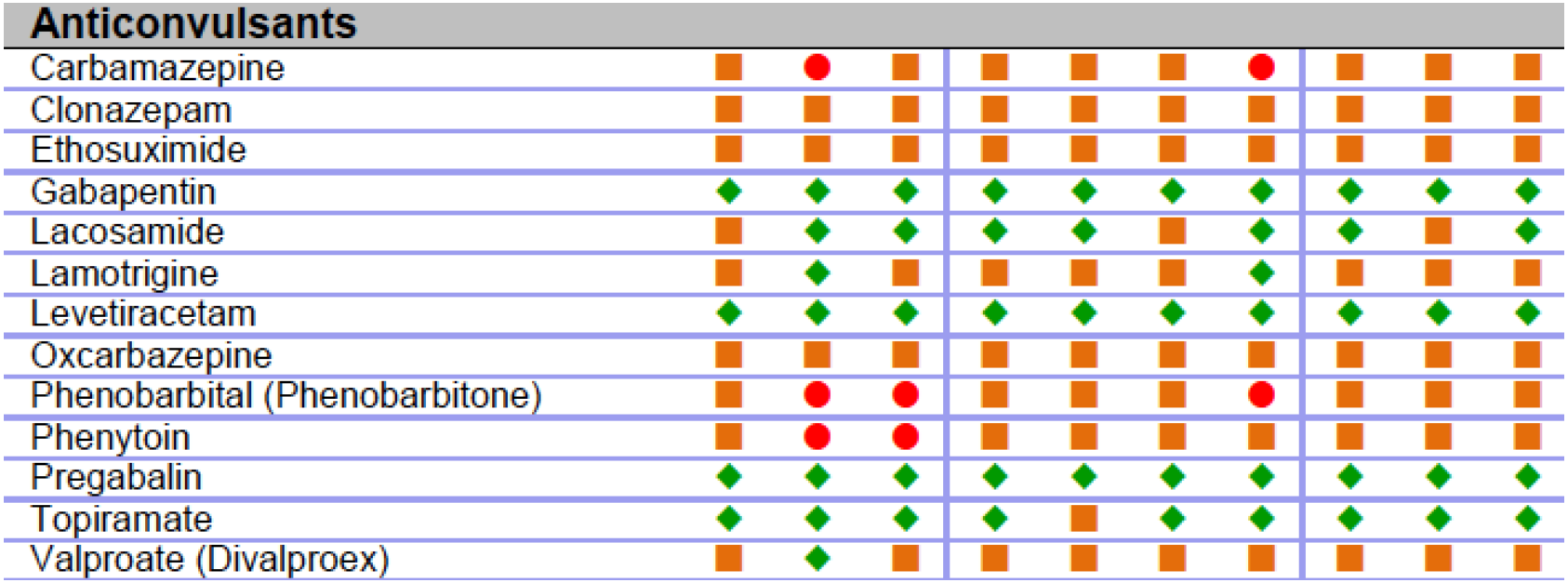
PIs require boosting

- PIs usually boosted with RTV
- RTV inhibits CYP3A4 in the liver, increasing PI exposure and t1/2[1]
- Less frequent dosing and lower daily dose
- RTV associated with **diarrhoea** and **nausea**, increased **lipids**, **drug** interactions[2]



1. Merry C, et al. AIDS 1997;11:F29-F33. 2. Ritonavir [package insert]. 3. Atazanavir [package insert].

Drug interactions



Anticonvulsants
Carbamazepine
Clonazepam
Ethosuximide
Gabapentin
Lacosamide
Lamotrigine
Levetiracetam
Oxcarbazepine
Phenobarbital (Phenobarbitone)
Phenytoin
Pregabalin
Topiramate
Valproate (Divalproex)

https://liverpool-web-production.s3.amazonaws.com/printable_charts/pdfs/000/000/019/original/PI_2016_Mar.pdf?1458223921

Drug interactions with RTV

Exposures Increase With RTV

- Maraviroc
- Antiarrhythmics
- Anticancer agents
- Anticonvulsants (some)
- Antidepressants (some)
- Beta-blockers
- Calcium channel blockers
- Colchicine
- Digoxin
- Erectile dysfunction drugs
- Glucocorticoids
- Methamphetamine
- Rifabutin
- Sedatives/hypnotics
- Statins (some)

Exposures Decrease With RTV

- Anticonvulsants (some)
- Antidepressants (some)
- Bupropion
- Ethinyl oestradiol
- Methadone
- Theophylline
- **Rifampicin**

Ritonavir [package insert].

Interactions with TB medications

	LPV/r	ATV/r	DRV/r
Rifampicin			
Isoniazid			
Pyrazinamide			
Ethambutol			

https://liverpool-web-production.s3.amazonaws.com/treatment_selectors/pdfs/000/000/012/original/TS_TB_2016_Mar.pdf?1458123010

What about pregnancy?

Guideline Categorization	NRTI	NNRTI	PI	INSTI
Preferred	ABC/3TC* TDF/FTC or 3TC† ZDV/3TC‡	EFV§	**LPV/RTV¶** **ATV/RTV**	
Alternative		NVP‖	**DRV/RTV** SQV/RTV**	RAL††
Insufficient data		RPV	FPV/RTV	DTG EVG/COBI
Not recommended‡‡	ABC/3TC/ZDV d4T ddl	ETR	IDV/RTV NFV RTV TPV	

DHHS Perinatal Guidelines. March 2014.

What about pregnancy?

Guideline Categorization	NRTI	NNRTI	PI	INSTI
Preferred	ABC/3TC* TDF/FTC or 3TC† ZDV/3TC‡	EFV§	**LPV/RTV¶** **ATV/RTV**	
Alternative		NVP‖	**DRV/RTV** SQV/RTV**	RAL††
Insufficient data				DTG
Not recommended‡‡	ABC/3TC/ZDV d4T ddI			

Drug	Defects/Live Births, n (> 200 First Trimester Exposures)	Prevalence, % (95% CI)
PIs		
• **ATV**	**19/878**	**2.2 (1.3-3.4)**
• **DRV**	**5/212**	**2.4 (0.8-5.4)**
• **LPV**	**26/1125**	**2.3 (1.5-3.4)**
• NFV	47/1211	3.9 (2.9-5.1)
• RTV	52/2260	2.3 (1.7-3.0)

DHHS Perinatal Guidelines. March 2014

Antiretroviral Pregnancy Registry. Interim Report. December 2013.

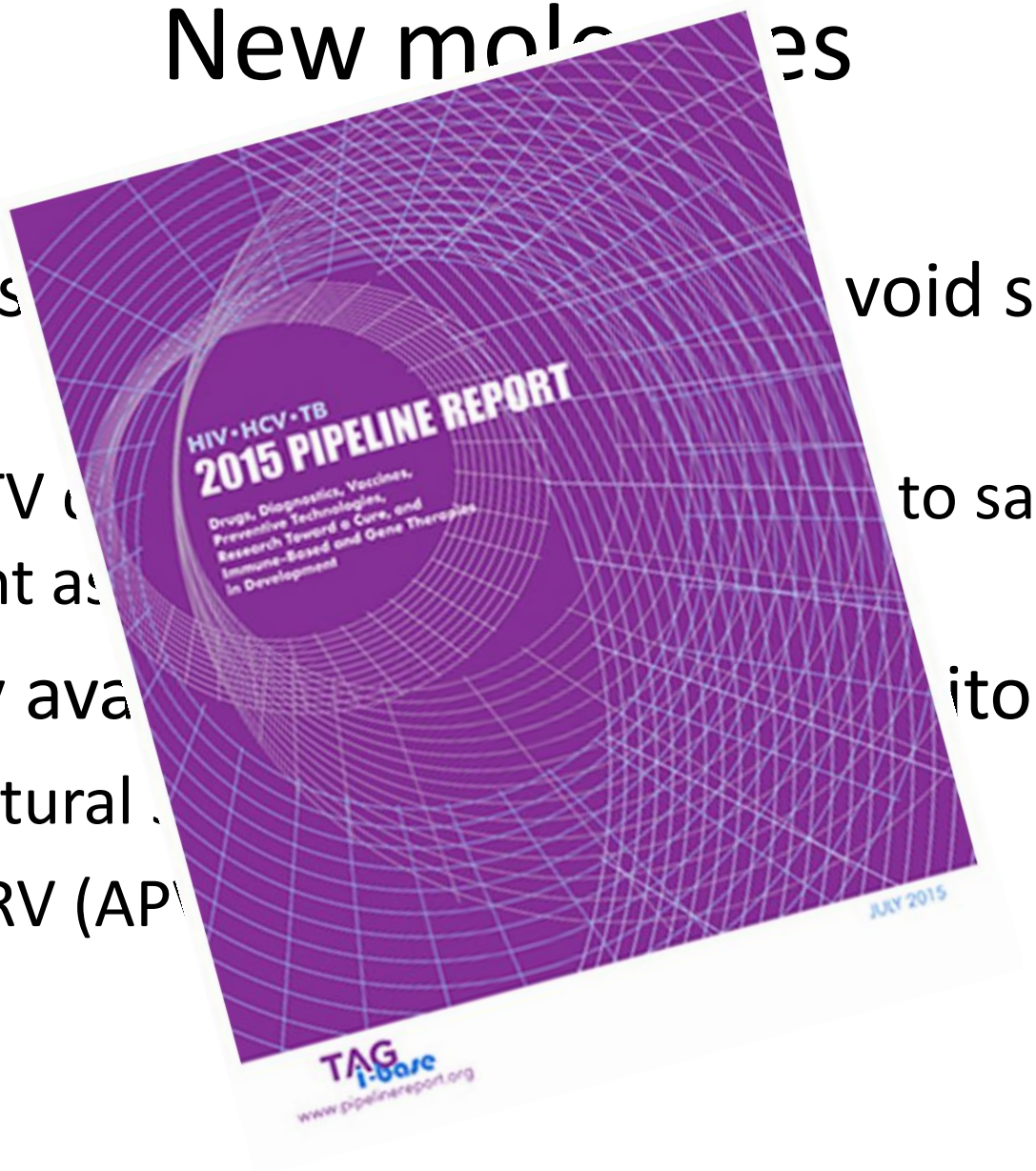
HOW DO WE MAKE PROTEASE INHIBITORS SAFER?

New molecules

- Optimise chemical structure to avoid side effects
  - Eg ATV does not cause dylipidaemia to same extent as other PIs
- Modify available HIV protease inhibitors
  - Structural similarity
  - Eg DRV (APV); LPV (RTV)

New mole es

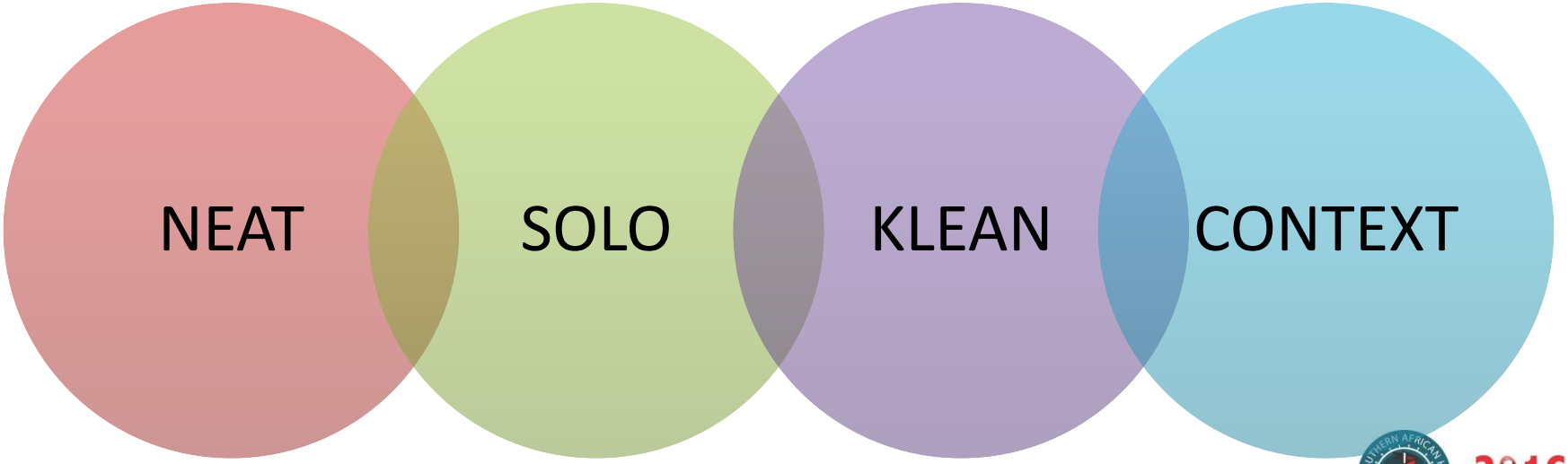
- Optimis void side effects
  - Eg ATV (to same extent as
- Modify ava itors
  - Structural .
  - Eg DRV (AP



Prodrugs of current PIs

FosAPV is phosphate ester prodrug of APV

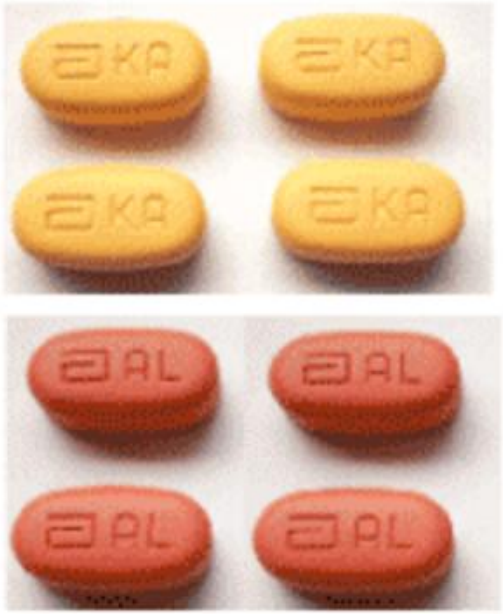
- fosAPV metabolised to APV
- Increases duration of action
- Improved the safety profile (KLEAN)



New formulations of existing PIs

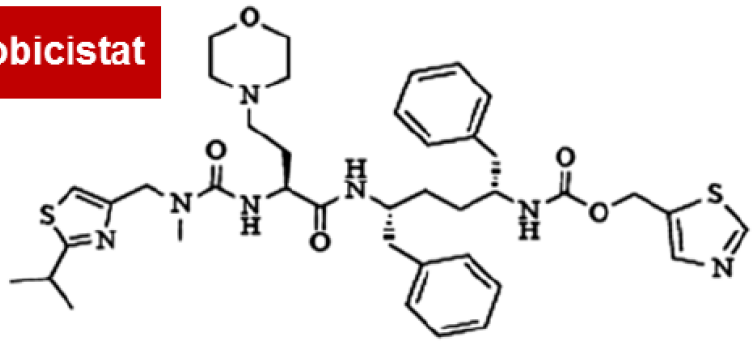
Kaletra SGCs

Kaletra tablets

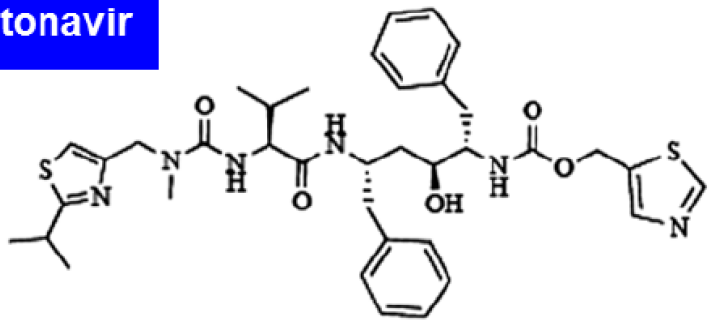


New PK boosters

Cobicistat



Ritonavir



	Cobicistat	Ritonavir
HIV replication	No activity	PI activity
CYP 3A4	Potent inhibitor	Potent inhibitor
Other CYPs	CYP 2D6, minimal effect CYP 2B6	CYP 2D6, CYP 2B6
P-gp	Minimal	Weak to moderate
Glucuronidation	Low	Inducer
Effect on **lipids**	Minimal	Moderate
Renal transporters	**Creatinine** effect	

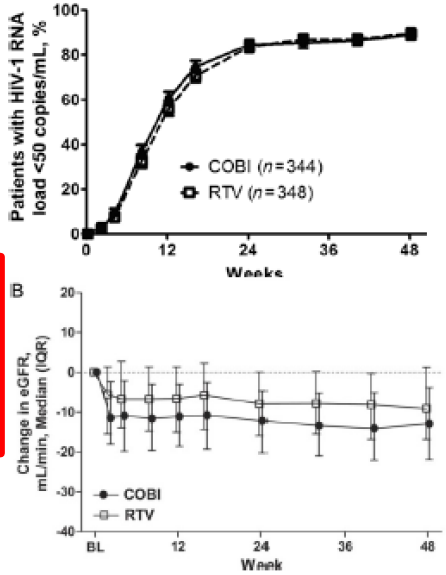
Cobicistat versus ritonavir

ATV

- ATVc (300/150) and ATVr (300/100) were bioequivalent
- RCT (N=692) powered for non-inferiority showed comparable efficacy through 48w

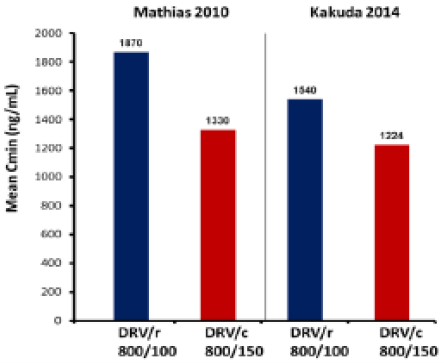
  Significant (but modest) differences in effect on eGFR by w8 (P<0.001)
  No differences in other renal adverse events, hyperbilirubinaemia, nausea

Deeks Drugs 2014 74:195–206
Gallant J Infect Dis. 2013



DRV

- DRV AUC and Cmax were bioequivalent
- DRV Cmin 25-30% lower (DRV/c 800/150 OD vs DRV/r 800/100 OD) - not considered clinically relevant.
- A non-inferiority trial has not been conducted.



Kakuda, J Clin Pharm 2014

Drug interactions with cobicistat

Exposure Increased With COBI

- Antacids
- Antiarrhythmics
- Benzodiazepines
- Beta-blockers
- Calcium channel blockers
- Erectile dysfunction drugs
- Inhaled/injectable corticosteroids
- OCPs (norgestimate)
- Statins

Increase COBI Exposure

- Azole antifungals
- Clarithromycin

Decrease COBI Exposure

- Rifabutin
- Carbamazepine
- Phenytoin

DHHS Adult Guidelines. May 2014.

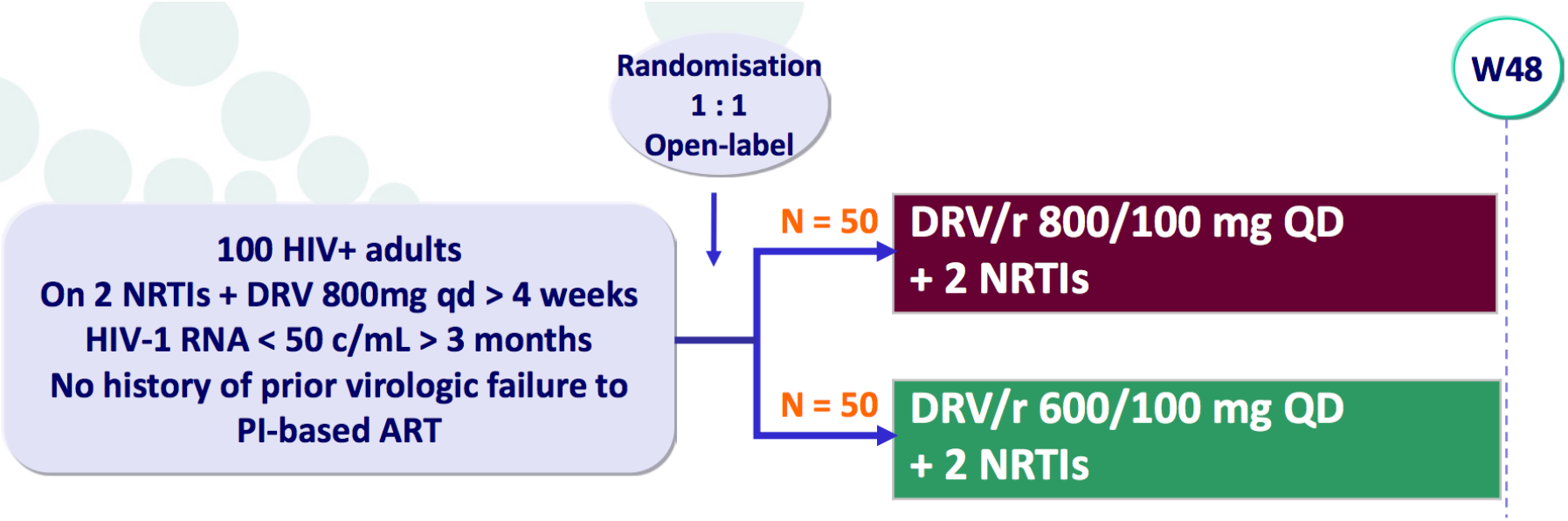
Use existing PIs in different ways: Lower doses

Atazanavir/ritonavir 200/100 mg is non-inferior to atazanavir/ritonavir 300/100 mg in virologic suppressed HIV-infected Thai adults: a multicentre, randomized, open-label trial: LASA

Conclusions: Higher dose ATV was associated with higher rates of treatment discontinuation.

ias2015.org/Abstract/AbstractDetail/661

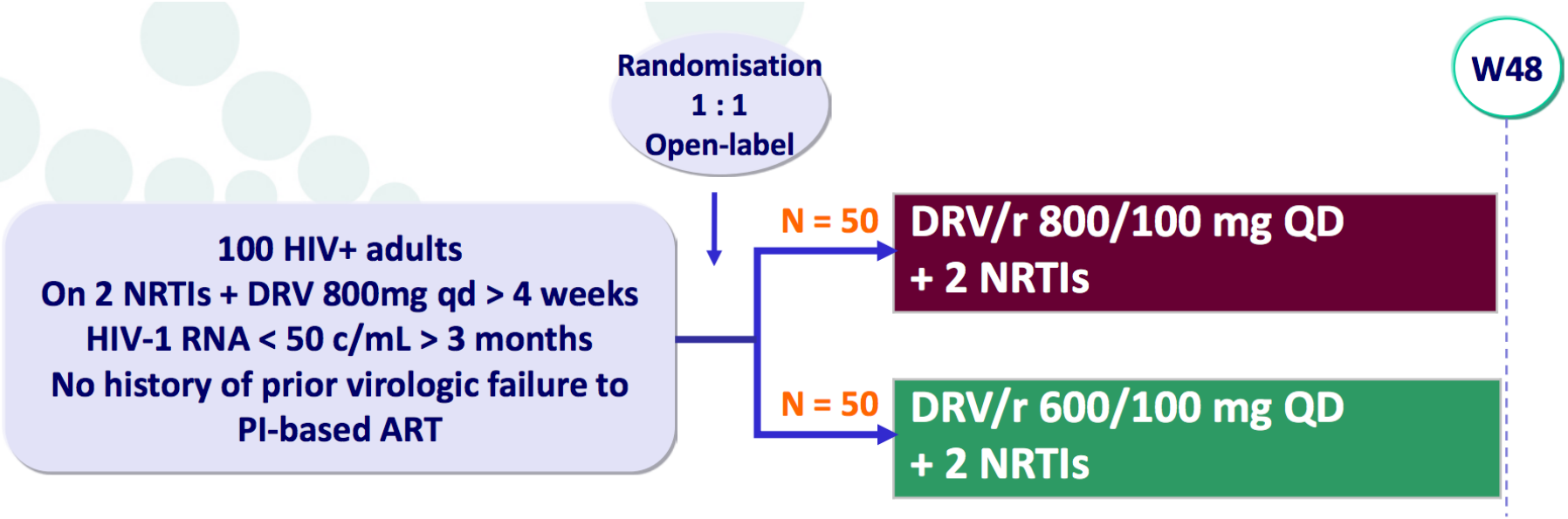
Lower doses



Reduced Darunavir Dose Is as Effective in Maintaining HIV Suppression as the Standard Dose in Virologically Suppressed HIV-Infected Patients. The DRV600 Study.

1. Molto J, Valle M, Ferrer E, et al. 15th Int Workshop on Clin Pharm of HIV and Hep Therapy. 19- 21 May 2014. Washington, DC. Abstract O_02.

Lower doses



Drug-related AEs	DRV 800 n=12	DRV 600 n=7
Gastrointestinal disturbances	6	4
Dislipidemia	5	-
Other <5%	1	3

1. Molto J, Valle M, Ferrer E, et al. 15th Int Workshop on Clin Pharm of HIV and Hep Therapy. 19- 21 May 2014. Washington, DC. Abstract O_02.

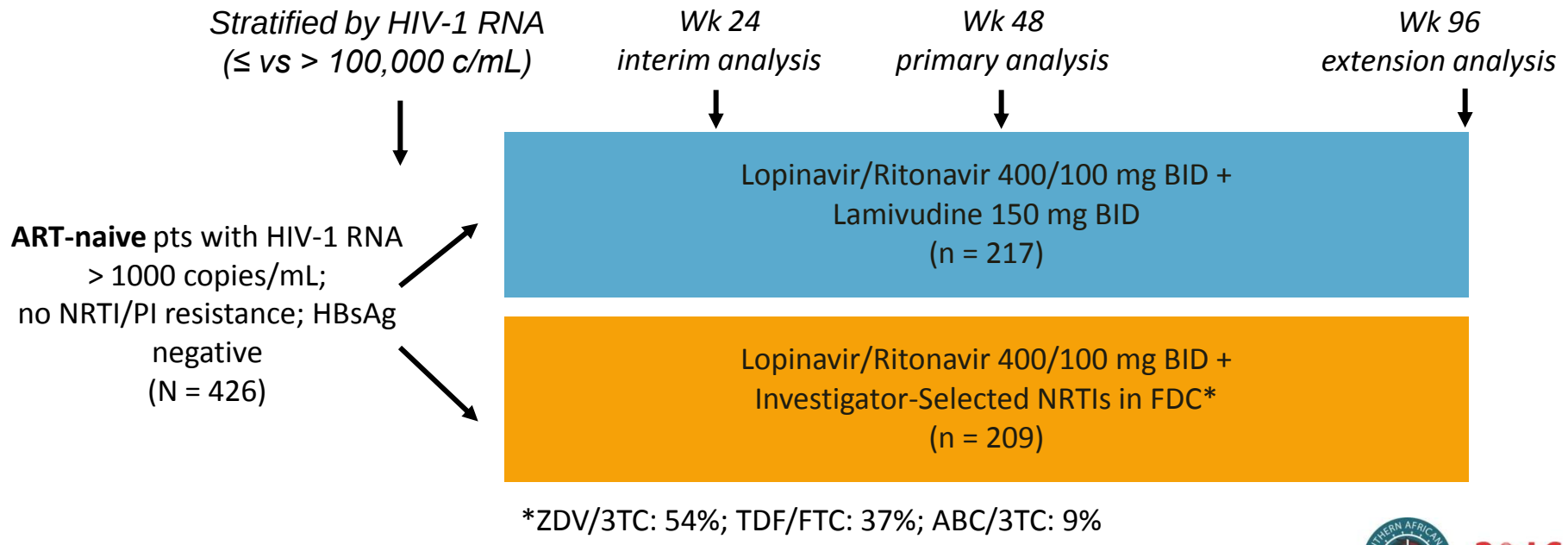
Different combinations Nuc-sparing or "nuc-lite" regimens

Regimen	Results
DRV/r + **RAL** (ACTG 5262)[1]	Poor performance at high VL
DRV/r + **RAL** (NEAT)[2]	Less effective at high VL, low CD4
DRV/r + **MVC** (MODERN)[3]	Less effective than standard ART
ATV/r + **RAL** (HARNESS – switch)[4]	Less effective than standard ART
LPV/r + **RAL** (PROGRESS)[5]	Small study; few pts with high VL
LPV/r + **EFV** (ACTG 5142)[6]	Poorly tolerated but effective
LPV/r + **3TC** (GARDEL)[7]	As effective as standard ART
LPV/r + **XTC** (OLE – switch)[8]	As effective as standard ART
ATV/r + **3TC** (SALT – switch)[9]	As effective as standard ART

1. Taiwo B, et al. AIDS. 2011;25:2113-2122. 2. Raffi, et al. CROI 2014. Abstract 84LB. 3. Stellbrink HJ, et al. IAD 2014. Abstract MOAB0101. 4. Van Lunzen J, et al. IAC 2014. Abstract A-641-0126-11307. 5. Reynes J, et al. AIDS Res Hum Retroviruses. 2013;29:256-265. 6. Daar ES, et al. Ann Intern Med. 2011;154:445-456. 7. Cahn P, et al. Lancet Infect Dis. 2014;14:572-580. 8. Gatell J, et al. AIDS 2014. Abstract LBPE17. 9. Perez-Molina JA, et al. IAC 2014. Abstract LBPE18.

GARDEL: Dual ART vs Triple ART

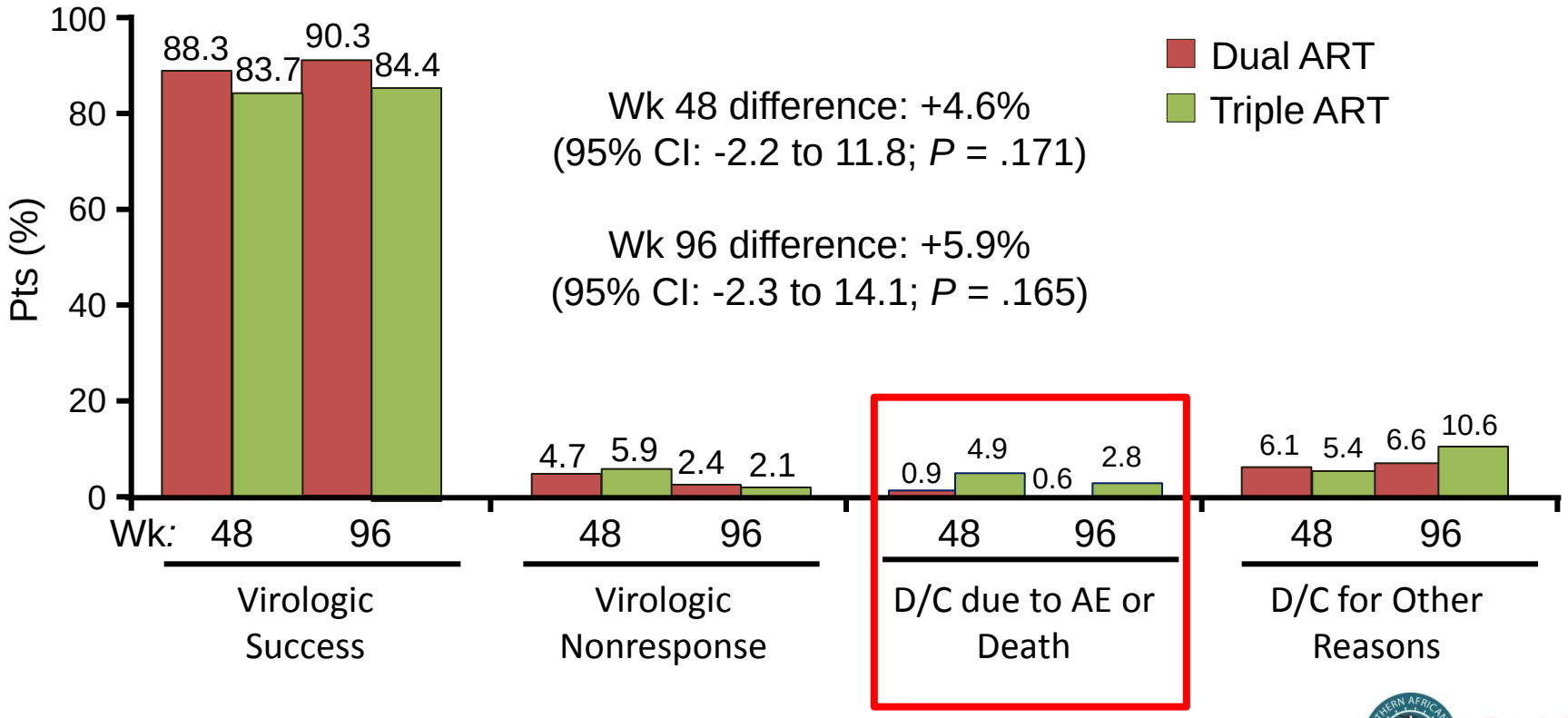
- Randomised, open-label phase III noninferiority trial
  - Primary endpoint: HIV-1 RNA < 50 c/mL (ITT-e, FDA snapshot analysis)
- Pts with virologic response at Week 48 offered extension to Week 96



Cahn P, et al. EACS 2015. Abstract 961.

GARDEL: Dual ART Noninferior to Triple ART at Wk 48 and Wk 96

- Safety and tolerability also similar between treatment arms



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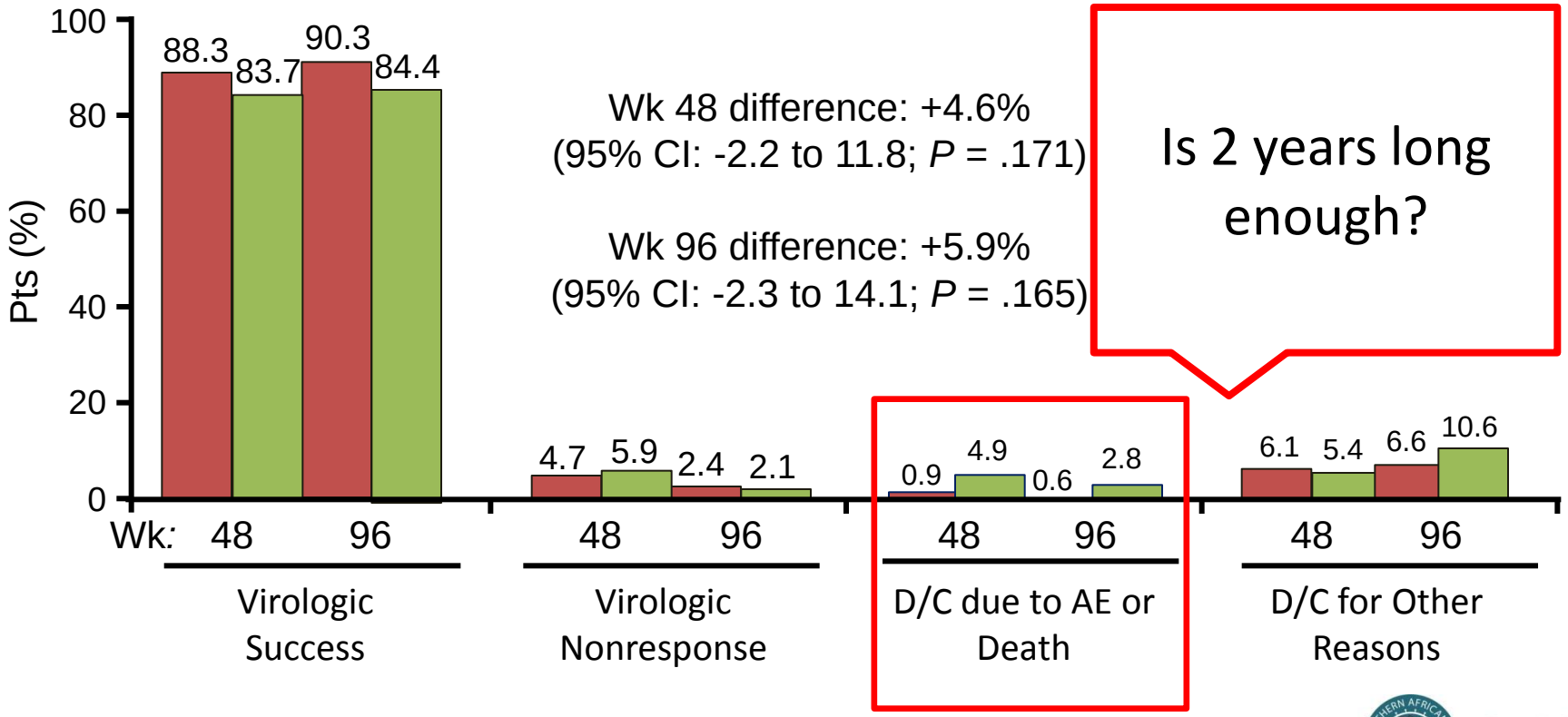

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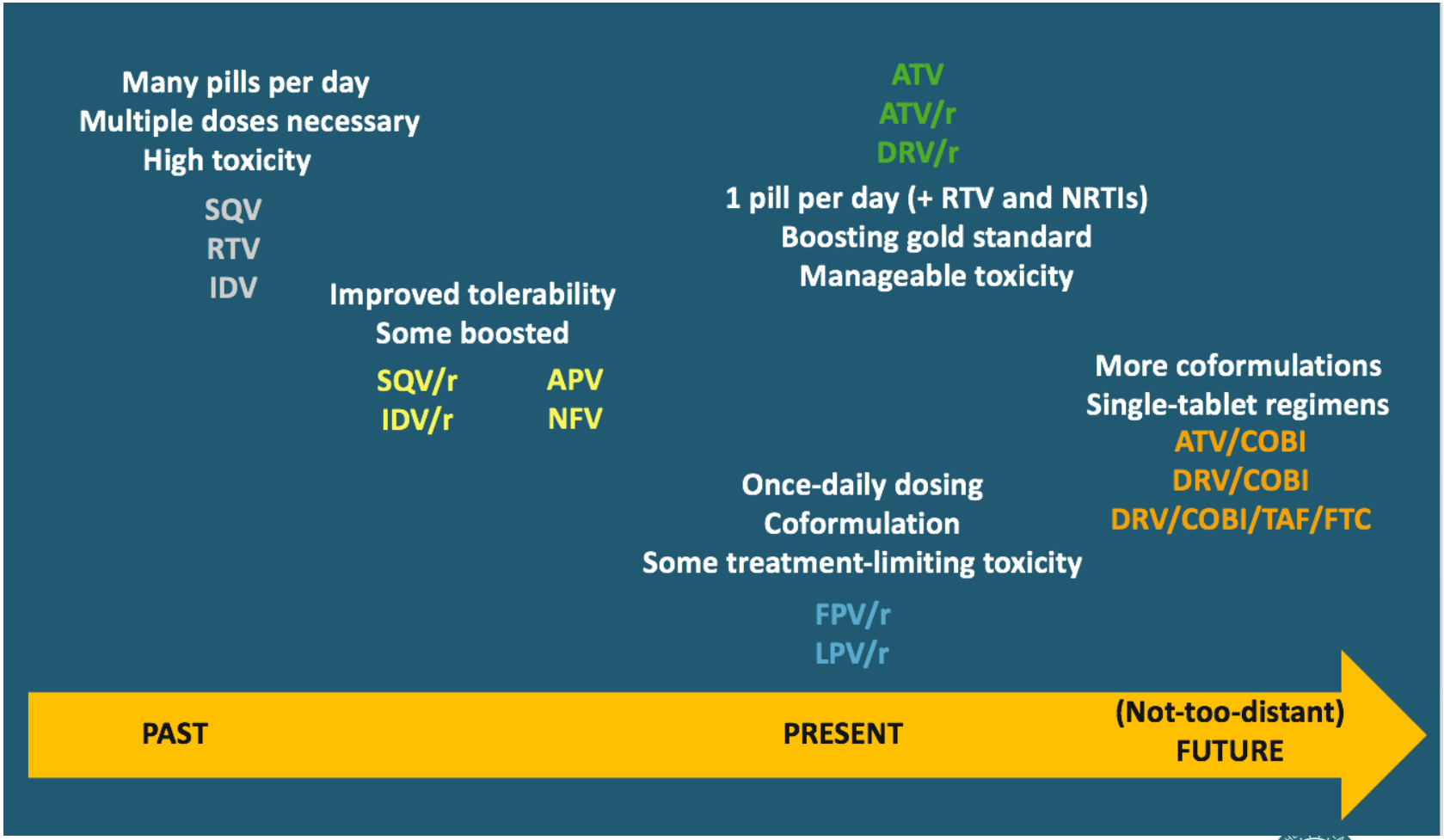
Evolution of PIs



http://www.clinicaloptions.com/HIV/Treatment%20Updates/Boosted%20PIs/Interactive%20Virtual%20Presentation/Slideset.aspx

In summary

- Not much new in PIs
- Look at using what we have better
  - Dosing
  - Combinations
  - Sequencing

Acknowledgements

- Francois Venter
- Saye Khoo
- Polly Clayden
- CCO

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