Kirby Institute

ASHM ART guidelines session

Why HIV integrase inhibitors (InSTIs) are first-line agents of choice

ASHM Conference Brisbane 2015

Mark Boyd MD, FRACP
Senior NHMRC Research Fellow
The Kirby Institute
for infection and immunity in society
UNSW Australia

Why InSTIs are first-line agents of choice

Declarations

- AbbVie
- Bristol-Myers Squibb
- Boehringer Ingelheim
- Gilead
- Janssen-Cilag
- Merck
- ViiV Healthcare

Why InSTIs are first-line agents of choice

Outline

- Pivotal (blinded, placebo-controlled) InSTI studies
- Open label studies

Why InSTIs are first-line agents of choice

Outline

- Pivotal (blinded, placebo-controlled) InSTI studies
- Open label studies

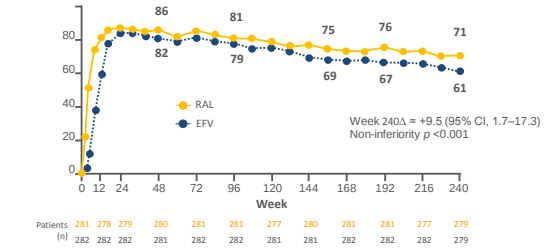
Why are InSTIs first-line agents of choice

Pivotal (blinded, placebo-controlled) InSTI studies

- STARTMRK: RAL versus EFV
  Rockstroh JK *et al. J Acquir Immune Defic Syndr* 2013;63:77–85
  Phase III, non-inferiority trial, n=563
- GS-US-236-0102/0103: EVG versus EFV and ATV/r
  Sax PE et al. *Lancet* 2012;379:2439–2448. *Randomised, double-blind trial, n=700*
  DeJesus E et al. *Lancet* 2012;379:2429-38. *Randomised, double-blind trial, n=700*
- SINGLE: DTG versus EFV
  Walmsley SL *et al. N Engl J Med* 2013;369:1807–1818
  Randomised, double-blind phase III trial, n=833
- SPRING-2: DTG versus RAL
  Raffi F *et al. Lancet* 2013;381:735–743
  Randomised, double-blind, active controlled, non-inferiority trial, n=822

STARTMRK: EFV versus RAL in ART-naïve PLH

- Double-blind Phase III trial of EFV versus RAL, each with TDF/FTC, in ART-naive participants

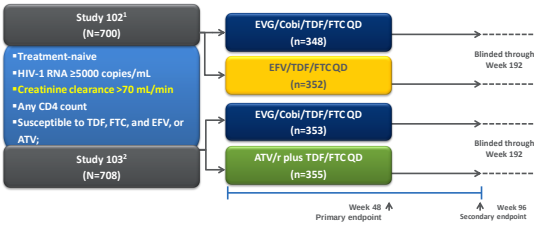


CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; VF, virological failure; VL, viral load.

Rockstroh JK *et al. J Acquir Immune Defic Syndr* 2013;63:77–85; Phase III, non-inferiority trial, N=563.

GS-US-236-0102/-0103: EVG/cobi versus EFV or ATV/r, all with TDF/FTC in ART-naïve PLH

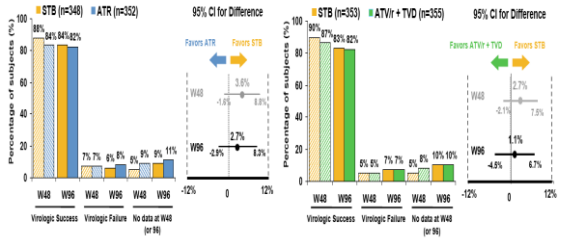
- Randomized, double-blind, active-controlled Phase III studies
- Primary endpoint: HIV-1 RNA < 50 copies/mL at Week 48



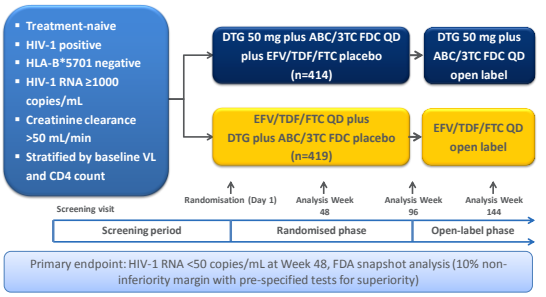
ATV, atazanavir; Cobi, cobicistat; FTC, emtricitabine; r, ritonavir-boosted; QD, once daily; TDF, tenofovir disoproxil fumarate

1. Wohl DA *et al. J Acquir Immune Defic Syndr.* 2014;65:e118–e120. Phase III, randomized, double-blind, active-controlled trial, N= 700.
2. Clumeck N *et al. J Acquir Immune Defic Syndr.* 2014;65:e121–e124. Phase III, randomized, double-blind, active-controlled trial, N= 708.

GS-US-236-102/-103: EVG/Cobi non-inferior to EFV and ATV/r, all with TDF/FTC through W96



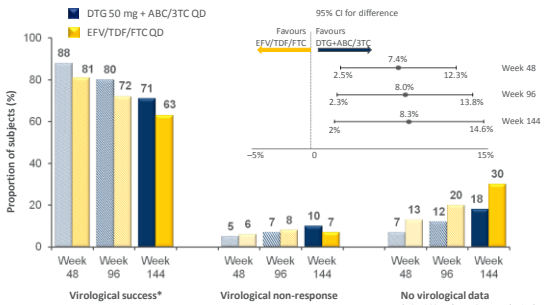
SINGLE: study design



3TC, lamivudine; ABC, abacavir; FDC, fixed-dose combination; HLA-B*5701, human leukocyte antigen, class I, B.

Walmsley SL *et al. N Engl J Med* 2013;369:1807–1818; Randomised, double-blind Phase III trial, N=833.

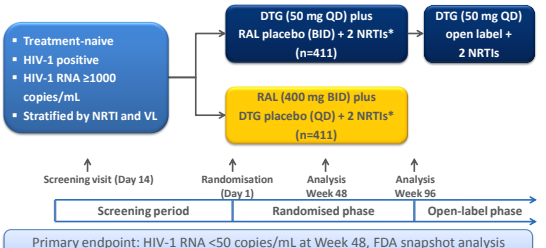
SINGLE: efficacy snapshot at Weeks 48, 96, 144



*HIV-1 RNA <50 copies/mL

Pappa K *et al. ICAAC* 2014:abstr H-647a; Randomised, double-blind Phase III trial, N= 833.

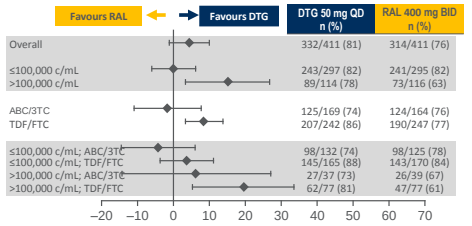
SPRING-2: study design



*Investigator's selection of ABC/3TC or TDF/FTC. NRTI, nucleoside reverse transcriptase inhibitors.

Raffi F *et al. Lancet* 2013;381:735–743; Randomised, double-blind, active-controlled, non-inferiority trial, N=822.

SPRING-2: virological response by baseline viral load and N(t)RTI backbone at week 96



- Proportion of DTG subjects achieving HIV-1 RNA <50 c/mL more pronounced in subjects with high baseline viral load, and in subjects receiving TDF/FTC
  - subject numbers were small and confidence intervals wide and overlapping

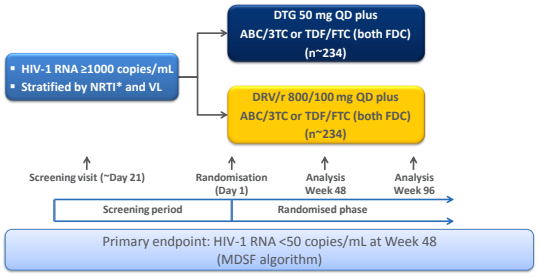
Raffi F, et al. Lancet Infect Dis 2013;13:927–35
Raffi F, et al. IAS 2013. Abstract TULBPE17

Why InSTIs are first-line agents of choice

Outline

- Pivotal (blinded, placebo-controlled) InSTI studies
- Open label studies

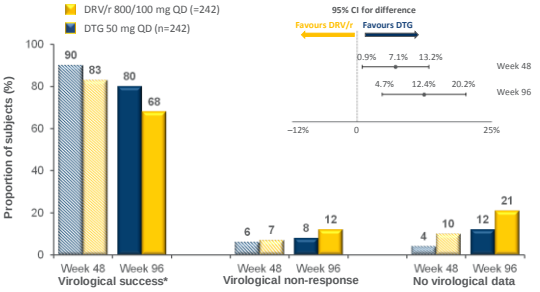
FLAMINGO: phase III trial in ART-naïve PLH



*Stratified by HIV-1 RNA >or ≤100,000 copies/mL and ABC/3TC or TDF/FTC. MDSF, missing, switch or discontinuation = failure.

Molina JM *et al. J Int AIDS Soc* 2014;17:19490; Multicentre, randomised, open-label, Phase IIb, non-inferiority study; N=484.

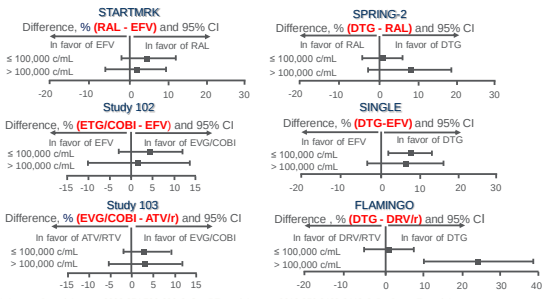
FLAMINGO: efficacy snapshot at W48 & W96



*HIV-1 RNA <50 copies/mL.

Molina JM *et al. HIV Drug Therapy* Glasgow 2014:abstr O153; Multicentre, randomised, open-label, Phase IIb, non inferiority study; N=484.

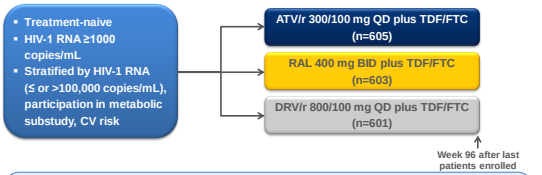
Why InSTIs are first-line agents of choice



1. Lennox J, et al. Lancet. 2009;374:796-806. 2. Sax PE, et al. Lancet. 2012;379:2439-2448. 3. De Jesus E, et al. Lancet. 2012;379:2429-2438. 4. Brinson C, et al. CROI 2013. Abstract 554. 5. Feinberg J, et al. ICAAC 2013. Abstract 1464a.

ACTG 5257: study design

- Open-label ATV/r versus DRV/r versus RAL as first-line ART (N=1809)



- Primary endpoints:
  - VF: time to HIV-1 RNA >1000 copies/mL (at Week 16 or before Week 24) or >200 copies/mL (at or after Week 24)
  - Tolerability failure: time to discontinuation of randomised component for toxicity
- Composite endpoint: the earlier occurrence of either VF or tolerability failure in a given participant
- Switch of regimens allowed for tolerability

BID, twice daily; CV, cardiovascular; DRV, darunavir.

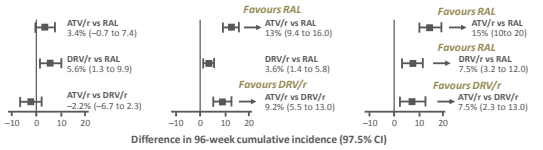
Lennox JL *et al. Ann Intern Med* 2014;161:461–471; Randomised (1:1:1), open-label Phase III study, N=1809.

ACTG 5257: primary endpoint analyses at W96

VF
- Regimens equivalent in time to VF

Tolerability failure
- Significantly greater incidence of treatment failure with ATV/r vs RAL or DRV/r
  - *in part due to high proportion of patients with hyperbilirubinemia*

Composite endpoint
- RAL superior to either boosted-PI
- DRV/r superior to ATV/r



Lennox JL *et al. Ann Intern Med* 2014;161:461–471; Randomised (1:1:1), open-label, phase III study, n=1809.

Emergent resistance in Phase 3 trials in ART naive

INSTI	Study	Resistance analysis population, n (%)	INSTI mutations	N(t)RTI Mutations
RAL	STARTMRK (n=279)[a]	9 (3.2)	4 (1.4)	3 (1.1)
	QDMRK (n=389)[b]	16 (4.1)	2 (0.5)	6 (1.5)
EVG	102 (n=350)[c]	14 (4)	7 (2)	8 (2.3)
	103 (n=353)[d]	12 (3.4)	4 (1.1)	4 (1.1)
DTG	SPRING-2 (n=411)[e]	20 (4.9)	0	0
	SINGLE (n=414)[f]	18 (4.3)	0	0
	FLAMINGO (n=234)[g]	2 (0.8)	0	0

[a] Multicentre, double-blind randomised controlled trial, N=566.
[b] Phase III, randomised, active-controlled, non-inferiority trial, N=775.
[c] Phase III, randomised, double-blind trial, N=700.
[d] Phase III, randomised, double-blind, non-inferiority trial, N=1017.
[e] Randomised, double-blind, non-inferiority study, N=411.
[f] Phase III, randomised, double-blind trial, N=833.
[g] Phase IIIb, randomised, open-label study, N=484.

* Not based on head-to-head comparisons.

White KL *et al. Viruses* 2014;6:2858–2879.

Selected DDIs of InSTIs

Agent	Potential DDIs
RAL[1]	▪ metabolized by UGT1A ▪ ATV increases RAL concentrations; dose adjustment not recommended ▪ avoid aluminum- and/or magnesium-containing antacids ▪ rifampin decreases RAL levels; double RAL dose if co-administered with rifampin
EVG/Cobi[2]	▪ metabolized by CYP3A, CYP2D6 ▪ cobicistat increases levels of drugs metabolized by CYP3A ▪ separate dosing with aluminum- and/or magnesium-containing antacids ▪ not recommended for use with rifamycins
DTG[3]	▪ metabolized by UGT1A, with contribution from CYP3A ▪ avoid use with etravirine unless co-administered with boosted PI; avoid dosing with nevirapine ▪ separate dosing with aluminum- and/or magnesium-containing antacids ▪ DTG may increase metformin concentrations; metformin dose adjustment may be needed; monitor clinically when starting/stopping DTG

1. Merck Sharp & Dohme. Isentress® (raltegravir) prescribing information. Singapore, 2014.
2. Gilead Sciences. Stribild® (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate) prescribing information. Singapore 2014.
3. ViiV Healthcare. Tivicay® (dolutegravir) prescribing information. Singapore 2014.

Kirby Institute