Mitä tapahtui HIV-medisiinassa 2013

12.2.2014

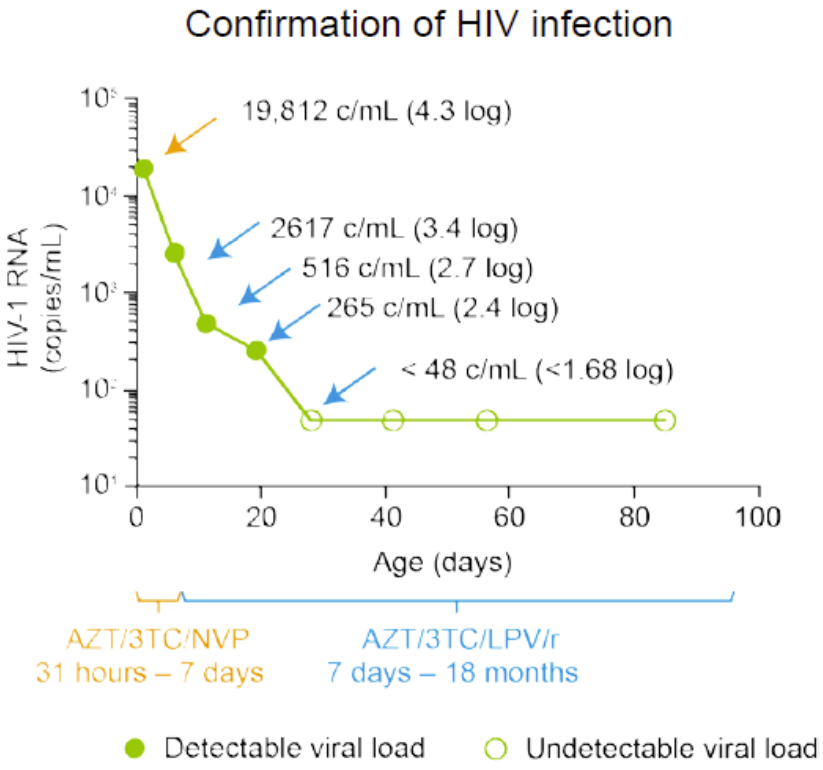
Matti Ristola

HIV Cure

(HIV:n eradikoiminen isännästä)

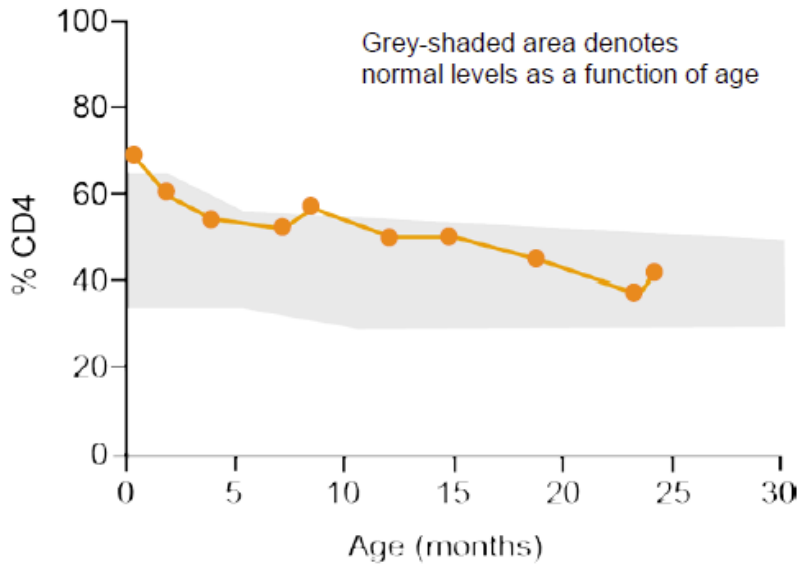
Missisippi Baby

- Alatiesynnytys 35. viikolla
- HIV-pikatesti positiivinen synnytyksen yhteydessä
- Äidin HIV VL 2423 kop/ml, CD4 644
- HIV-lääkitys aloitettiin 31 tuntia syntymästä
- Lapsen HIV DNA (30 tuntia) ja HIV RNA (31 tuntia) positiivisia



Missisippi Baby

- 18 kk: katosi seurannasta ja HIV-lääkitys loppui
- 23 kk: palasi seurantaan. HIV VL mittaamattomissa
  - immunologisissa parametreissa ei viitettä HIV-infektiosta
- Seuranta jatkuu



HIV Cure ja luuydinsiirto

- Nature 3.7.2013 / IAS:n kongressi
  - Henrich ja Kuritzkes raportoivat IAS'n kongressissa kaksi potilasta, joiden he arvelevat parantuneen pysyvästi HIV-infektiosta
  - Molemmilla oli ennen lymfoomaan sairastumista tehoava HIV-lääkitys
  - Molemmille tehtiin lymfooman hoidon osana luuydinsiirto (luovuttajat eivät olleet CCR5-delta32/delta 32)
  - HIV-lääkitystä jatkettiin 8 kuukautta luuydinsiirron jälkeen
  - Raportointihetkellä toinen oli ollut 15 viikkoa ja toinen 7 viikkoa ilman HIV-lääkitystä eikä heillä lääkityksen lopettamisen jälkeen voitu havaita veressä HI-virusta
  - Hyljintäreaktion arveltiin tuhonneen HI-virukset

HIV Cure ja luuydinsiirto

- Nature 6.12.2013 / News
  - Henrich ja Kuritzkes, että HI-virus oli ilmaantunut molempien potilaiden vereen
  - Remissioiden kesto 32 viikkoa ja 12 viikkoa HIV-lääkityksen lopettamisesta

HIV Cure: Mitä tapahtuu laboratorioissa

Luontaiset puolustusmekanismit

- HIV:ta rajoittavat tekijät
  - APOBEC-3G (kohde: Vif)
  - TRIM5α (kohde SIV)
  - Tetherin (BST-2) (kohde: Vpu)
  - Uusi: SAMHD1 (kohde Vpx)
- Interferonin indusoima tekijä
  - Uusi: MX2

Miten luontaista immuniteettia voisi hyödyntää HIV:n eradikaatiossa

- SAMHD1 voi estää HIV:n lisääntymistä lepotilassa olevissa soluissa
- MX2 estää HIV:ta infektoimasta isännän soluja

HIV-lääkehoidon uudet ohjeet

2013 Update: EACS Guidelines for Treatment of HIV-Infected Pts in Europe

- Recommendation for ART initiation remains at CD4+ cell counts < 350 cells/mm^3
  - ART can be considered at higher CD4+ counts, depending on patient readiness

Guideline	AIDS or HIV-Related Symptoms	CD4+ Cell Count		
		< 350	350-500	> 500
EACS[1]	**Yes**	**Yes**	**Consider**	**Consider**
US DHHS[2]	Yes	Yes	Yes	Yes
IAS-USA[3]	Yes	Yes	Yes	Yes
WHO[4]	Yes	Yes	Yes	Not addressed*

*ART may be recommended for the HIV+ partner in serodiscordant couples as prevention of transmission.

1. EACS Guidelines, February 2013. 2. DHHS Guidelines, February 2013.
3. IAS-USA Guidelines, July 2012. 4. WHO ART Guidelines, June 2013.

2013 Update: EACS Guidelines for Treatment of HIV-Infected Pts in Europe

Recommended First-Line Agents	
NRTIs	**Third Agent**
ABC/3TC or TDF/3TC	**NNRTIs** ▪ EFV ▪ RPV
	Boosted PIs ▪ ATV/RTV ▪ DRV/RTV
	INSTIs ▪ RAL

- Changes in initial regimen recommendations in 2013 EACS guidelines:
  - NNRTIs: NVP now alternative rather than preferred
  - Boosted PIs: LPV/RTV now alternative rather than preferred
  - INSTIs: TDF/FTC/EVG/COBI added as alternative regimen

EACS Guidelines, October 2013.

DHHS Guidelines: October 2013 Update on Integrase Inhibitors

	Preferred Regimens	Alternative Regimens
NNRTI	▪ EFV/TDF/FTC	▪ EFV + ABC/3TC ▪ RPV/TDF/FTC or RPV + ABC/3TC
Boosted PI	▪ ATV/RTV + TDF/FTC ▪ DRV/RTV + TDF/FTC	▪ ATV/RTV + ABC/3TC ▪ DRV/RTV + ABC/3TC ▪ FPV/RTV + (TDF/FTC or ABC/3TC) ▪ LPV/RTV + (TDF/FTC or ABC/3TC)
INSTI	▪ **RAL + TDF/FTC** ▪ **EVG/COBI/TDF/FTC** ▪ **DTG + ABC/3TC** ▪ **DTG + TDF/FTC**	▪ **RAL + ABC/3TC**

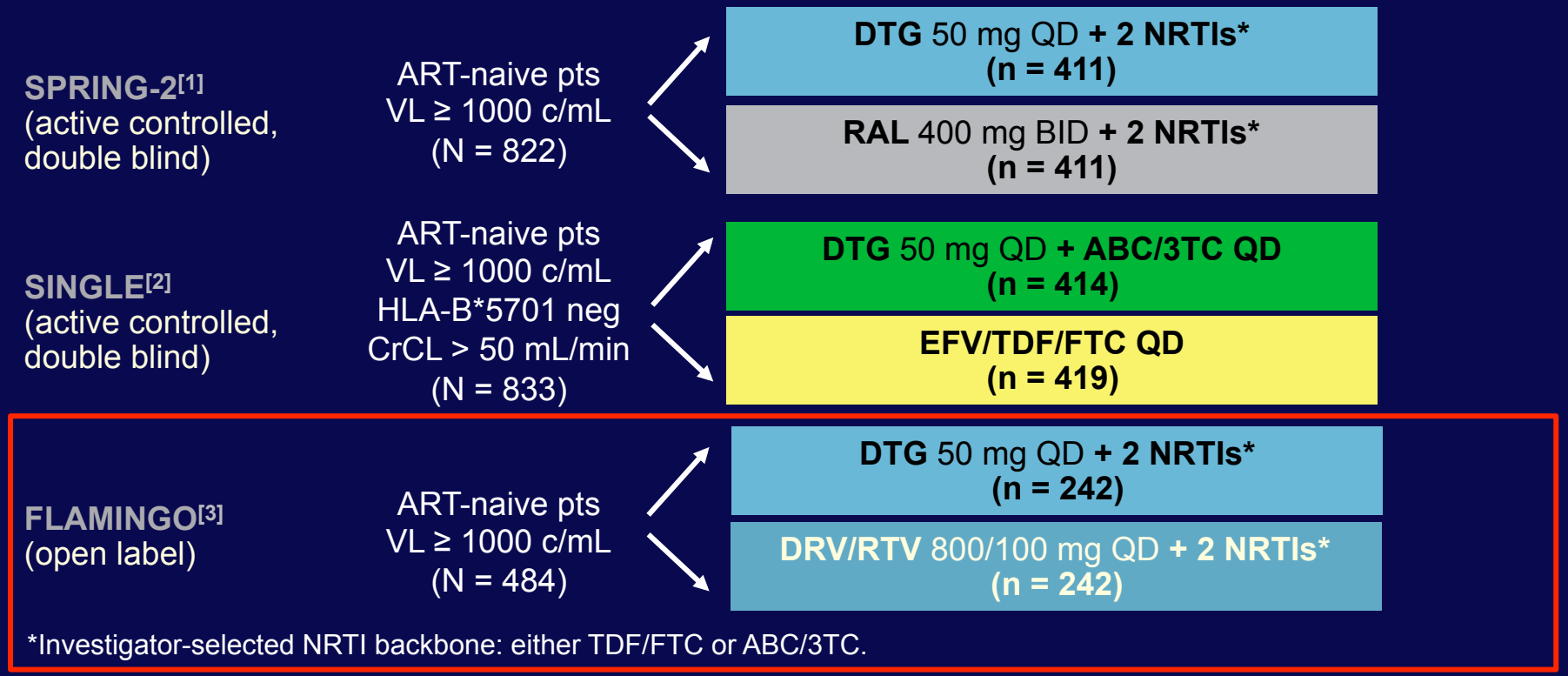
- All 3 integrase inhibitors are now part of preferred first-line regimens

DHHS. Guidelines. February 2013. DHHS. Recommendation on INSTIs. October 2013.

Uusi integraasinestäjä dolutegraviiri

Dolutegravir Phase III Trials in Treatment-Naive Patients

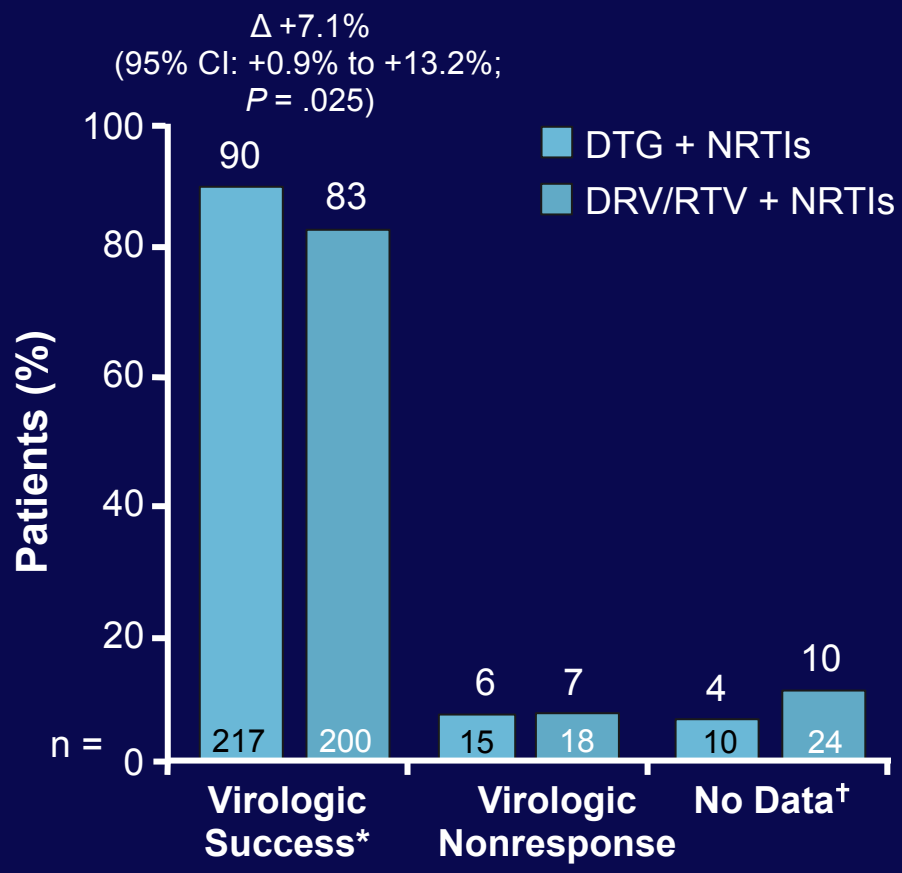
- Randomized, noninferiority phase III studies
- Primary endpoint: HIV-1 RNA < 50 c/mL at Wk 48



*Investigator-selected NRTI backbone: either TDF/FTC or ABC/3TC.

1. Raffi F, et al. Lancet. 2013;381:735-743. 2. Walmsley S, et al. ICAAC 2012. Abstract H-556b.
3. Feinberg J, et al. ICAAC 2013. Abstract H-1464a.

FLAMINGO: DTG Superior to DRV/RTV + 2 NRTIs in Tx-Naive Patients at Wk 48

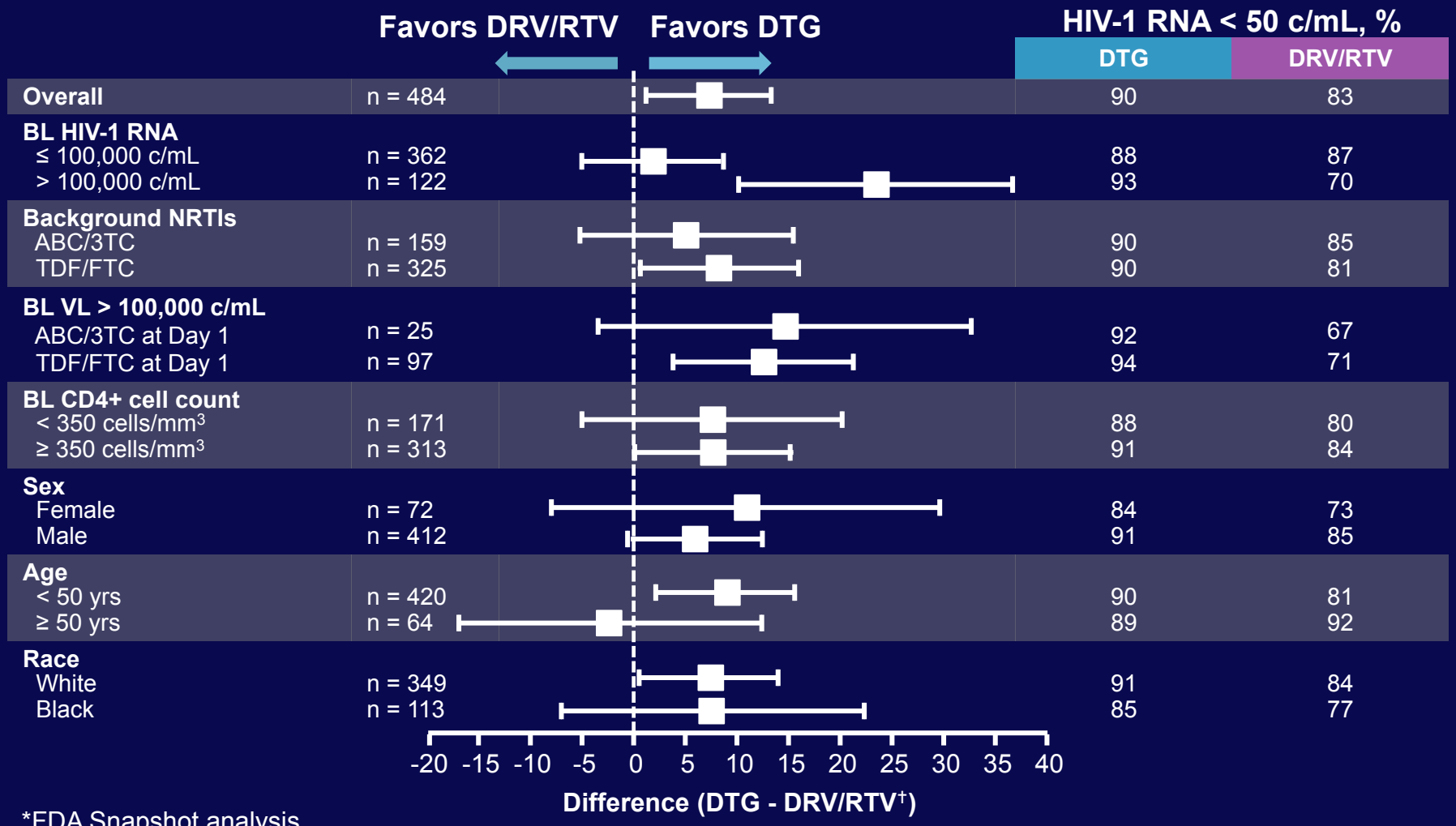


*HIV-1 RNA < 50 c/mL as defined by FDA Snapshot algorithm
†Discontinued for AE, death, or missing data.

- Treatment-related study d/c:
  - 1% in DTG arm vs 4% in DRV/RTV arm
- More diarrhea with DRV; more headache with DTG
- 2 pts (< 1%) in each arm met criteria for VF
  - No pts with resistance in either arm
- Similar increase in CD4+ cell count at Wk 48:
  - +210 cells/mm^3 in each arm

Feinberg J, et al. ICAAC 2013. Abstract H-1464a.

FLAMINGO: Subgroup Analysis* at Wk 48

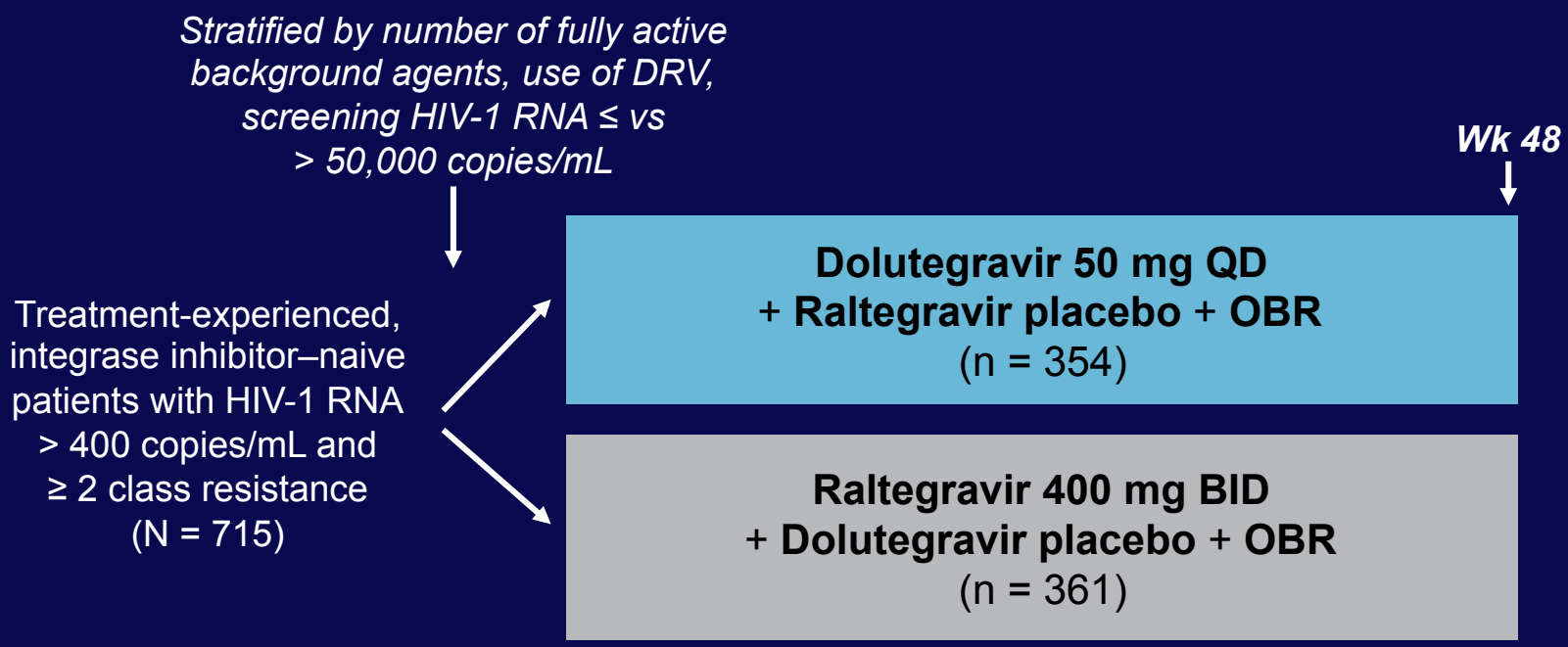


*FDA Snapshot analysis.
†Unadjusted.

Clotet B, et al. EACS 2013. Abstract LBPS4/6. Reproduced with permission.

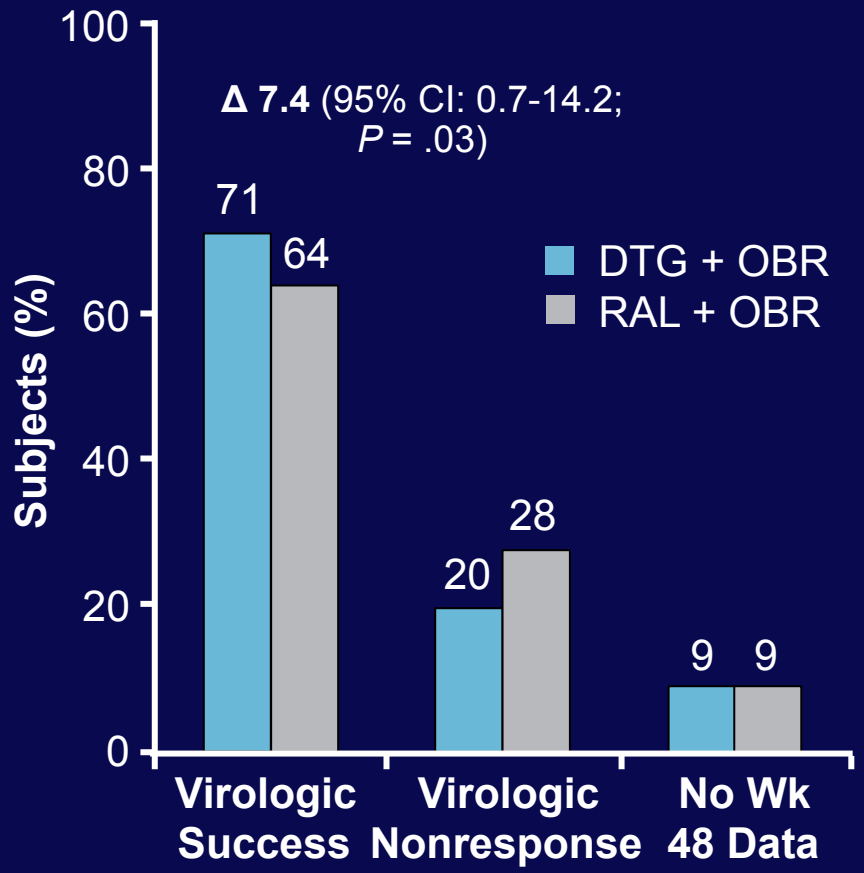
SAILING: Dolutegravir vs Raltegravir in ART-Exp'd, Integrase Inhibitor–Naive Pts

- Phase III randomized, double-blind, double-dummy, noninferiority study



Cahn P, et al. IAS 2013. Abstract WELBB03. Cahn P, et al. Lancet. 2013;382:700-708.

SAILING: Superior Rate of Virologic Suppression With DTG vs RAL at Wk 48



- Lower incidence of resistance at VF with DTG vs RAL
  - Integrase resistance: 1% vs 5%
  - OBR resistance: 1% vs 3%
- Both regimens well tolerated with similar AE profiles
  - Grade 2-4: 8% vs 9%
  - Discontinuations: 3% vs 4%
- No difference in outcome between study arms when combined with fully active DRV/RTV

Cahn P, et al. IAS 2013. Abstract WELBB03. Graphic used with permission.

Pitkävaikutteiset HIV-lääkkeet

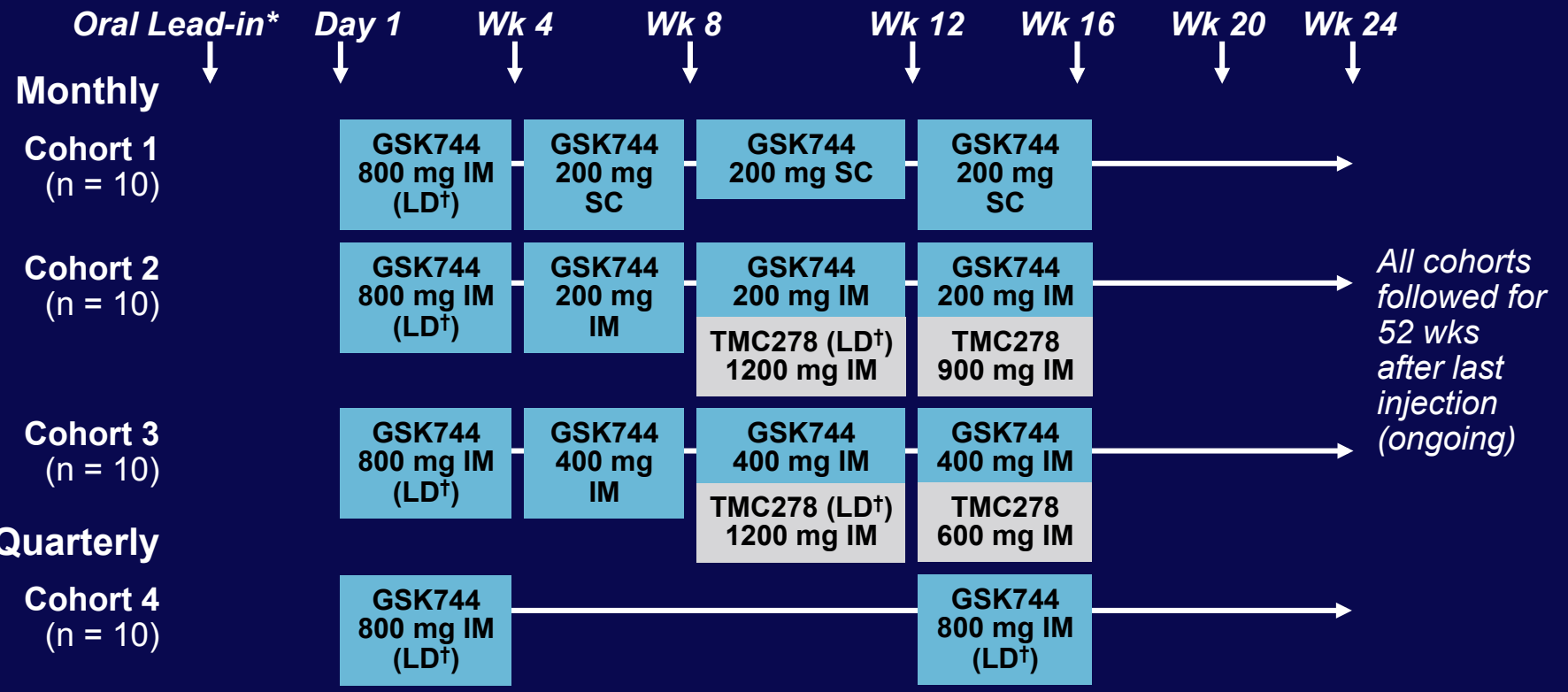
Long-Acting GSK1265744 and TMC278

- Nanosuspensions: drug nanocrystals suspended in liquid
  - Increased drug dissolution rate
  - Nanocrystal design allows for low injection volume
- Potential use as long-acting injections for ART regimens, PrEP
  - GSK1265744 (DTG analogue) dosed monthly or quarterly
  - TMC278 nanosuspension of RPV dosed monthly

Spreen W, et al. IAS 2013. Abstract WEAB0103.

Coadministration of Long-Acting GSK1265744 and TMC278

- Randomized, open-label, repeated-dose phase I trial in healthy adults



*GSK744 30 mg/day for 14 days, then 7-day washout.
†Loading dose given as split injection dose (2 x 2 mL).

Spreen W, et al. IAS 2013. Abstract WEAB0103.

Favorable Drug Concentrations With GSK1265744 and TMC278 Injections

- PK results
  - GSK1265744 injected every 4 wks or every 12 wks achieved plasma levels > protein-adjusted IC_{90}
  - TMC278 dosed every 4 wks achieved plasma levels comparable to those achieved by oral RPV 25 mg/day in HIV-infected patients
- GSK1265744 safe, well tolerated alone and in combination with TMC278
- Findings support phase II study of GSK1265744 + TMC278 as 2-drug ART regimen

Spreen W, et al. IAS 2013. Abstract WEAB0103.

Perustutkimuksen kehittelemiä uusia HIV-lääkkeitä

- Viruksen proteiinin ja isäntäsolun kofaktorin interaktion estäminen
- Etuja
  - uusien kohdemolekyylien pipeline
  - lääkeresistenssi ei ehkä kehity helposti
- Esteitä
  - proteiini-proteiini interaktiot haasteellisia
  - toksisuus ?

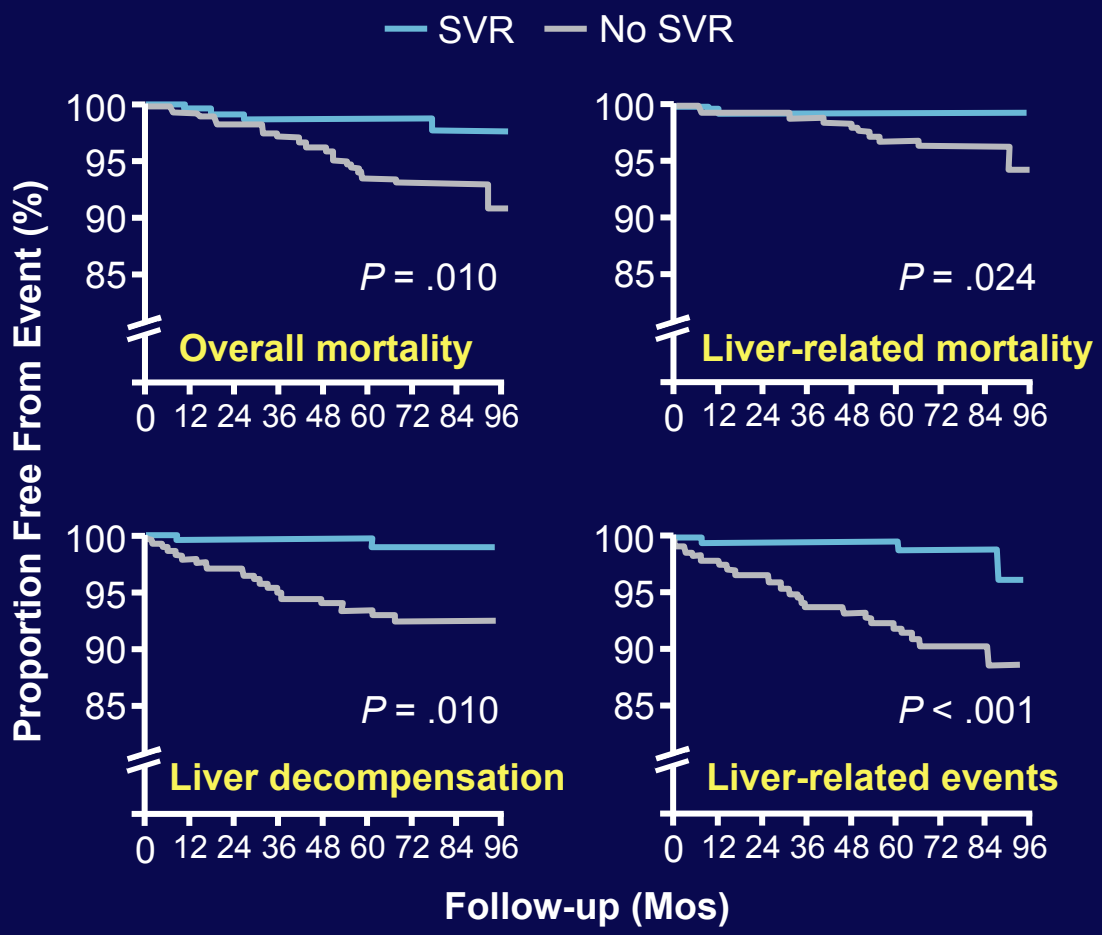
LEDGIN’it

- *in vitro* -vaiheessa
- uusi antiretroviraaliluokka
- LEDGIN’it estävät HIV:n integroitumisen isännän DNA:han eri mekanismilla kuin integraasinestäjät *(Kessel ym. JBC 2012)*
- eri kohdemolekyyli kuin nykyisillä integraasinestäjillä (isännän kofaktori LEDG/p75) *(Christ ym. Nature 2010)*
- LEDGIN’it heikentävät syntyvien HIV-partikelien infektiivisyyttä *(Jurado ym. PNAS 2013)*

HCV/HIV –koinfektion hoito

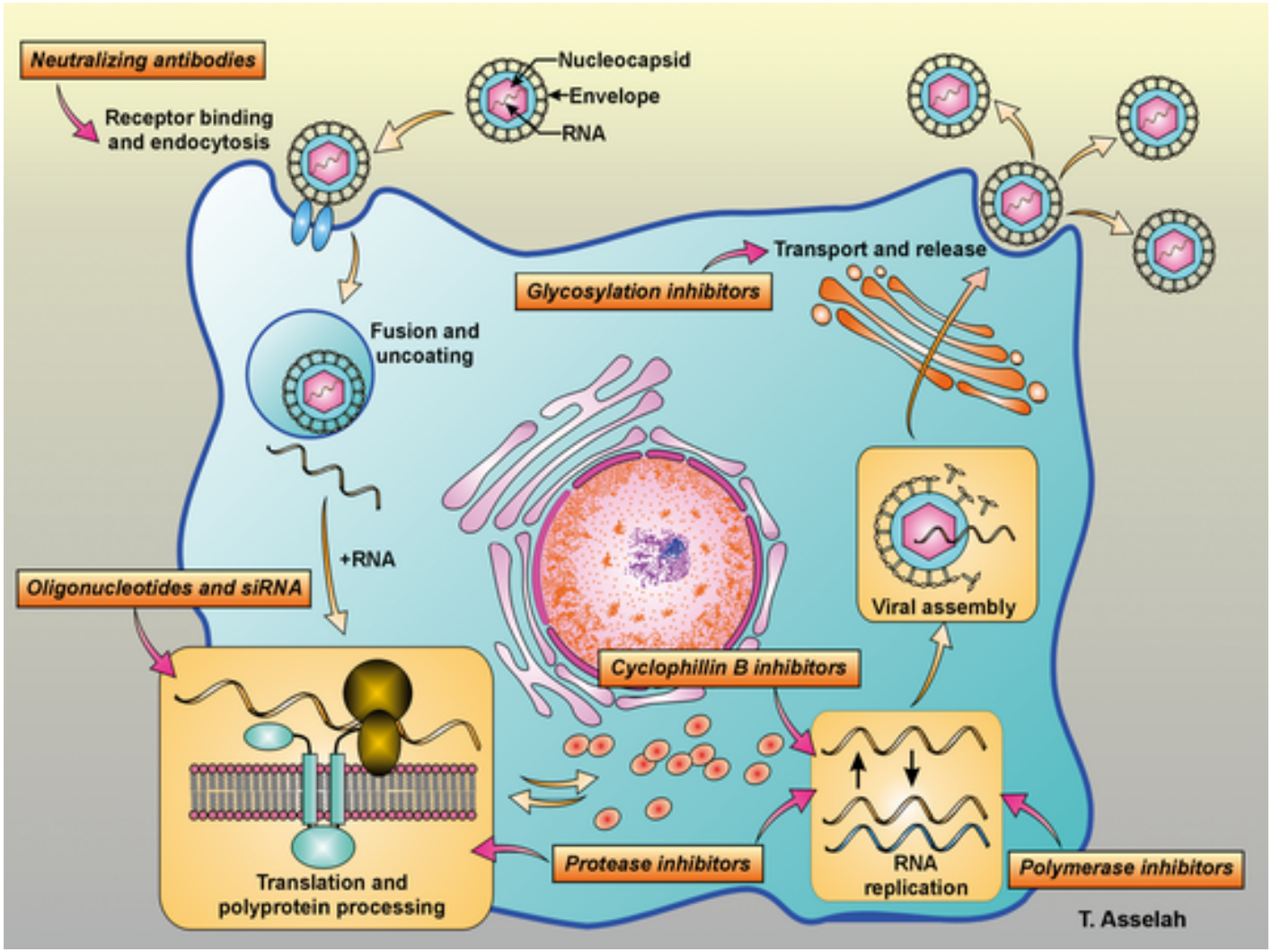
SVR Associated With Lowered Morbidity, Mortality in HIV/HCV Pts With F0-F2

- Retrospective analysis of 695 HIV/HCV-coinfected pts with baseline METAVIR F0-F2 scores treated with IFN/RBV between 1/2000-1/2008 in 19 centers in Spain
- Median follow-up (IQR):
  - No SVR: 59.3 mos (40.6-79.2)
  - SVR: 59.5 mos (42.8-81.8)
- SVR significantly associated with decreased overall mortality and secondary liver outcomes



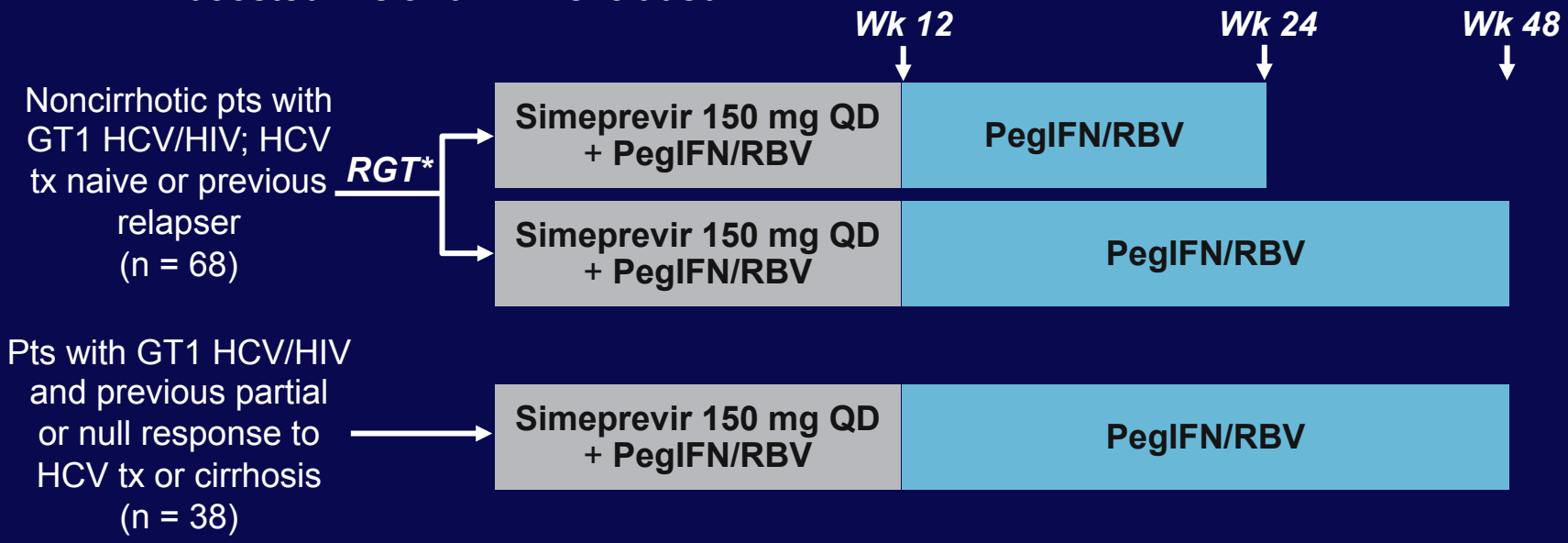
Berenguer J, et al. ICAAC 2013. Abstract H-1527. Reproduced with permission.

HCV-lääkkeiden kohteita



C212 Study: Simeprevir + PegIFN/RBV in GT1 HCV/HIV-Coinfected Patients

- Primary analysis of phase III TMC435-C212 trial (N = 106)
  - 82% white; 82% GT1a HCV; 12% not on ART
  - Of pts on ART, 99% on NRTI, 87% on RAL, 15% on RPV, 3% on MVC, 3% on ENF; boosted PIs and EFV excluded

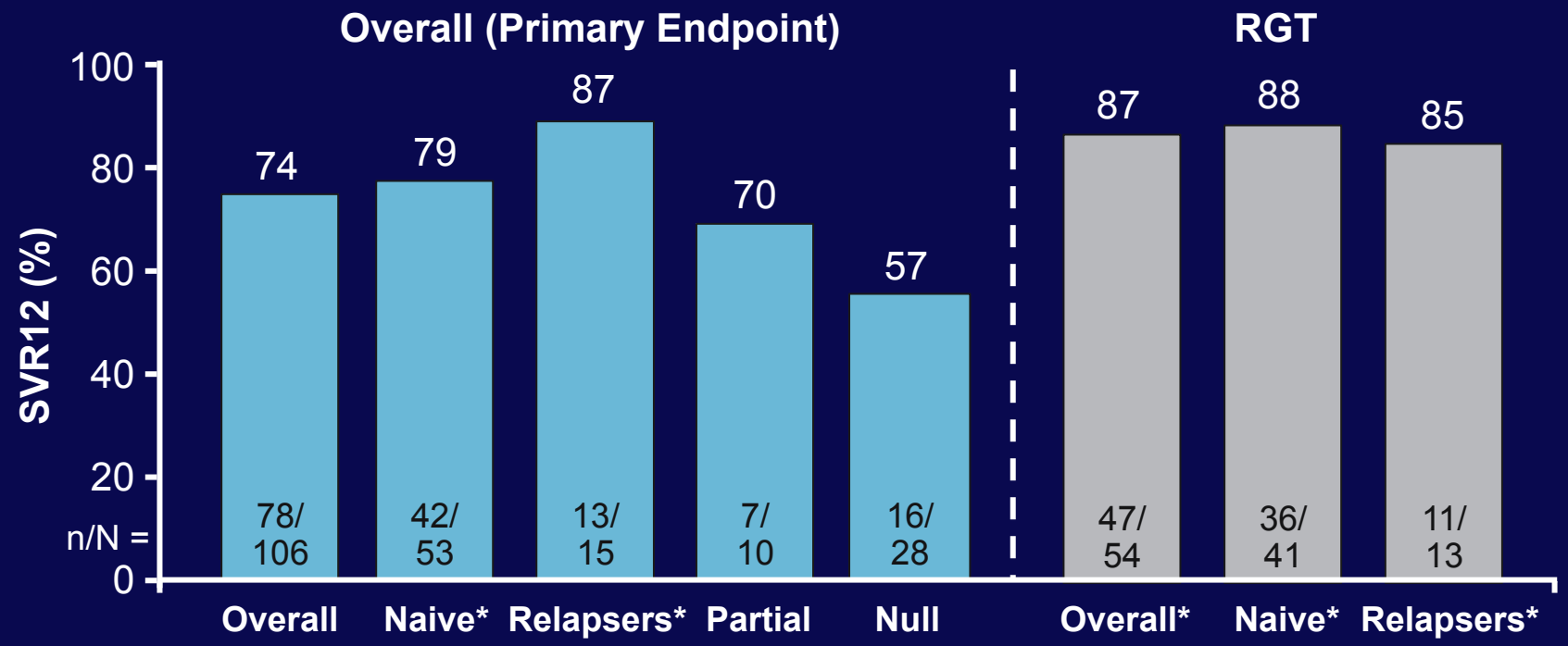


*Response-guided therapy: Pts with HCV RNA < 25 IU/mL (either detectable or undetectable) at Wk 4 and undetectable HCV RNA at Wk 12 received 24 total wks of therapy; all others received 48 wks.

Dieterich D, et al. EACS 2013. Abstract LBPS9/5. Reproduced with permission.

C212 Study: SVR12 With Simeprevir + PegIFN/RBV in Coinfected Patients

- 89% of noncirrhotic pts (54/61) met RGT criteria
- Safety profile similar to that seen in monoinfected pts
  - Pruritus and photosensitivity in 20% and 2%, respectively

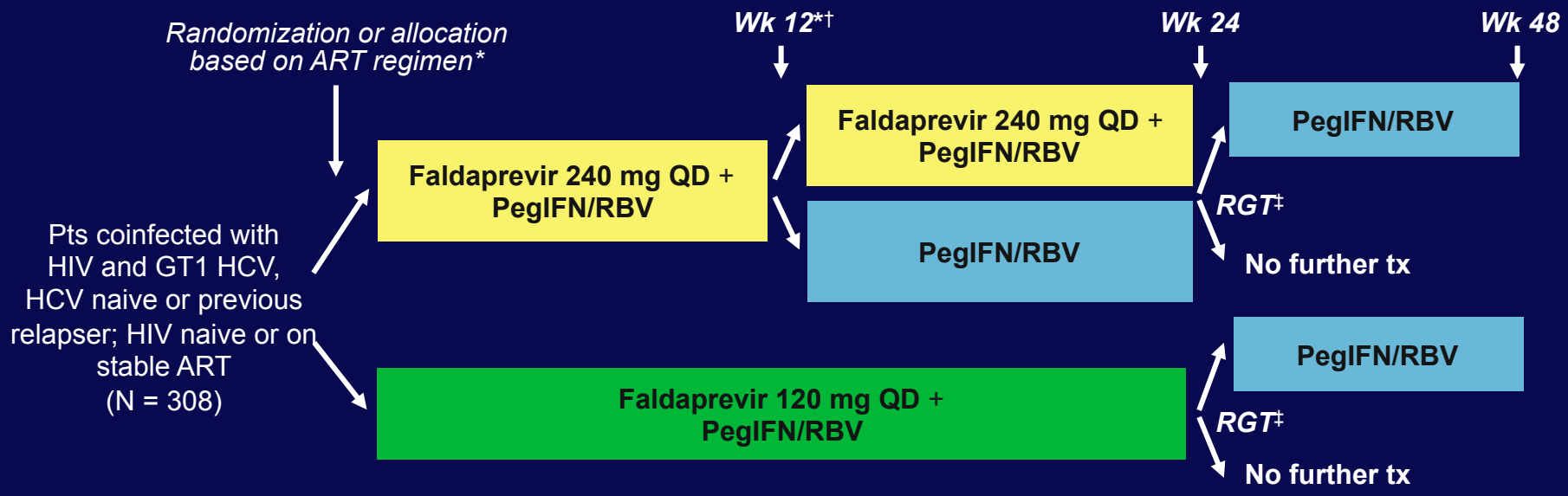


*Includes only noncirrhotic patients.

Dieterich D, et al. EACS 2013. Abstract LBPS9/5. Reproduced with permission.

STARTVerso 4: Faldaprevir + PegIFN/RBV in GT1 HCV/HIV-Coinfected Pts

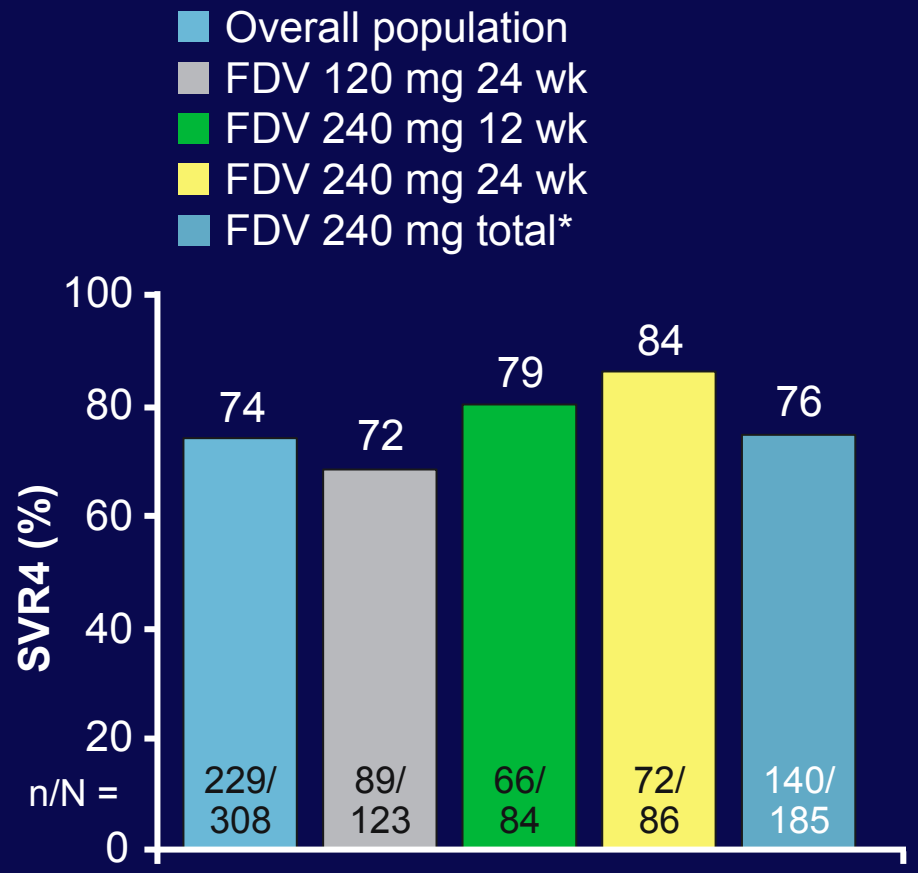
- Preliminary analysis of phase III STARTVerso 4 trial
  - 83% white/14% black, 79% GT1a HCV, 4% not on ART, 27% on EFV-based ART, 22% on ATV/RTV or DRV/RTV-based ART, 46% on RAL-based ART



*All pts on boosted PIs allocated to 120-mg dose arm.
†At Wk 12, pts receiving 240 mg QD + P/R were rerandomized 1:1 to continue triple therapy or to P/R to Wk 24.
‡Response-guided therapy: At Wk 24, pts with ETS were rerandomized to continued P/R vs no further treatment; pts without ETS continued P/R to Wk 48. ETS defined as HCV RNA < 25 IU/mL at Wk 4 and HCV RNA < 25 IU/mL, target not detected at Wk 8.

Dieterich D, et al. CROI 2013. Abstract 40LB. Rockstroh J, et al. EACS 2013. Abstract PS9/7.

STARTVerso 4: SVR4 With Faldaprevir + PegIFN/RBV in HCV/HIV-Coinfected Pts



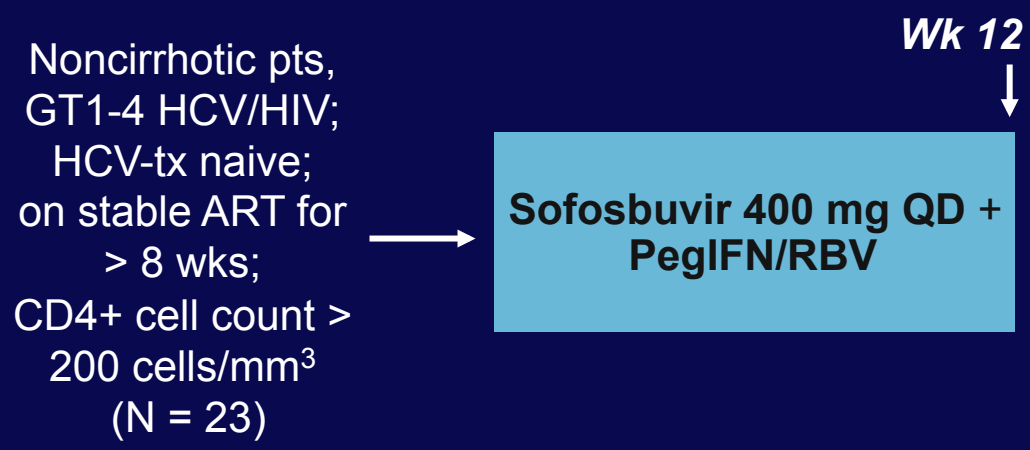
*Includes additional pts who dropped out before Wk 12.

- AE profile consistent with HCV-monoinfected pts
- High SVR rates in both cirrhotic and noncirrhotic pts
  - Cirrhotic: 76%
  - Noncirrhotic: 74%
- SVR rates by *IL28B* genotype
  - CC: 89%; CT: 67%; TT: 67%

Rockstroh J, et al. EACS 2013. Abstract PS9/7. Reproduced with permission.

Sofosbuvir + PegIFN/RBV in GT1-4 HCV/HIV-Coinfected Patients

- Single-center, open-label, single-arm trial
  - 92% white; 82% GT1 HCV; 30% on EFV; 22% on ATV/RTV; 26% on RAL; 17% on DRV/RTV; 4% on RPV



	SVR12, %
Overall	91
By ART regimen	
▪ Boosted PI (n = 14)	93
▪ NNRTI (n = 11)	91
▪ RAL (n = 7)	100

Rodriguez-Torres M, et al. IDWeek 2013. Abstract 714.