The HIV Integrase Inhibitor Elvitegravir (EVG/r) Has Potent and Durable Antiretroviral Activity in Treatment-Experienced Patients with Active Optimized Background Therapy (OBT)

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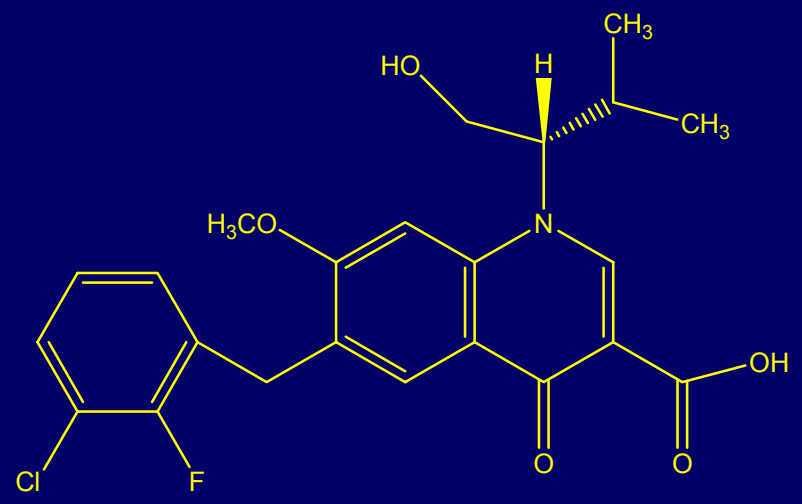
Background on Elvitegravir (EVG)

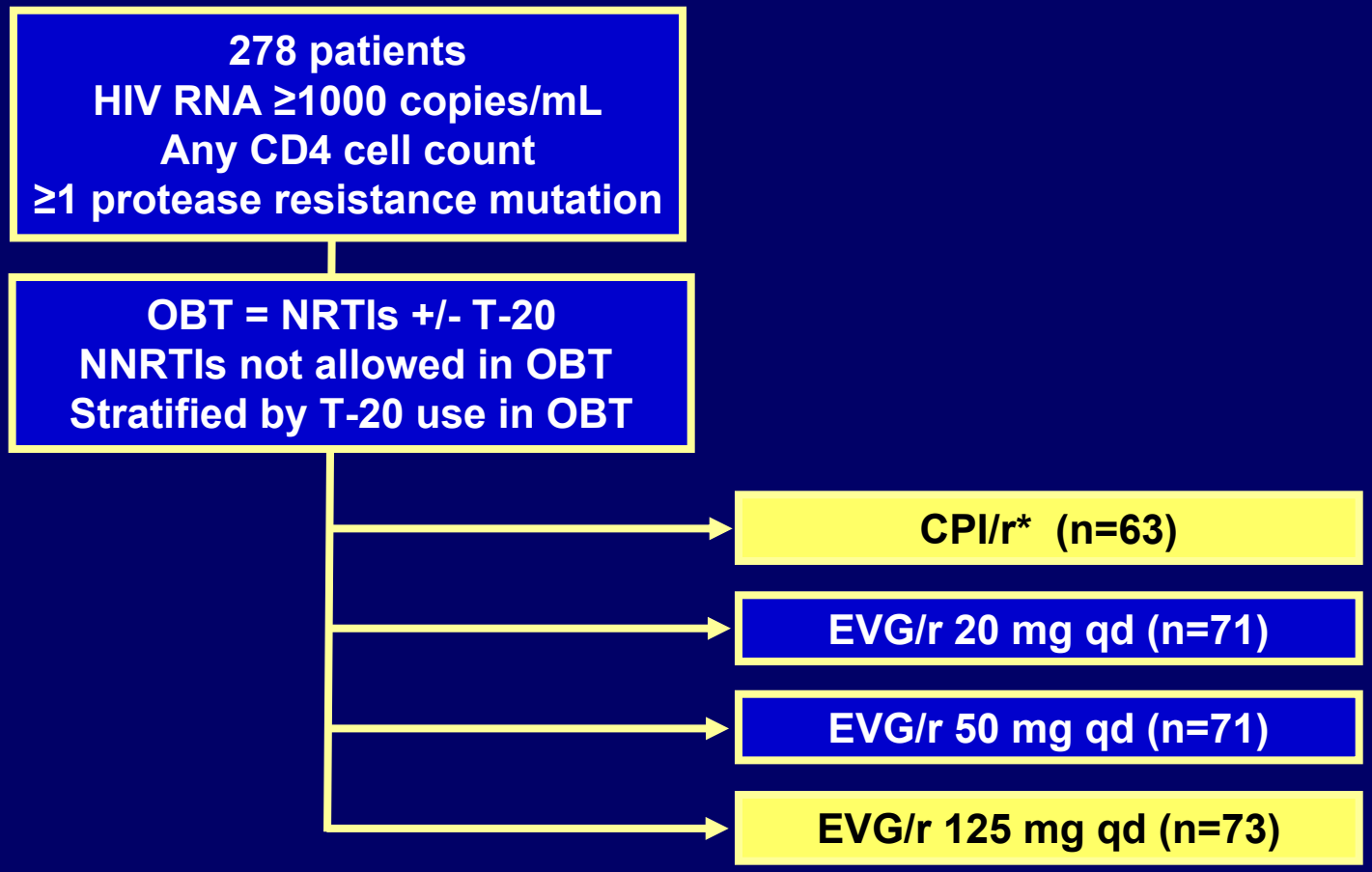


- Dihydroquinoline carboxylic acid strand transfer inhibitor of HIV integrase
- Serum-free IC_{50} = 0.2 nM; EC_{90} = 1.2 nM in PBMCs
- Active against NRTI-, NNRTI-, and PI-resistant isolates tested
- No dose-limiting chronic animal toxicity

Phase 2 Study Design

- Randomized, active-controlled, partially-blinded (dose of EVG), dose-finding study
- Non-inferiority study of EVG (boosted with ritonavir) and comparator PIs (CPI/r)
- Optimized Background Therapy (OBT) consisted of NRTIs +/- T-20 at investigator's discretion
- PI use in EVG/r arms initially prohibited due to lack of drug-drug interaction data; DSMB permitted adding DRV or TPV after Week 8
  - Two EVG/r 125 mg subjects added PI prior to Week 16 (both Week 15)
- Primary endpoint was time-weighted average change from baseline in HIV RNA through 24 weeks ($DAVG_{24}$)

Phase 2 Study Schema



*CPI/r included 49% darunavir, 27% tipranavir

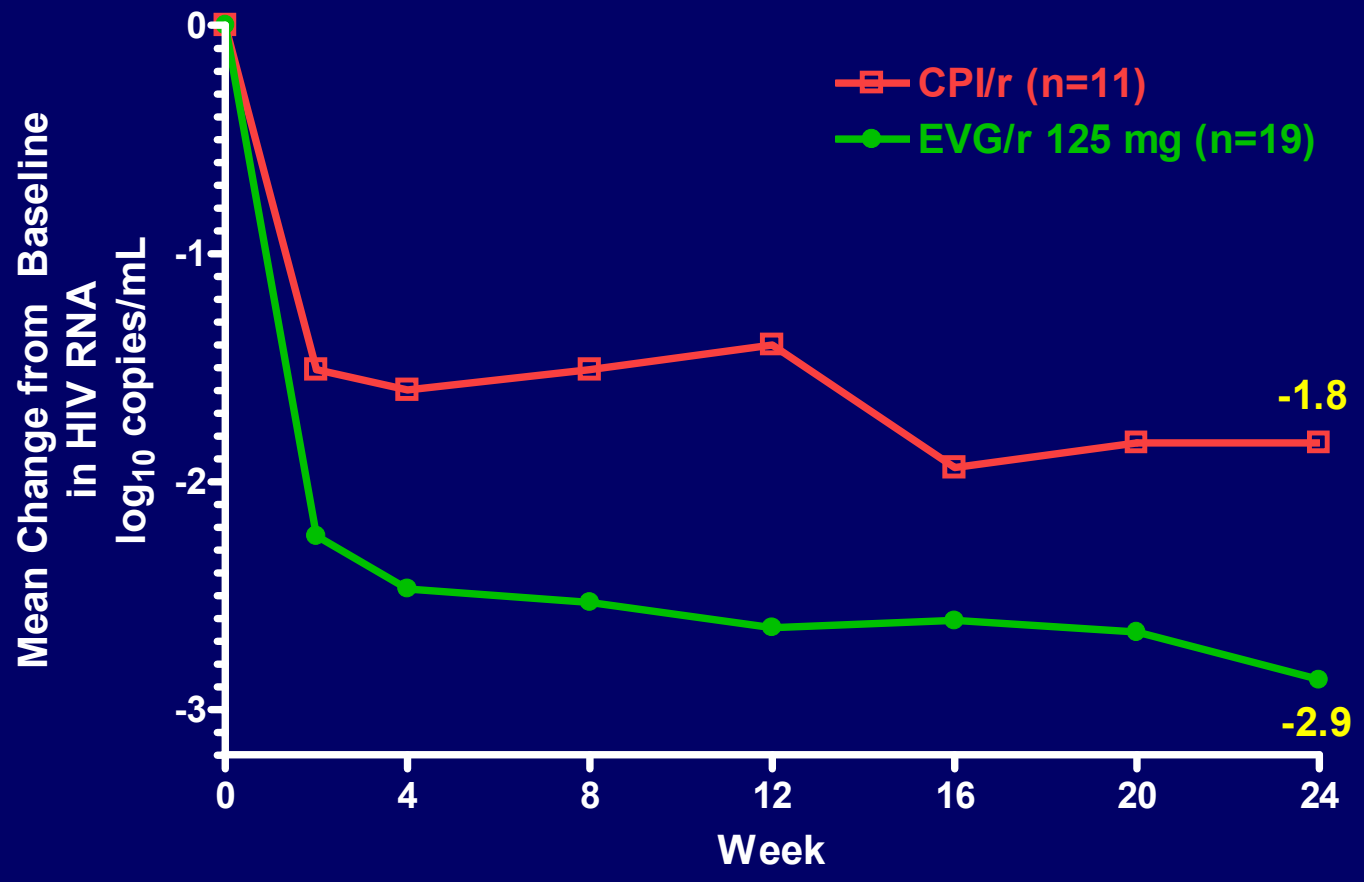
Baseline Characteristics

Baseline Parameters	CPI/r n=63	EVG/r 125 mg n=73
Mean HIV-1 RNA, $\log_{10}$c/mL	4.54	4.71
Mean CD4 cells/mm^3	158	157
Genotypic Sensitivity Score (GSS) =0 for all NRTIs in OBT	32 (51%)	35 (48%)
Median # NRTI Resistance Mutations	5	5
Median # Thymidine Analog Mutations	3	3
Median # PI Resistance Mutations	11	11
First Use of T-20	12 (19%)	19 (26%)
Median # ARVs in OBT including T-20	3	3

DAVG Overall and for Subsets with First Use of T-20

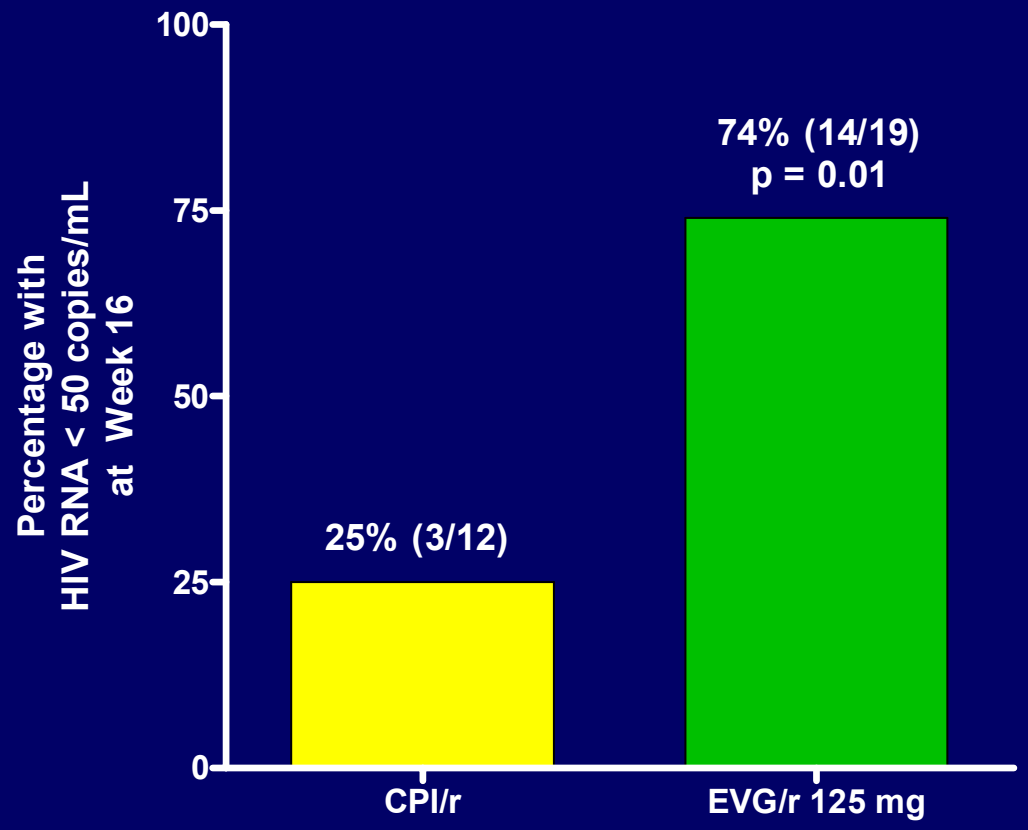
ITT	CPI/r	EVG/r 125 mg	p-value
$DAVG_{24}$, overall Mean, log_{10} copies/mL	-1.2 (n = 61)	-1.7 (n = 73)	p = 0.02
$DAVG_{16}$, first use of T-20 Mean, log_{10} copies/mL	-1.5 (n = 11)	-2.5 (n = 19)	p = 0.02
$DAVG_{24}$, first use of T-20 Mean, log_{10} copies/mL	-1.6 (n = 11)	-2.6 (n = 19)	p = 0.03

Change from Baseline in HIV RNA with First Use of T-20: CPI/r vs. EVG/r 125 mg



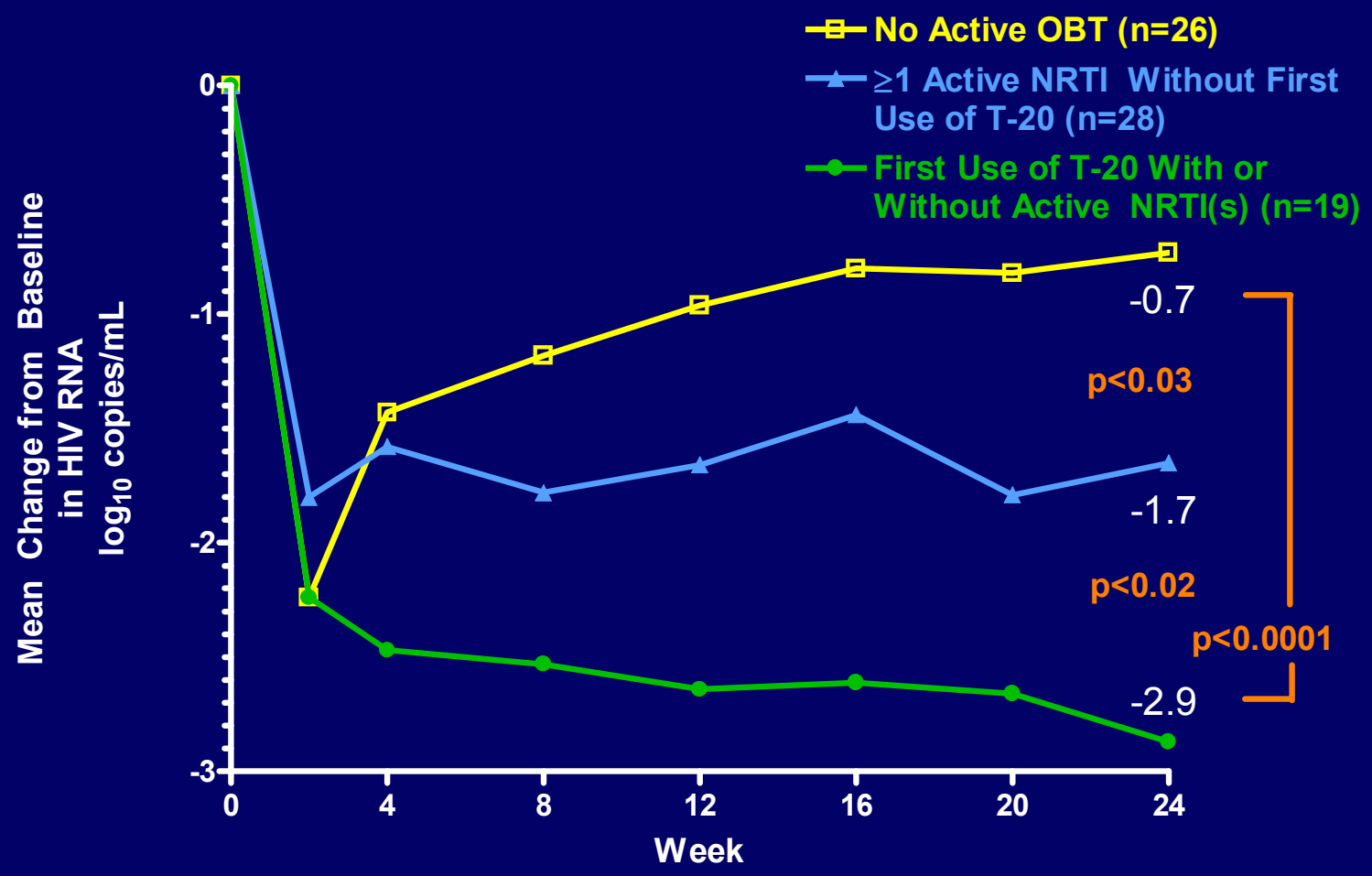
Data from patients after changing regimen were excluded

HIV RNA < 50 copies/mL at Week 16 for Patients with First Use of T-20



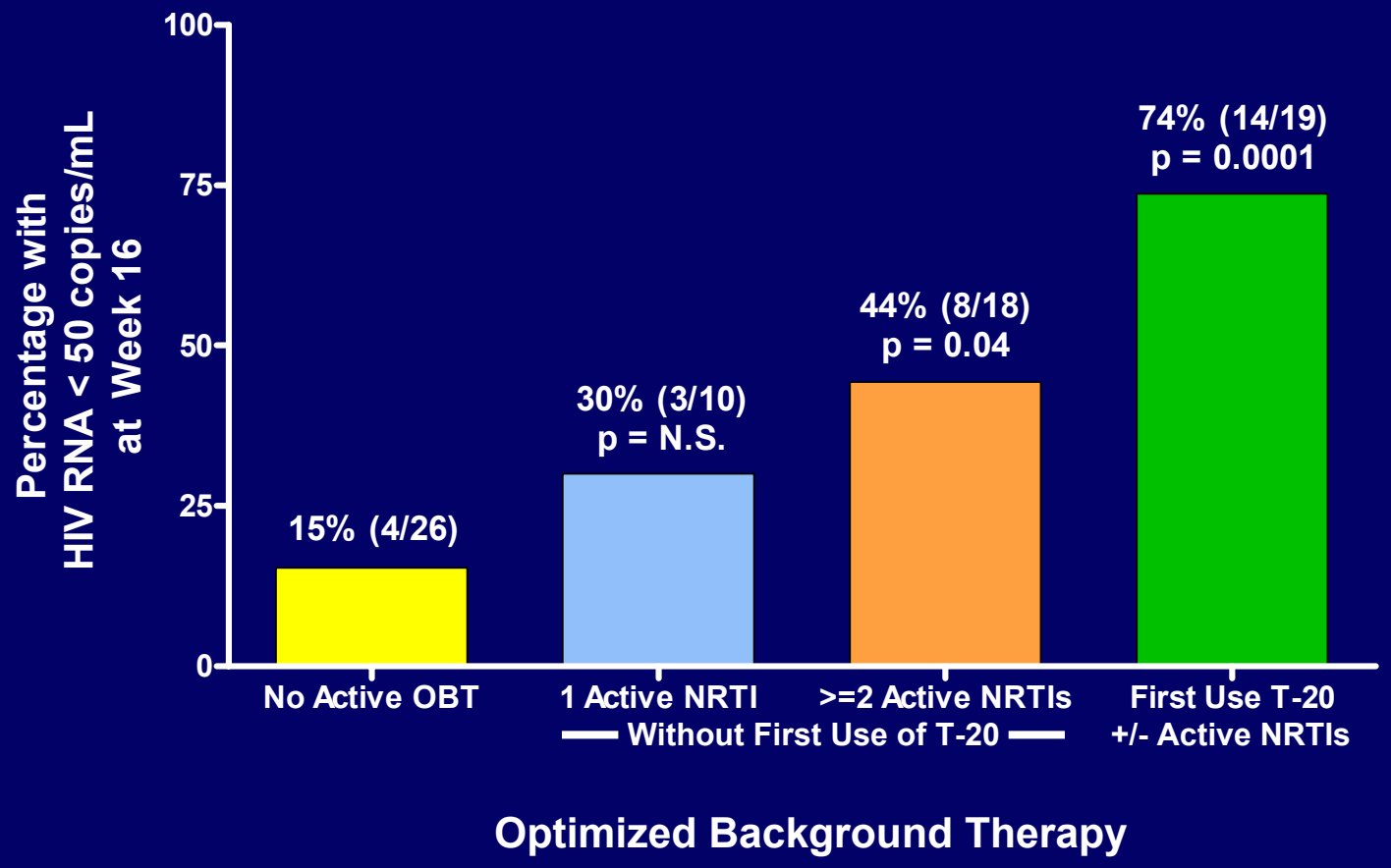
ITT, missing = failure
One subject in CPI/r group did not have any post-baseline HIV RNA measurements

Change in HIV RNA With EVG/r 125 mg: Influence of Gradations in Activity of OBT



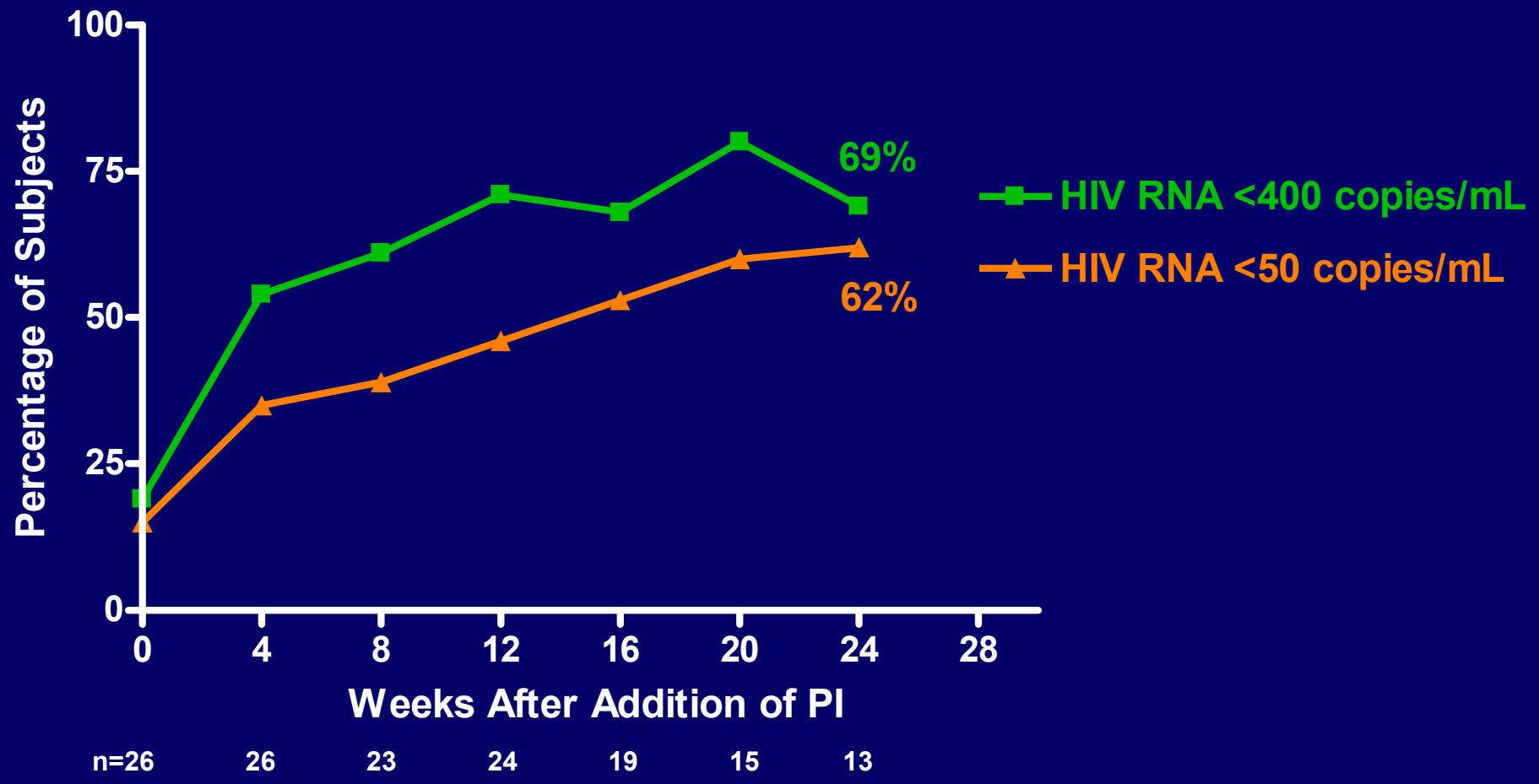
Data from EVG/r 125 mg patients after addition of a PI were excluded

Week 16 HIV RNA < 50 copies/mL for Patients Receiving EVG/r 125 mg: Impact of Gradations in Activity of OBT



ITT, missing = failure
p-values calculated by Fisher's Exact Test vs. No Active OBT

Virologic Suppression After Addition of Protease Inhibitors to OBT of EVG/r 125 mg Subjects



- Mean HIV RNA = 3.9 $\log_{10}$ copies/mL prior to adding PI
- Mean change in HIV RNA after PI = -1.0 $\log_{10}$ copies/mL (median follow-up 24 weeks)

Conclusions

- Decline in HIV RNA with EVG/r 125 mg is rapid, however, active OBT is critical to maintain virologic response
- Magnitude and durability of virologic response are enhanced when EVG/r 125 mg is combined with another potent agent (T-20)
- Boosted PIs add durable, potent efficacy to EVG/r 125 mg
- Plan further evaluation of EVG/r + boosted PIs and other potent agents

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