A Phase 3b Open-Label Pilot Study to Evaluate Switching to Elvitegravir/Cobicistat/Emtricitabine/ Tenofovir Alafenamide (E/C/F/TAF) Single Tablet Regimen in Virologically-Suppressed HIV-1 Infected Adults Harboring the NRTI Resistance Mutation M184V and/or M184I (GS-US-292-1824): Week 12 Results

Perez-Valero I, Llibre JM, Lazzarin A, di Perri G, Pulido F, Molina JM, Esser S, McNicholl IR, Lorgeoux RP, Margot N, Shao Y, Piontkowsky D, Das M, Haubrich R.

Background and Rationale

- M184V/I
  - Occurs in up to 64% of treated patients with prior virologic failure[1]
  - Confers resistance to emtricitabine/lamivudine (FTC/3TC), but results in increased susceptibility to tenofovir (TFV)[2]
  - M184 mutations may not preclude response to E/C/F/TDF or E/C/F/TAF
    - TAF, with 4-fold higher intracellular TFV-DP than TDF, may have additional activity against resistance mutations including M184V/I[3]

- A single tablet regimen (STR) for switch could:
  - improve adherence
  - reduce pill burden

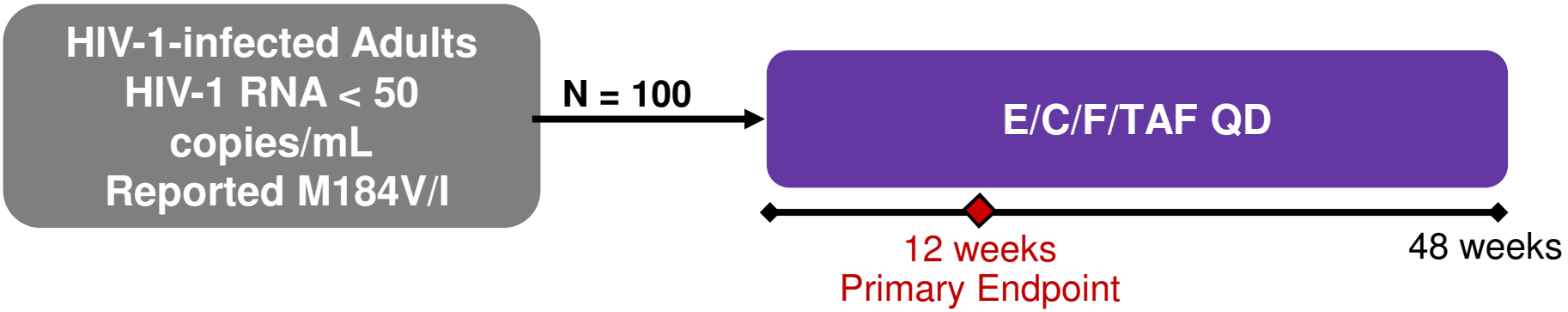
1. Marconi CID 2008;46:1589. 2. Turner D. Clin Diagn Lab Immunol. 2003;10: 979–981.. 3. Margot. Antiviral Res. 2016; 132:50

Study Objectives

- Primary Objective
  - To evaluate the efficacy and safety of E/C/F/TAF fixed dose combination (FDC) in maintaining HIV-1 RNA < 50 copies/mL at Week 12 using pure viral response (PVR)
- Secondary Objectives
  - To determine the safety and tolerability of E/C/F/TAF FDC in participants switching from 2 NRTI plus third antiretroviral agent regimens
  - To evaluate the development of new resistance mutations in participants who develop virologic failure after switching to E/C/F/TAF FDC
  - To determine the durability of efficacy at Weeks 24 and 48 in maintaining HIV-1 RNA < 50 copies/mL using PVR

Study Design

Multicenter, International, open label, single arm study



Primary Objective

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Primary Endpoint

- HIV-1 RNA <50 copies/mL at Week 12 using pure virologic response (PVR)

Study Design (continued)

- Part 1
  - In Part 1, up to 50 participants with only M184V and/or M184I
  - Safety monitoring to assure that the true value of PVR is above 80%
  - Primary endpoint analysis of Week 12 safety and efficacy data - the current analysis
- Part 2
  - Contingent on acceptable efficacy results of Part 1 (>80%), entry criteria expanded
  - Enrollment criteria expanded to allow participants with M184V and/or M184I with up to 2 TAMs (now enrolling)
    - TAMs include the M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E/N/R mutations.

Key Inclusion/ Exclusion Criteria

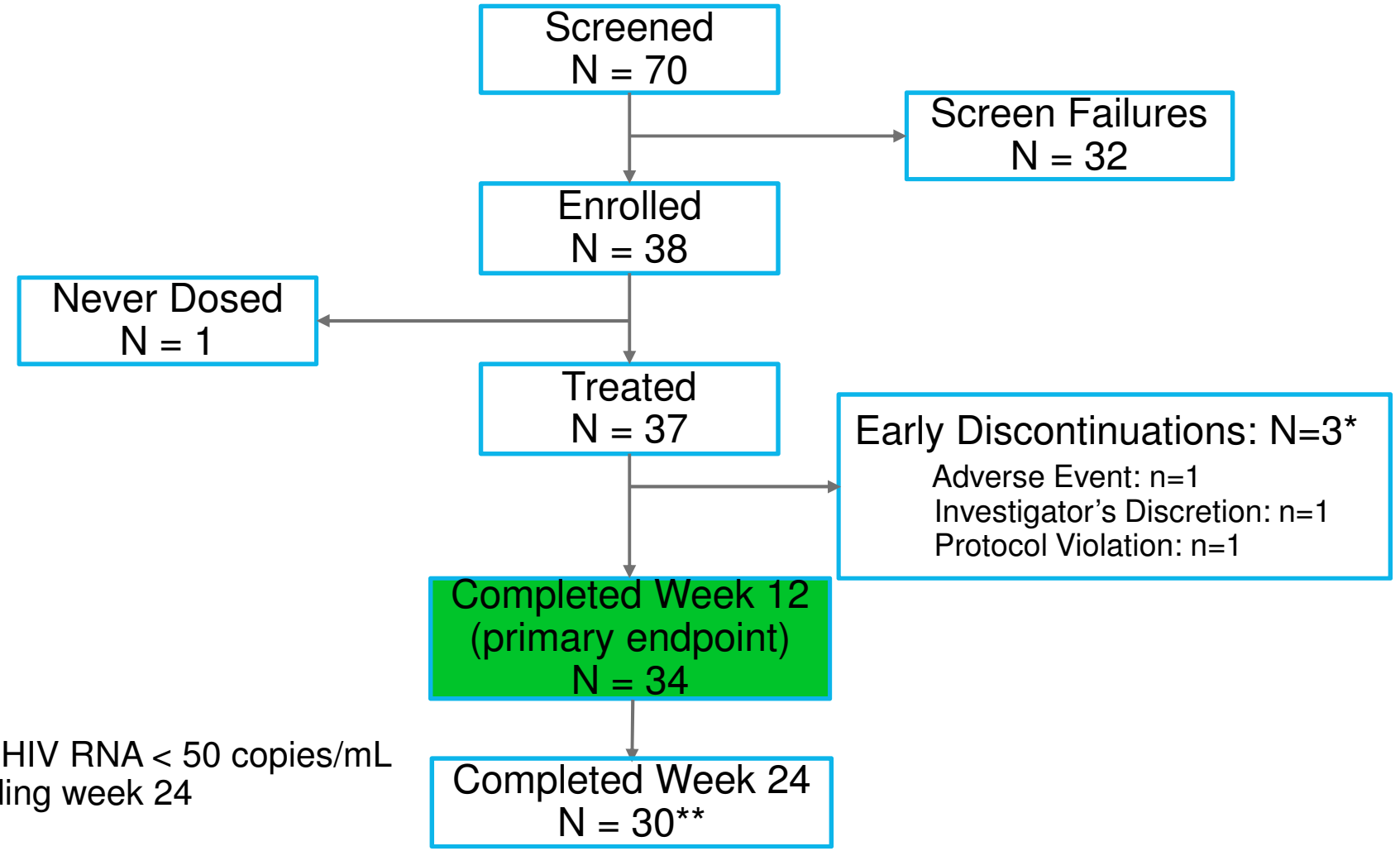
- HIV-1 RNA < 50 copies/mL at screening and for at least 6 months
  - One “blip” (HIV-1 RNA > 50) was acceptable
- Currently receiving FTC/TDF or ABC/3TC + 3rd agent for ≥ 6 months
- M184V and/or M184I on historical genotype
  - no exclusionary PI or INSTI mutations on historical genotype
  - no TAMS, INSTI or PI mutations by proviral DNA genotype (done at screening)
- No prior virologic failure on PI or INSTI regimen
- Estimated GFR ≥ 30 mL/min (Cockcroft-Gault formula)

Baseline Characteristics

	E/C/F/TAF n=37
Median age, years (range)	51 (22-76)
Female	8 (22%)
Race/ethnicity	
White	27 (73%)
Black or African descent	7 (19%)
Hispanic/Latino ethnicity	6 (16%)
HIV-1 RNA <50 copies/mL, baseline	37 (100%)
Median CD4 count, cells/mm^3 (range)	724 (143-1503)
CD4 <200 cells/mm^3	1 (3%)
Median estimated GFR_{CG}, mL/min (range)	94 (36-215)
Baseline Regimen*	
NNRTI	11%
INSTI	32%
PI	54%
FTC/TDF	54%

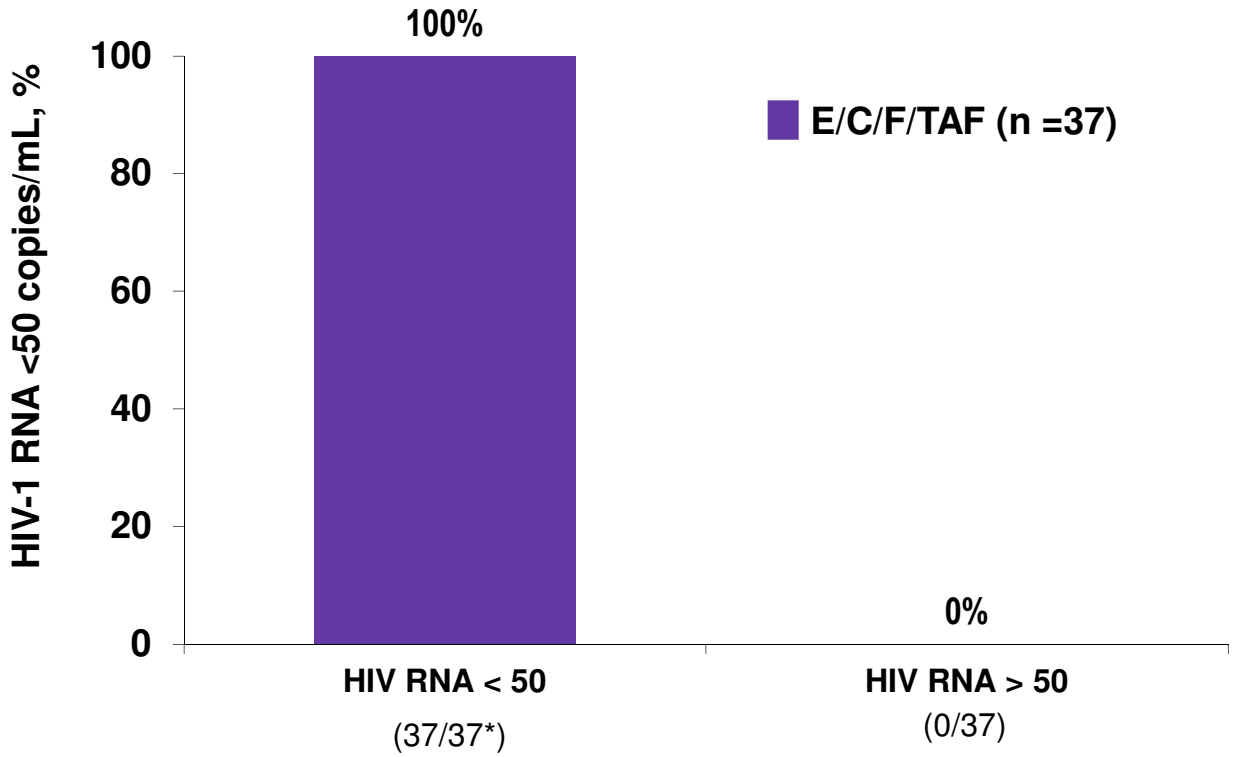
* 1 patient was on E/C/F/TDF; 1 patient was on FTC/TDF + ETR + RAL

Subject Disposition



*3/3 had HIV RNA < 50 copies/mL
** 4 pending week 24

Pure Virologic Response (HIV RNA < 50 copies/mL) at Week 12



Week 12 Primary Analysis:

- No virological failures
- No emergence of new resistance

Week 24 (observed data up to 04 Sept 2017)

- 30/30 (100%) with HIV-1 RNA <50 copies/mL (missing=excluded)

* One participant was receiving E/C/F/TDF (excluded entry regimen) and was included in this analysis

Treatment-Emergent Adverse Events (AEs)

Adverse Event	E/C/F/TAF n=37 n (%)
Any Treatment-Emergent AE (TEAE)	27 (73)
Any Grade 2, 3 or 4 TEAE	14 (38)
Any Grade 3 or 4 TEAE*	5 (14)
Increased cholesterol, triglycerides	1
Inadequate control diabetes mellitus	1
Tonsillar carcinoma	1
Proteinuria	1
Renal failure	1

* All were grade 3 and none were considered drug-related by the investigator

Treatment-Emergent Adverse Events

Adverse Event (all Grades, ≥5%)	E/C/F/TAF n=37 n (%)
Headache	6 (16)
Diarrhea	5 (14)
Asthenia	4 (11)
Viral Upper respiratory tract infection	4 (11)
Cough	4 (11)
Bronchitis	2 (5)
Back pain	2 (5)
Intertrigo	2 (5)
Hypertension	2 (5)

Study Drug-Related Adverse Events (AEs)

	E/C/F/TAF n=37 n (%)
Any Treatment-Emergent Study Drug-Related AE*	7 (19%)
Any Treatment-Emergent Grade 3 or 4 Study Drug-Related AE	0
AEs Leading to Premature Study Drug Discontinuation†	1 (3%)

*diarrhea (1), asthenia (2), fatigue (1), headache (2), skin burning sensation (1), hypertension (1), muscle spasms (1)
† muscle spasms

Treatment-Emergent Grade 3-4 Lab Abnormalities

Lab Test	E/C/F/TAF n=37 n (%)
Any Grade 3-4 Lab Abnormality	5 (14)
Glycosuria	2 (5)
LDL, fasting	1 (4)*
Triglycerides, fasting	1 (4)*
Hematuria	1 (3)†
Hyperglycemia, fasting	1 (4)*
Creatinine	1 (3)
Hyponatremia	1 (3)
Hyperbilirubinemia	1 (3)

N = 1 Grade 4 lab abnormality (fasting triglycerides)

*n=28; †n=31; N varies due to availability of fasting or urine samples

Any Treatment-Emergent Serious Adverse Events (SAEs)

	Related to Study Drug?	E/C/F/TAF n=37 n (%)
Treatment-Emergent SAE	None	4 (11)
tonsillar carcinoma	No	1 (3)
proteinuria*	No	1 (3)
acute kidney injury/ renal failure**	No	1 (3)
pulmonary embolism	No	1 (3)

* 47 year old white male with diabetes mellitus type 2, dyslipidemia, 2+ proteinuria at baseline: developed 3+ proteinuria at Week 36. Creatinine 1.1 Day 1; 0.98 W48. Completed 48 weeks E/C/F/TAF without interruption

** 76 year old black male with diabetes mellitus type 2, dyslipidemia, hypertension (poorly controlled), renal insufficiency: hospitalized Day 57 with hypotension, cough, diarrhea, renal failure requiring dialysis. E/C/F/TAF discontinued as no data on dosing in dialysis. Investigator considered event not related to E/C/F/TAF. As last on-study HIV RNA < 50 copies/ mL, subject was a PVR

Adverse Event Leading to Premature Study Drug Discontinuation

Adverse Event	E/C/F/TAF n=37 n (%)
Adverse Event	1 (3)
Muscle spasms	1 (3)*

* Investigator deemed that the Grade 2 AE of muscle spasms was study-drug related
- 67 year old white male switched from F/TDF+ATV+ritonavir
- Muscle cramps, calf, on Day 13
- E/C/F/TAF discontinued Day 43, AE resolved Day 52
- Electrolytes and other labs normal

Conclusions

- In this open-label study of participants with HIV-1 virus harboring the M184V and/or M184I mutation, switching to E/C/F/TAF:
  - Maintained virologic suppression (100%) using the week 12 PVR endpoint
  - Was well tolerated with no study-drug related Grade 3 or 4 adverse events and few discontinuations due to adverse events
- Switching to E/C/F/TAF merits further study and may be an option for patients with pre-existing M184V and/or M184I mutations.

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  V Abril López de Medrano, M Andreoni, JR Arribas Lopez, L Bernard, M Bickel, M Castaño Carracedo, D Coulston, E DeJesus, A Di Biagio, G Di Perri, C Duvivier, S Esser, J Gallant, M Galli, D Hagins, E Lazaro, A Lazzarin JM Llibre, J Mallolas, A Mills, C Miralles Álvarez, JM Molina, O Osiyemi, I Poizot-Martin, T Prazuck, D Prelutsky, P Pugliese, F Pulido, F Raffi, M Ramgopal, G Richmond, D Salmon-Ceron, J Schattenberg, P Sellier, P Shalit, HJ Stellbrink

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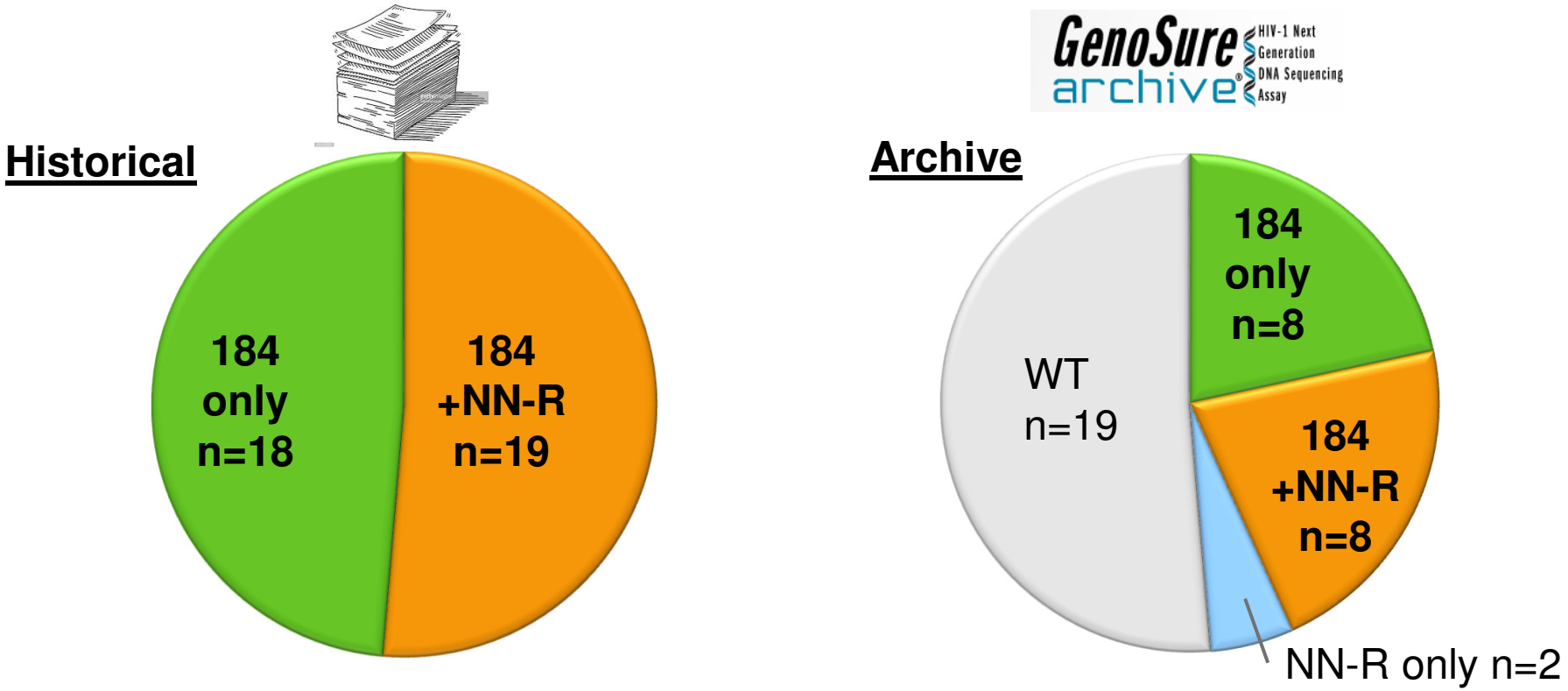
Back-Up

Screen Failures

Reason	Number of Participants Failing
Did not meet resistance criteria of M184V and/or M184I with no TAMS	17
Detectable viral load at screening	4
Hematology profile did not meet inclusion criteria	2
Antiretroviral regimen not meeting inclusion criteria	1
Total bilirubin > 1.5 mg/dL and/or abnormal direct bilirubin	1
Previous viral failure on PI/r or INSTI	2
Malignancy within last 5 years or ongoing	2
AIDS defining condition at screening	1
Hepatitis C therapy required during study	1
Contraindicated concomitant medication	1

Baseline Resistance (n=37)



- Historical: All patients had M184V/I
  - About ½ patients also have NNRTI-R HIV-1
- Archive: M184V/I in < ½ patients
  - Differences between HGR (circulating virus) and archive (integrated virus) reflect timing difference between the 2 compartments