Epzicom QD vs Truvada QD, Both with Kaletra QD, in ART-Naïve Patients: The HEAT Study 96 Weeks Analysis Results

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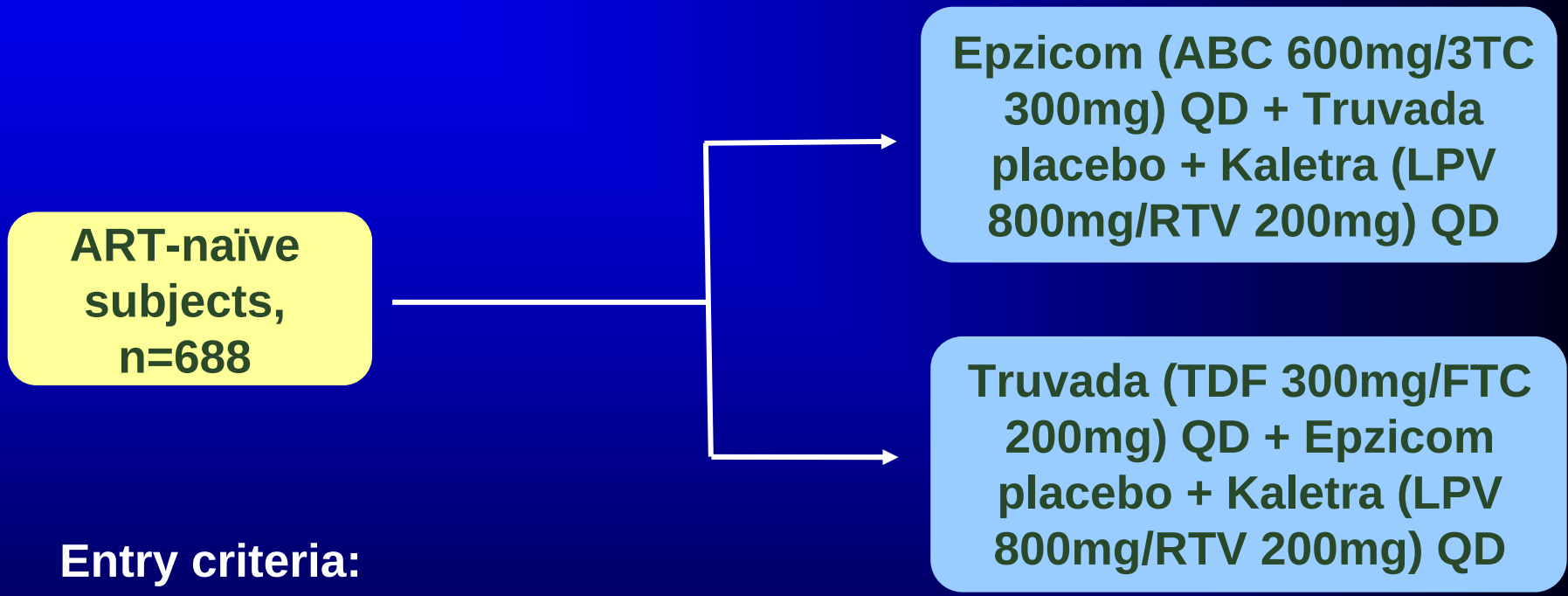
Objectives

- **To establish that EPZICOM QD is virologically noninferior to Truvada QD when administered in combination with Kaletra QD over 48 weeks in ART-naïve HIV-1 infected subjects.**
- **To compare the safety and tolerability of Epzicom QD versus Truvada QD when administered in combination with Kaletra QD over 96 weeks in ART-naïve HIV-1 infected subjects**

Study Design

Phase IV, randomized (1:1), double blind, 96 week study conducted at 78 sites in the US



Entry criteria:

- **HIV-1 RNA ≥1000 c/mL**
- **No CD4 cell count restrictions**

Stratified by entry HIV-1 RNA <100,000 c/mL or ≥100,000 c/mL

Endpoints

- **Primary**
  - Proportion of subjects with plasma HIV-1 RNA <50 copies/mL at Week 48.
  - Treatment-limiting adverse events, Grade 2-4 adverse events, events moderate to severe in intensity, and Serious Adverse Events over 96 weeks.
- **Secondary**
  - Treatment-limiting adverse events, Grade 2-4 adverse events, events moderate to severe in intensity, and Serious Adverse Events over 48 weeks.
  - Proportion of subjects with plasma HIV-1 RNA <50 copies/mL at Week 96.
  - Proportion of subjects with plasma HIV-1 RNA <400 copies/mL at Weeks 48 and 96.
  - Absolute values and change from baseline in plasma HIV-1 RNA and CD4+ cell counts at Weeks 48 and 96.
  - Time to virologic failure and time to loss of virologic response (TLOVR) based on HIV-1 RNA <50 and <400 copies/mL.
  - Change in HIV genotypic mutations and phenotypic resistance at the first point of virologic failure compared to baseline.

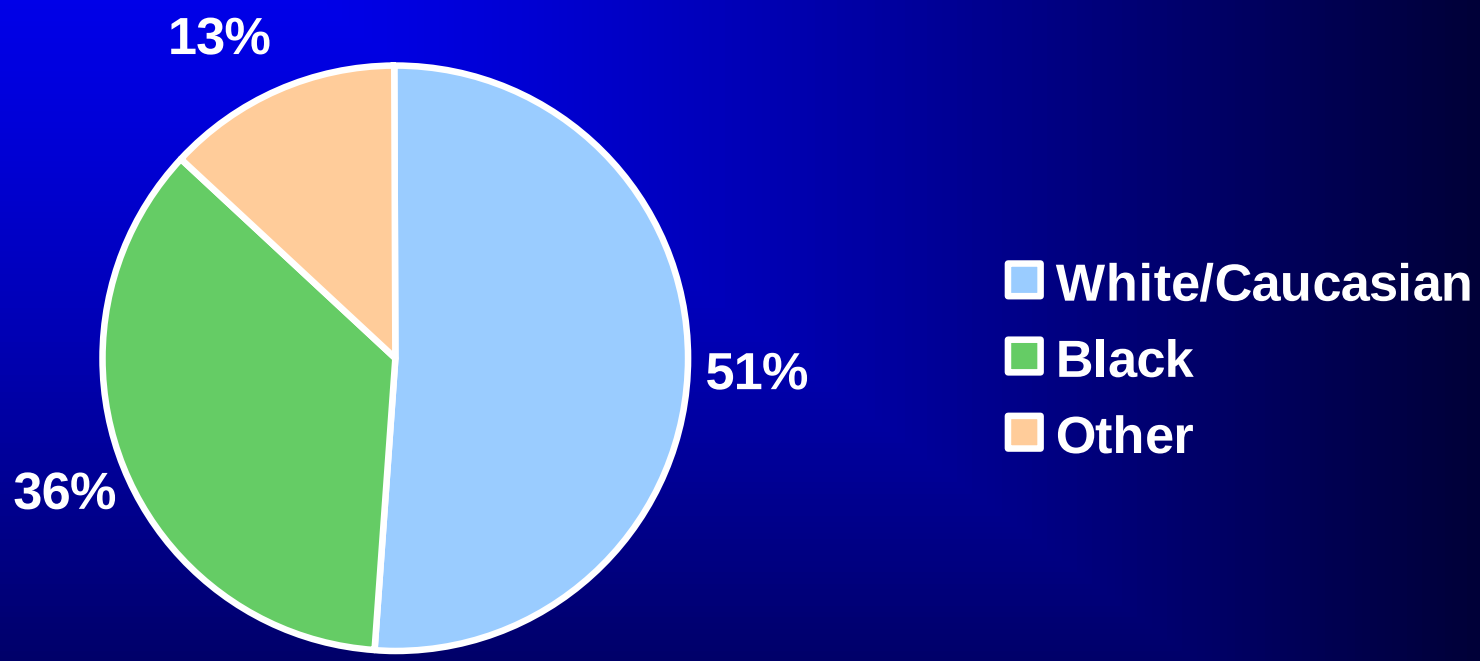
Protocol-Defined Virologic Failure

- **Virologic failure is defined as one of the following:**
  - **Week 24: no confirmed plasma HIV-1 RNA <200 copies/mL by Week 24; or confirmed reduction of plasma HIV-1 RNA levels to <50 copies/mL with a subsequent increase to ≥200 copies/mL on two consecutive occasions, at least 2 weeks and no more than 4 weeks apart.**
  - **After Week 24: plasma HIV-1 RNA levels ≥200 copies/mL on 2 consecutive occasions, at least 2 weeks and no more than 4 weeks apart**

Subject Accounting

	Epzicom n (%)	Truvada n (%)
All randomized	347	347
Intent-to-treat (ITT) population	347 (100%)	347 (100%)
ITT-Exposed (ITT-E) population	343 (99%)	345 (>99%)
Per-protocol population	338 (97%)	336 (97%)
Safety population (treatment received)	343	345

Racial Distribution (ITT-E), n=688



Baseline Characteristics (ITT-E)

	Epzicom (N=343)	Truvada (N=345)	Total (N=688)
Mean age, years	38	39	38
Male	84%	80%	82%
HIV-1 Risk Factors			
Homosexual	214 (64%)	206 (61%)	420 (62%)
Heterosexual	117 (35%)	139 (41%)	256 (38%)
IDU	20 (6%)	17 (5%)	37 (5%)
CDC Class C	55 (16%)	57 (17%)	112 (16%)
Hepatitis			
Hep B Positive	19 (6%)	9 (3%)	28 (4%)
Hep C Positive	27 (8%)	24 (7%)	51 (7%)

Baseline Characteristics, cont.

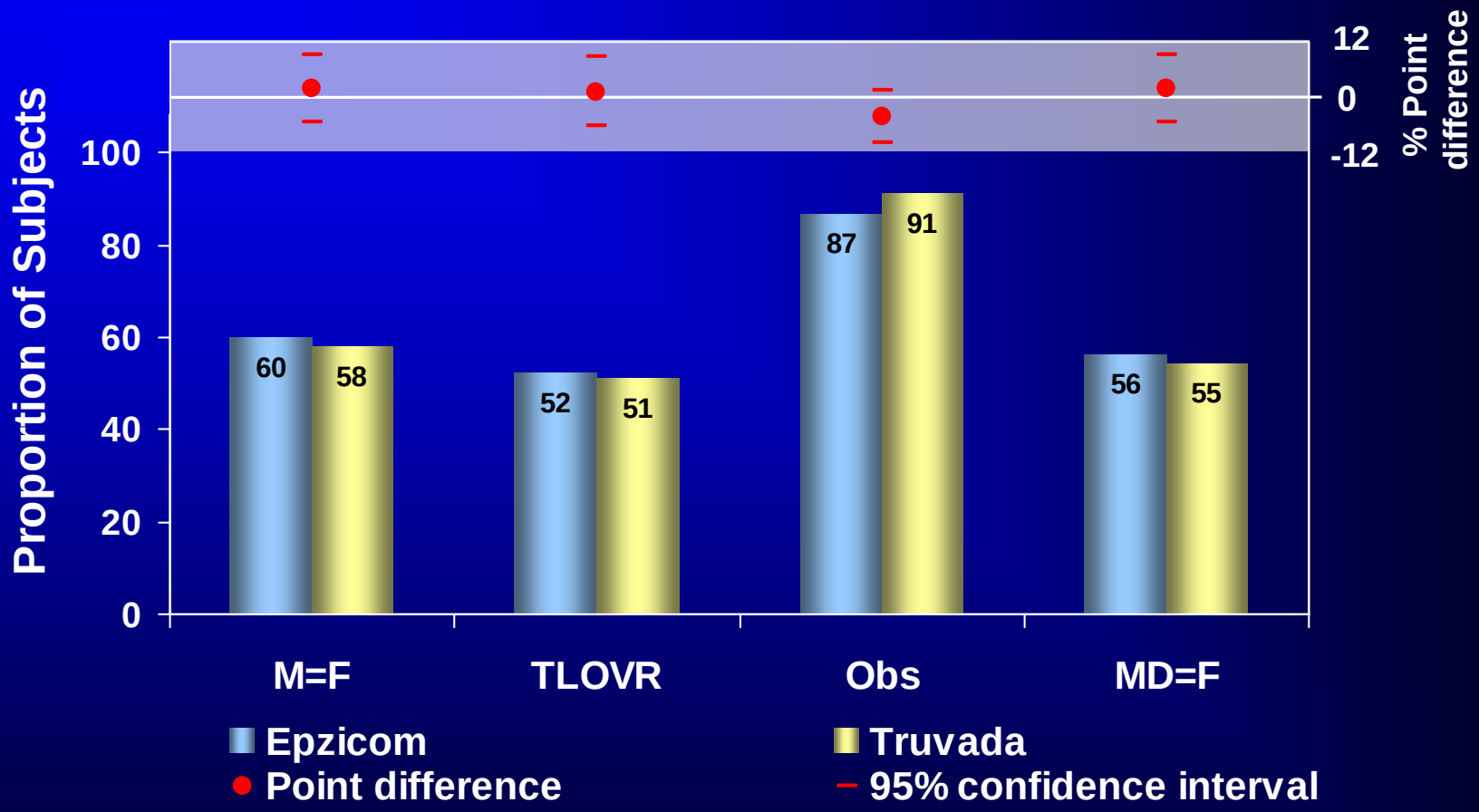
	Epzicom (N=343)	Truvada (N=345)	Total (N=688)
Median HIV-1 RNA, $\log_{10}$ c/mL	4.90	4.84	4.88
HIV-1 RNA <100,000 c/mL	188 (55%)	205 (59%)	393 (57%)
HIV-1 RNA ≥100,000 c/mL	155 (45%)	140 (41%)	295 (43%)
Median CD4 count, cells/mm^3	214	193	202
<50 cells/mm^3	61 (18%)	70 (20%)	131 (19%)
50 - <200 cells/mm^3	99 (29%)	110 (32%)	209 (30%)
≥200 cells/mm^3	183 (53%)	165 (48%)	348 (51%)

Subject Disposition

	Epzicom (N=343)	Truvada (N=345)	Total (N=688)
Completion Status			
Completed	234 (68%)	221 (64%)	455 (66%)
Prematurely withdrawn	109 (32%)	124 (36%)	233 (34%)
Primary Reason for withdrawal			
n	109	124	233
Adverse event	20 (18%)	21 (17%)	41 (18%)
Protocol violation	2 (2%)	0	2 (<1%)
Protocol defined virologic failure	8 (7%)	6 (5%)	14 (6%)
Lost to follow-up	45 (41%)	52 (42%)	97 (42%)
Subject decision	13 (12%)	23 (19%)	36 (15%)
Non-compliance	10 (9%)	11 (9%)	21 (9%)
Disease progression	0	1 (<1%)	1 (<1%)
Other	11 (10%)	10 (8%)	21 (9%)

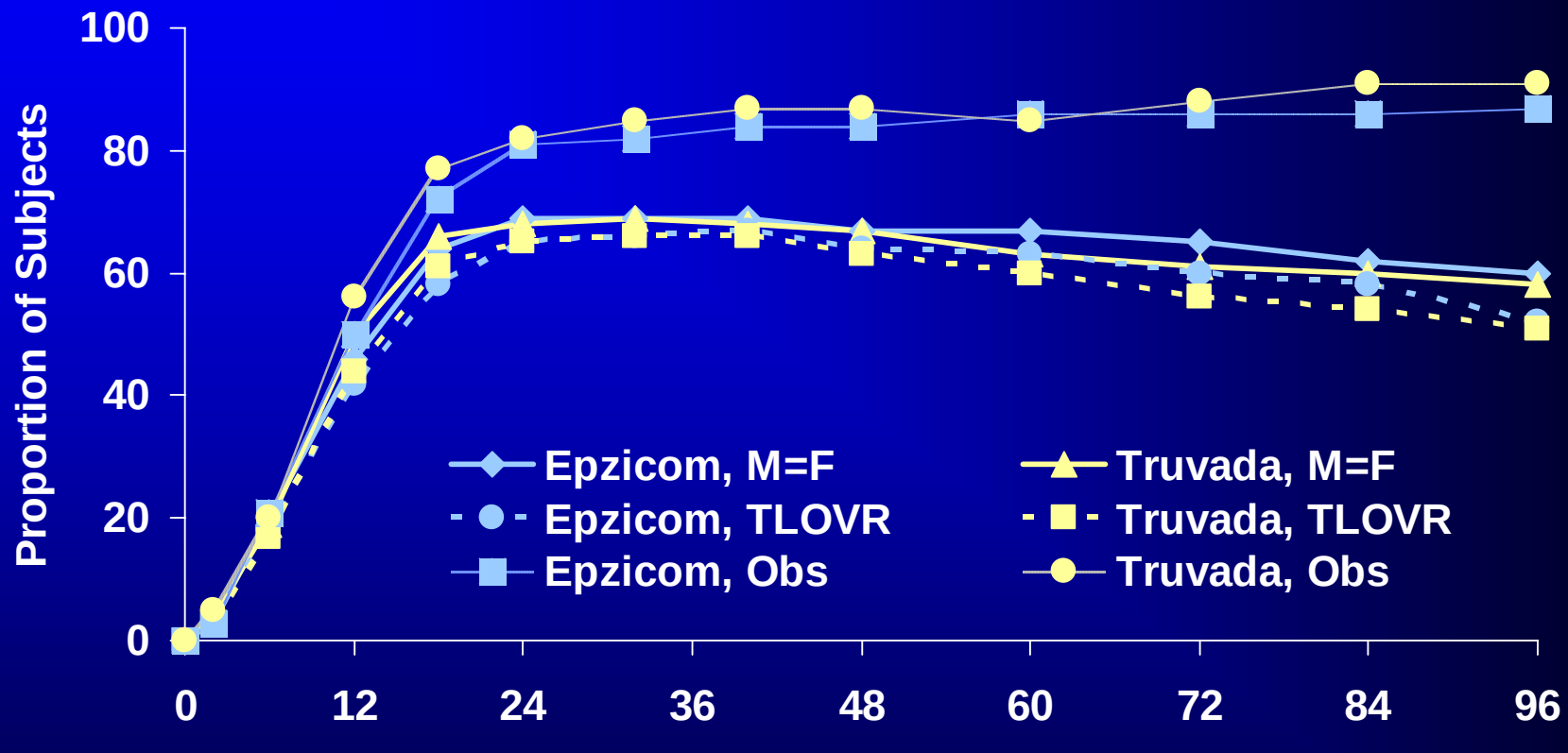
There were 8 deaths during the study, 1 (<1%) in the Epzicom arm and 7 (2%) in the Truvada arm; none were attributable to study drug.

ITT-E: HIV-1 RNA <50 c/mL at Week 96



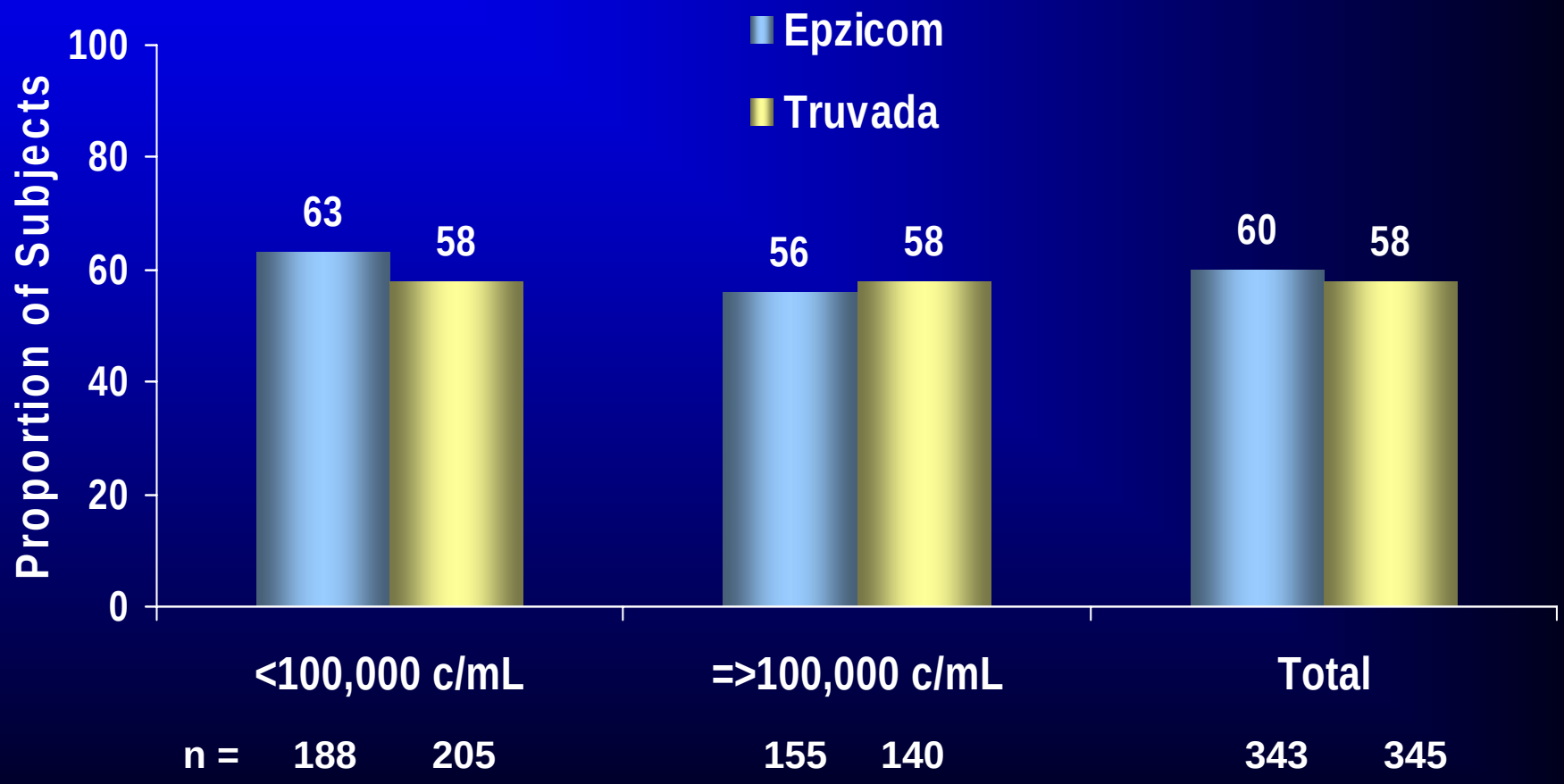
Results are stratified by baseline HIV-1 RNA

ITT-E: HIV-1 RNA <50 c/mL

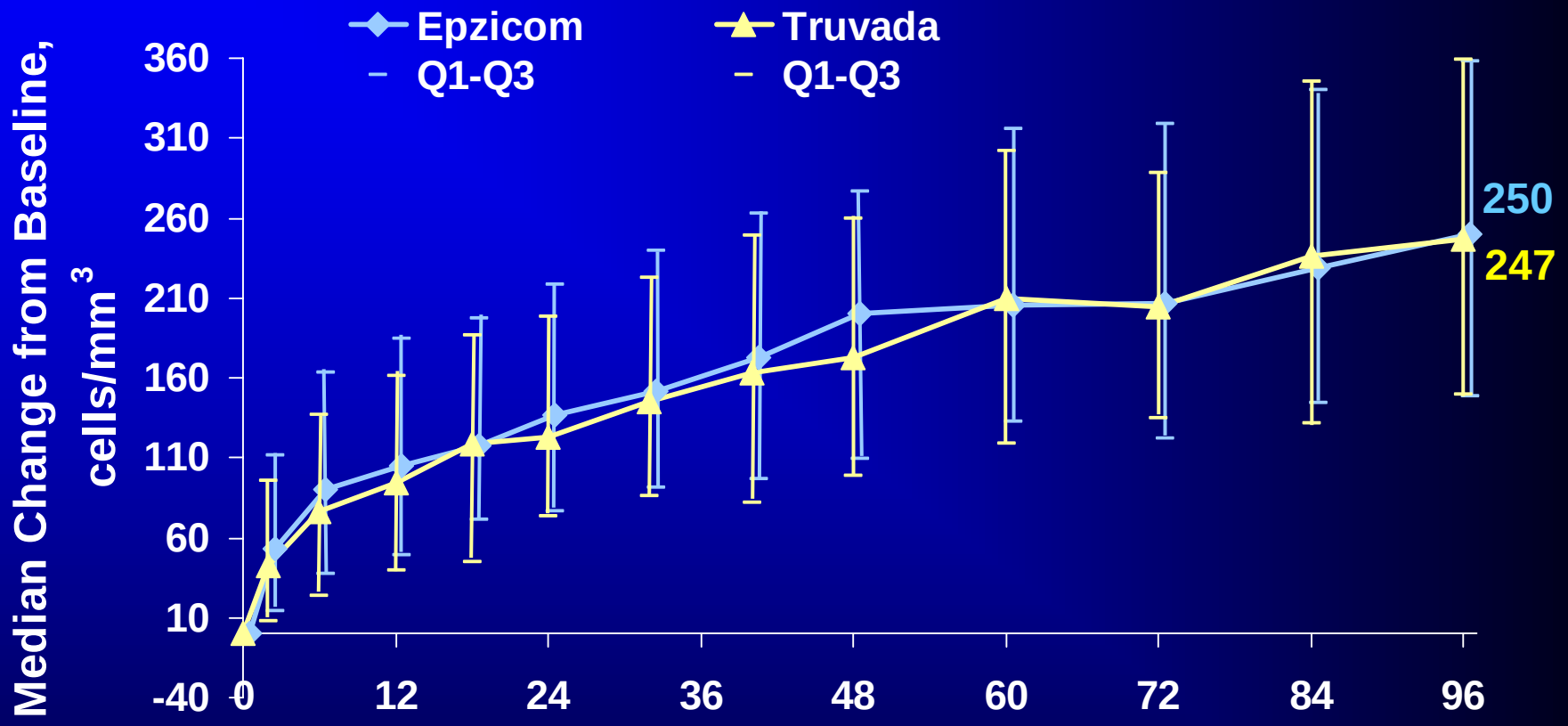


n (obs)									
Epzicom =343	312	295	290	282	275	268	258	249	236
Truvada = 345	308	286	280	272	267	255	238	229	219

HIV-1 RNA <50 c/mL at Week 96 by Baseline HIV-1 RNA (ITT-E, M=F)



Change from Baseline in CD4+ Cell Count (ITT-E, Obs)

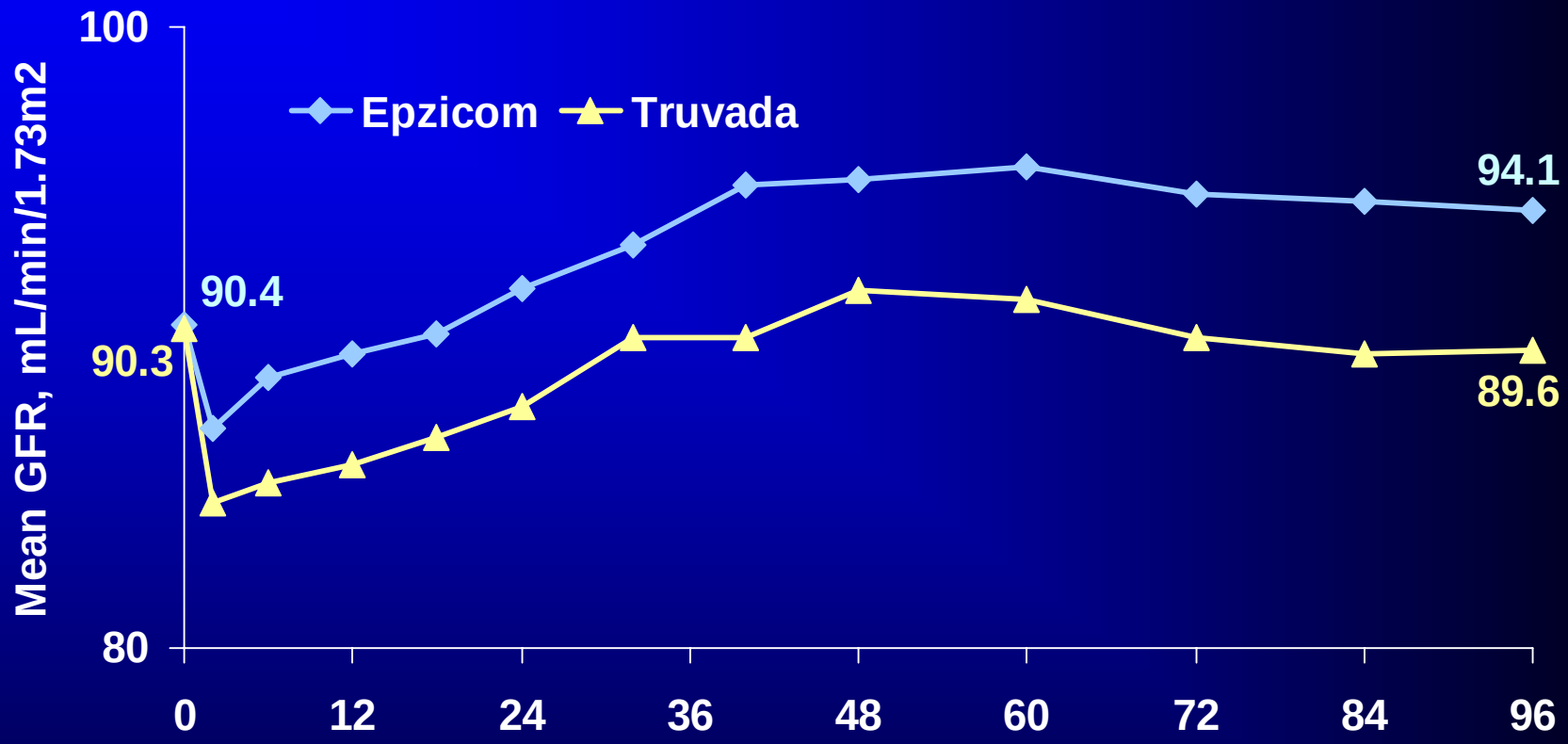


Median CD4+, cells/mm^3	214									466
	193									445
n (obs)										
Epzicom =	343	310	294	285	275	272	267	255	248	234
Truvada =	345	306	287	277	270	267	254	237	230	218

Overall Summary of Adverse Events (AEs)

	Epzicom (N=343)	Truvada (N=345)
Grade 2-4 AEs	274 (80%)	275 (80%)
Severe or Grade 3-4 AEs	102 (30%)	96 (28%)
Serious AEs	42 (12%)	45 (13%)
AEs Leading to Study Discontinuation	19 (6%)	22 (6%)
Death	1 (<1%)	7 (2%)

Glomerular Filtration Rate (GFR, MDRD)



n (obs)									
Epzicom =	343	317	297	289	284	276	267	257	247	236
Truvada =	345	308	292	278	272	268	256	236	230	219

Protocol-Defined Virologic Failures (ITT-E)

	Epzicom (N=343)	Truvada (N=345)	Total (N=688)
Virologic failures (VFs)	49 (14%)	48 (14%)	97 (14%)
Confirmed rebound to =>200 c/mL	28 (8%)	24 (7%)	52 (8%)
Failure to achieve confirmed <200 c/mL by Week 24	21 (6%)	24 (7%)	45 (7%)
Unconfirmed rebound at last visit (Suspected virologic failures)	12 (3%)	11 (3%)	23 (3%)

Resistance through 96 Weeks

	Epzicom	Truvada
Protocol Defined virologic failures	49	48
With Geno data at both BL and VF	45	41
No treatment-emergent mutations	27 (60%)	19 (46%)
Treatment-emergent mutations	18 (40%)	22 (54%)
NRTI-associated mutations	11 (24%)	17 (41%)
K70K/R, K70R	2	0
K65K/R	0	1
D67N	1	0
K219E	1	0
M41L	1	0
M184V, M184M/V, M184M/I, M184A/V, M184I, M184M/I/V	11	17
NNRTI-associated mutations	4 (9%)	3 (7%)
V90V/I	2	3
L100I	1	0
Y181Y/C	1	0
PI associated mutations	11 (24%)	7 (17%)
Major PI mutation*	1	0
Minor PI mutation	11	7

* Major PI associated mutations were detected in a single patient and were as follows: G48V, I54M, V82A, I84V.

Conclusions

- **In combination with Kaletra (LPV/r) QD, Epzicom (ABC/3TC) QD was comparable to Truvada (TDF/FTC) QD, in virologic and immunologic efficacy over 96 weeks**
- **The number of subjects with protocol-defined virologic failure was similar between the two treatment groups [EPZ: 14% vs TVD: 14%]**
- **Both regimens were well-tolerated and they were comparable in safety with few study discontinuations due to AEs**

Acknowledgements

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