Poster #1509

Emergence of HIV-1 Drug Resistance Through Week 48 in the Global Women's WAVES Study: Elvitegravir/Cobicistat/Emtricitabine/Tenofovir DF vs. Atazanavir + Ritonavir + Emtricitabine/Tenofovir DF

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Introduction

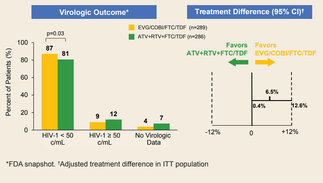
- Women comprise nearly half of the people living with HIV-1, but continue to be under-represented in HIV-1 antiretroviral treatment studies
- The **W**omen **A**ntiretro**V**iral **E**fficacy and **S**afety study (WAVES) is the first all-women, international, randomized, double-blind phase 3 trial designed to evaluate the efficacy, safety, and tolerability of two approved regimens (GS-US-236-0128) (Figure 1)
  - At 48 weeks, EVG/COBI/FTC/TDF was superior to ATV+RTV+FTC/TDF with response rates of 87% and 81%, respectively (Figure 2)
- This poster describes the resistance analyses at baseline and through Week 48
  - Resistance development was rare (0% EVG/COBI/FTC/TDF; 1% ATV+RTV+FTC/TDF)

Figure 1. Design of WAVES: the Phase 3 Study GS-US-236-0128 in Treatment-Naïve Women

Key eligibility criteria:
HIV-1 RNA > 500 copies/mL
Estimated GFR > 70 mL/min
No history of prior antiretroviral therapy
Sensitivity to FTC, TDF, and ATV
Stratification by HIV-1 RNA (≤ 100,000 copies/mL, > 100,000 copies/mL to ≤ 400,000 copies/mL, > 400,000 copies/mL) and race (Black or non-Black)

EVG/COBI/FTC/TDF: elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate
ATV+RTV+FTC/TDF: atazanavir + ritonavir + emtricitabine/tenofovir disoproxil fumarate

Figure 2. Virologic Outcome at Week 48 (HIV-1 RNA < 50 copies/mL), Study 236-0128



*FDA snapshot. †Adjusted treatment difference in ITT population

- Mean CD4 cell increase in both study arms: 196 cells/mm^3

Objectives of WAVES Resistance Studies

- Determine the impact of pre-existing HIV-1 drug resistance and HIV-1 subtype on treatment outcome through Week 48
- Describe resistance development through Week 48 in women with virologic failure or early discontinuation
- Describe HIV-1 deep sequencing results at baseline and virologic failure, and compare to population sequencing results

Methods

- **Screening Genotypic Analysis:** Genotypic analyses of HIV-1 protease (PR) and reverse transcriptase (RT) were performed at screening (GenoSure® MG, Monogram Biosciences)
  - Subjects with resistance to study drugs were excluded
  - No genotyping of integrase (IN) was conducted at screening
  - Nucleotide sequences from isolates designated "Complex Subtype" by the Monogram report were analyzed for subtype using the Rega website and reassigned if a clear subtype could be determined
- The **Resistance Analysis Population (RAP)** consisted of any study participant meeting the following criteria:
  - Suboptimal virologic response
    - < 1 $\log_{10}$ below baseline at Week 8 and HIV-1 RNA > 50 c/mL, confirmed at the next scheduled or unscheduled visit, with HIV-1 RNA ≥ 400 c/mL
  - Virologic rebound: two consecutive visits with HIV-1 RNA
    - ≥ 400 c/mL after achieving HIV-1 RNA < 50 c/mL (or at a single visit if at Week 48)
    - > 1 $\log_{10}$ increase from nadir and HIV-1 RNA ≥ 400 c/mL
  - Early discontinuation
    - HIV-1 RNA ≥ 400 c/mL at last visit, at or after Week 8
- **Post-Baseline Resistance Analyses:** Subjects who qualified for resistance testing had genotypic and phenotypic analyses of the PR and RT genes (PhenoSense GT®, Monogram Biosciences) and the IN gene (GeneSeq® IN and PhenoSense® IN, Monogram Biosciences) at the confirmation of failure visit or last visit
  - Genotypic and phenotypic PR, RT, and IN testing was also conducted at baseline for those subjects in the resistance analysis population
- **Deep Sequencing:** Deep sequencing of HIV-1 PR, RT, and IN was performed retrospectively on baseline and virologic failure timepoint samples from subjects in the resistance analysis population who did not later resuppress their HIV-1, and on baseline samples from all subjects in the EVG/COBI/FTC/TDF treatment arm
  - This analysis used the deepTypeHIV assay and Illumina MiSeq (SeqIT). Resistance substitutions were analyzed at mutation frequency cutoffs of 15% and 2%

Results

Table 1. HIV-1 Subtype and Outcome

- HIV-1 subtype had no impact on emergent resistance among women with virologic failure through Week 48

Subtype	Percent of Total Subjects (n)	Week 48 Snapshot			Week 48 Resistance Analysis (Resistance Developed/Analyzed)	
		HIV-1 RNA < 50 copies/mL	HIV-1 RNA ≥ 50 copies/mL	No Data in Window	EVG/COBI/FTC/TDF	ATV+RTV+FTC/TDF
B	25.6% (147)	74.8% (110)*	17.0% (25)*	8.2% (12)	0/5	1/7
Non-B	74.4% (428)	87.1% (373)	8.2% (35)	4.7% (20)	0/13	2/14
A or A1	46.1% (265)	84.9% (225)	9.8% (26)	5.3% (14)	0/11	2/11
AB	0.2% (1)	100% (1)	0	0	0/0	0/0
AE	4.9% (28)	96.4% (27)	3.6% (1)	0	0/2	0/0
AG	4.7% (27)	85.2% (23)	7.4% (2)	7.4% (2)	0/0	0/0
C	4.7% (27)	92.6% (25)	3.7% (1)	3.7% (1)	0/0	0/2
D	7.8% (45)	91.1% (41)	6.7% (3)	2.2% (1)	0/0	0/1
F1	0.2% (1)	0	100% (1)	0	0/0	0/0
G	1.9% (11)	90.9% (10)	0	9.1% (1)	0/0	0/0
Complex	4.0% (23)	91.3% (21)	4.3% (1)	4.3% (1)	0/0	0/0

*Most subjects with HIV-1 subtype B were located in the US (107/147, 90%), where the proportion of subjects with HIV-1 RNA < 50 copies/mL was lower than in the rest of the study, 68% in the EVG/COBI/FTC/TDF group and 70% in the ATV+RTV+FTC/TDF group. In the US, the proportion of subjects with at least 95% study drug adherence rate through Week 48 was 61%.
†Of the 25 HIV-1 subtype B subjects who had HIV-1 RNA ≥ 50 copies/mL at Week 48, 9 subjects were lost to follow up, 5 subjects were non-compliant with study drug, 5 subjects were failures due to other reasons and had last available HIV-1 RNA ≥ 50 copies/mL, 2 subjects added a new ARV, and 4 subjects had HIV-1 RNA ≥ 50 copies/mL at their Week 48 visit.

Results (cont'd)

Figure 3: Distribution of WAVES Enrollment Worldwide and HIV-1 Subtype (n=575)

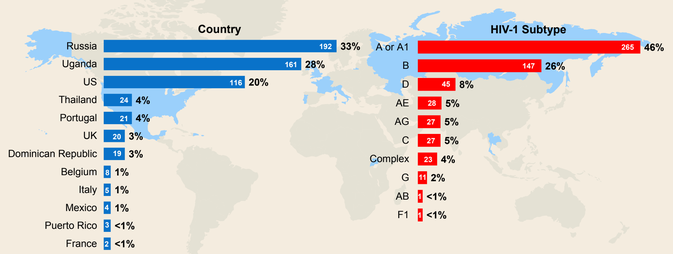


Table 2. Baseline PR and RT Resistance Mutations and Outcome

- Baseline PR and RT resistance mutations had no impact on virologic failure with resistance development through Week 48
  - Subjects with the pre-existing primary drug resistance mutations A62V or K103N in RT had comparable efficacy to the rest of the study population
  - Four subjects had the exclusion mutation M184I at low levels by deep sequencing: 3 of these subjects were virologic successes at Week 48 and 1 subject was lost to follow up with last available HIV-1 RNA < 50 copies/mL

Resistance Mutation	Percent of Subjects (n/n tested) by Population Sequencing	Percent of Subjects (n/n tested) by Deep Sequencing, ≥ 15%	Percent of Subjects (n/n tested) by Deep Sequencing, ≥ 2%	Week 48 HIV-1 RNA < 50 copies/mL by Snapshot, % (n/n with resistance)*	Week 48 Resistance Analysis (Resistance Developed/Analyzed)	
					EVG/COBI/FTC/TDF	ATV+RTV+FTC/TDF
Any Primary NRTI Mutation[b]	15.3% (88/575)	15.2% (47/309)	16.5% (51/309)	78.9% (75/95)	0/5	0/3
M41L	0.9% (5)	0	0	60.0% (3/5)	0/0	0/0
A62V[a]	13.6% (78)	14.9% (46)	14.9% (46)	78.8% (63/80)	0/4	0/3
D67N	0.2% (1)	0	0.3% (1)	100% (2/2)	0/0	0/0
F77L	0.2% (1)	0	0	100% (1/1)	0/1	0/0
M184I/V	0	0	1.3% (4)[c]	75.0% (3/4)	0/0	0/0
L210W	0.2% (1)	0.3% (1)	0.3% (1)	100% (2/2)	0/0	0/0
K219E/N/Q/R	0.2% (1)	0.3% (1)	0.3% (1)	100% (3/3)	0/0	0/0
Any Primary NNRTI Mutation[c]	20.0% (115/575)	17.8% (55/309)	27.8% (86/309)	75.0% (111/148)	0/8	3/10
V90I	7.1% (41)	5.8% (18)	9.1% (28)	68.0% (34/50)	0/5	0/3
A98G	0.3% (2)	0.3% (1)	0.6% (2)	100% (3/3)	0/0	0/0
K101E/H/P	0.7% (4)	1.0% (3)	1.3% (4)	100% (7/7)	0/0	0/1
K103N	3.0% (17)	2.9% (9)	3.2% (10)	77.8% (14/18)	0/2	1/3
K103S	0.5% (3)	0.3% (1)	0.3% (1)	33.3% (1/3)	0/1	0/0
V106A/M/I	1.9% (11)	1.9% (6)	3.9% (12)	82.4% (14/17)	0/0	1/1
V108I	0.5% (3)	0.6% (2)	1.0% (3)	50.0% (2/4)	0/0	0/0
E138A/G/K/Q/R	6.6% (38)	6.1% (19)	7.4% (23)	81.8% (36/44)	0/0	1/3
V179D/F/L/T	1.4% (8)	1.3% (4)	1.9% (6)	60.0% (6/10)	0/0	0/0
G190A/E/Q/S	0.5% (3)	0.3% (1)	1.0% (3)	80.0% (4/5)	0/0	0/0
P225H	0	0	0.3% (1)	100% (1/1)	0/0	0/0
M230I/L	0	0	3.6% (11)	81.8% (9/11)	0/1	0/0
Any Primary PI Mutation[d]	1.7% (10/575)	1.3% (4/309)	8.1% (25/309)	76.7% (23/30)	0/2	0/0
D30N	0	0	0.3% (1)	100% (1/1)	0/0	0/0
V32I	0	0.3% (1)	0.6% (2)	50.0% (1/2)	0/0	0/0
L33F	0.5% (3)	0.3% (1)	0.6% (2)	75.0% (3/4)	0/0	0/0
M46I/L	0.7% (4)	0	2.3% (7)	80.0% (8/10)	0/1	0/0
G48V	0	0	3.9% (12)	83.3% (10/12)	0/1	0/0
I50L/V	0.2% (1)	0	0	100% (1/1)	0/0	0/0
Q58E	0.3% (2)	0.6% (2)	0.6% (2)	50.0% (1/2)	0/0	0/0
L90M	0.2% (1)	0.3% (1)	0.3% (1)	0	0/0	0/0

*This analysis includes any subject with resistance detected by either population or deep sequencing.
[a] Primary NRTI resistance mutations are M41L, A62V, K65R, D67N, T69 insertions, K70E/R, L74I/V, V75I, F77L, Y115F, F116Y, Q151M, M184I/V, L210W, T215F/Y, and K219E/N/Q/R in RT.
[b] Primary NNRTI resistance mutations are V90I, A98G, L100I, K101E/H/P, K103N/S, V106A/M, V108I, E138A/G/K/Q/R, V179D/F/L/T, Y181C/I/V, Y188C/H/L, G190A/E/Q/S, H221Y, P225H, F227C, and M230I/L in RT.
[c] Primary PI resistance mutations are D30N, V32I, L33F, M46I/L, I47A/V, G48V, I50L/V, I54L/M, Q58E, T74P, L76V, V82A/F/I/L/S/T, I84V, N88S, and L90M in PR.
[d] The most common pre-existing NRTI-associated substitution was A62V, and all subjects with this substitution were located in Russia.
[e] Four subjects had the exclusion mutation M184I at low levels by deep sequencing, and 3 of these subjects were virologic successes at Week 48, and one subject was lost to follow up with the last available HIV-1 RNA < 50 copies/mL.

Table 3: Baseline IN Resistance Mutations and Outcome

- Baseline IN resistance mutations had no impact on virologic failure with resistance development through Week 48
  - Subjects with the pre-existing primary drug resistance mutation T97A in IN had high efficacy

Resistance Mutation	Percent of Subjects (n/n tested) by Deep Sequencing, ≥ 15%	Percent of Subjects (n/n tested) by Deep Sequencing, ≥ 2%	Week 48 HIV-1 RNA < 50 copies/mL by Snapshot, % (n/n with resistance)	Week 48 Resistance Analysis (Resistance Developed/Analyzed)	
				EVG/COBI/FTC/TDF	ATV+RTV+FTC/TDF
Any Primary IN Mutation[a]	3.2% (10/309)	4.9% (15/309)	93.3% (14/15)	0/0	1/1
E92G/Q	0	0.3% (1)	100% (1)	0/0	0/0
T97A	3.2% (10)[c]	3.6% (11)	90.9% (10)	0/0	1/1
S147G	0	0.6% (2)	100% (2)	0/0	0/0
N155H/S	0	0.3% (1)	100% (1)	0/0	0/0
Any Secondary IN Mutation[b]	56.0% (173/309)	62.8% (194/309)	87.1% (169/194)	0/12	3/3
M50I[d]	16.8% (52)	23.6% (73)	86.3% (63)	0/3	0/0
H51Y	0	0.3% (1)	100% (1)	0/0	0/0
L68I/V	0.6% (2)	2.3% (7)	100% (7)	0/0	0/0
V72A/N/T	1.6% (5)	2.3% (7)	100% (7)	0/0	0/0
L74M	2.6% (8)	2.9% (9)	88.9% (8)	0/0	0/0
Q95K/R	0.3% (1)	0.6% (2)	50.0% (1)	0/1	0/0
S119P/R/T[d]	40.1% (124)	40.1% (124)	87.9% (109)	0/8	2/2
F121C/Y	0	0.3% (1)	0	0/0	0/0
A128T	0	1.3% (4)	75.0% (3)	0/0	0/0
E138A/K	0.3% (1)	0.3% (1)	100% (1)	0/0	0/0
G140A/C/S	0	0.3% (1)	100% (1)	0/0	0/0
Q148I/K/L/P/R	0	1.3% (4)	100% (4)	0/0	0/0
S153A/F/Y	0	1.3% (4)	50.0% (2)	0/1	0/0
E157K/Q	3.2% (10)	6.5% (20)	85.0% (17)	0/0	1/1
E170A	0	0.3% (1)	100% (1)	0/0	0/0
R263K	0	0.6% (2)	100% (2)	0/0	0/0

[a] Primary IN resistance mutations are T66A/I/K, E92G/Q, T97A, Y143C/H/R, S147G, Q148H/K/R, and N155H/S in IN.
[b] Secondary IN resistance mutations are M50I, H51Y, L68I/V, V72A/N/T, L74M, Q95K/R, G118R, S119P/R/T, F121C/Y, A128T, E138A/K, G140A/C/S, P145S, Q146I/K/L/P/R, V151A/L, S153A/F/Y, E157K/Q, G163K/R, E170A, and R263K in IN.
[c] Baseline samples from the 10 subjects with T97A at ≥ 15% were sent for population IN sequencing, and the presence of T97A was confirmed. Phenotyping of these samples found that 5 of these samples showed a > 2.5-fold change in susceptibility to EVG.
[d] The most prevalent resistance substitutions observed were S119P and M50I, which are known polymorphisms.

Table 4: Emergent Drug Resistance in Subjects with Virologic Failure Through Week 48

	EVG/COBI/FTC/TDF n=289 (% of RAP, % of total N)	ATV+RTV+FTC/TDF n=286 (% of RAP, % of total N)
Resistance Analysis Population (RAP)	18 (6.2%)	21 (7.3%)
Subjects who resuppressed HIV-1 RNA to < 50 copies/mL while on study drugs	11 (61.1%; 3.8%)	9 (42.9%; 3.1%)
Developed resistance mutations to study drugs	0	3 (14.3%; 1.0%)
Any NRTI-R	1 (5.6%; 0.3%)*	3 (14.3%; 1.0%)
M184V/I	0	3 (14.3%; 1.0%)
K65R	0	0
Any NNRTI-R	0	1 (4.8%; 0.3%)†
Any INSTI-R	0	0
Any primary PI-R	0	0

* One subject developed D67D/N, but remained phenotypically susceptible to all drugs in their regimen.
† One subject developed A98A/G, but this subject resuppressed HIV-1 RNA to < 50 c/mL while on study drug.

Table 5: Deep Sequencing Did Not Find Additional Study Drug-Related Mutations

- Total Resistance Analysis Population n = 39
  - 33 had no emergent resistance by population or deep sequencing
  - 3 had emergent resistance to study drugs by population and deep sequencing
  - 3 had emergent resistance, but not to study drugs

Subject Number	Treatment Group	Subtype	Time of Virology Analysis	Developed Resistance to Study Drugs	Population Genotype (Deep Genotype ≥ 2%, Variant Frequency)				Phenotype (Fold-Change vs. Wild-Type)*					
					Primary INSTI-R	PI-R	NRTI-R	NNRTI-R	INSTI	PI	NRTIs		NNRTIs	
									EVG	ATV	FTC	TFV	EFV	NVP
1	ATV+RTV+FTC/TDF	B	W8	Yes	None (None)	None (None)	**M184M/I/V** (**M184I**, 25.5%)	(V106V/I/M)[c] [(V106I), 76.5%)]	1.00	1.25	2.11	0.58	0.70	0.93
2	ATV+RTV+FTC/TDF	A1	W48	Yes	None (None)	None (None)	**M184M/I/V** (**M184V**, 54.6%; **M184I**, 44.9%)	None (None)	No data	1.03	4.95	0.65	0.70	0.70
3	ATV+RTV+FTC/TDF	A1	W16	Yes	None (None)	None (None)	**M184V** (**M184V**, 99.4%)	(K103N) [(K103N), 99.1%]	1.38	0.78	>102	0.54	16.9	75
4	ATV+RTV+FTC/TDF	A1	W24	No	None (No DS data)	None (No DS data)	None (No DS data)	**A98A/G**[c] (No DS data)	1.62	AF	AF	AF	AF	AF
5	EVG/COBI/FTC/TDF	B	W32	No	None (No DS data)	None (No DS data)	**D67D/N**[c] (No DS data)	None (No DS data)	1.33	0.92	1.41	1.13	1.09	1.73
6	EVG/COBI/FTC/TDF	B	W16	No	None (None)	None (None)	None (None)	None (**K101E**[c], 23.1%)	0.87	0.54	1.13	0.92	0.81	0.59

DS = deep sequencing; AF = assay failure; W = week
* Phenotypes with fold-changes above the biological or lower clinical cutoff are shaded red. Phenotypes are listed for elvitegravir, atazanavir, emtricitabine, tenofovir, efavirenz, and nevirapine.
[a] Mutations listed in parentheses were present at baseline by population sequencing and are not considered to be developed resistance mutations.
[c] Resistance mutations detected were not associated with resistance to study drugs.

Conclusions

- Among 575 women worldwide, high efficacy was observed in women treated with EVG/COBI/FTC/TDF and ATV+RTV+FTC/TDF at Week 48
- HIV-1 subtype did not affect treatment outcome and/or resistance development
- EVG/COBI/FTC/TDF had high efficacy in subjects with pre-existing primary drug resistance mutations, including A62V and K103N in RT, and T97A in IN
- Both drug regimens demonstrated a high barrier to resistance
  - No women developed primary resistance to study drugs in the EVG/COBI/FTC/TDF group
  - Three women in the ATV+RTV+FTC/TDF group (1.0%) developed the primary resistance mutation M184V/I in RT
- Deep sequencing did not detect additional emergent resistance to study drugs

References

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2. Squires et al., Lancet HIV 2016, 3 (9): e410-e420.
3. Varghese et al., AIDS Research and Human Retroviruses 2010, 26 (12): 1323-1326.

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