Genotypic Analysis of the Global Clinical Trial of Treatment-Naïve Women: WAVES

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Background

- Transmitted HIV-1 variants associated with drug resistance are frequent (5-20%)[1,2] and vary across time and by geographic location
- Presence of resistance mutations may impact subsequent outcome of patients treated with antiretroviral agents

[1]Poon et al. Plos One. 2011; 6(6): e21189.
[2]Wheeler et al. AIDS. 2010; 24:12-3-1212

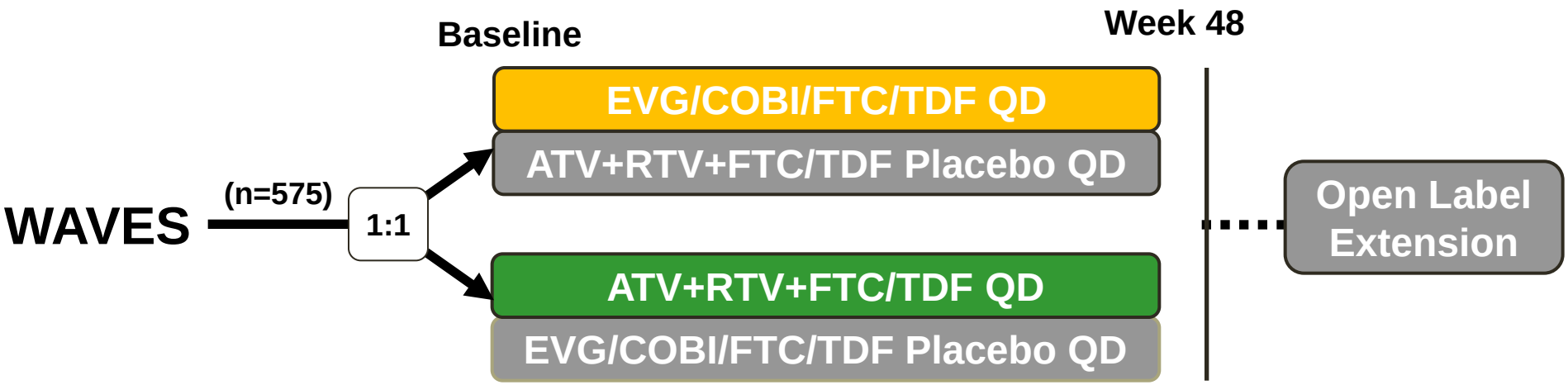
Waves Overview

Women Antiretroviral Efficacy and Safety study (WAVES) is the first women only, international, randomized, double-blind, phase 3 clinical trial designed to evaluate the safety and efficacy of two recommended regimens

Objectives

- Determine the global distribution of women enrolled in WAVES
- Describe the global HIV-1 subtype distribution of subjects enrolled in WAVES
- Determine the frequency of HIV-1 resistance mutations in the protease and reverse transcriptase genes of WAVES participants

WAVES Study Design



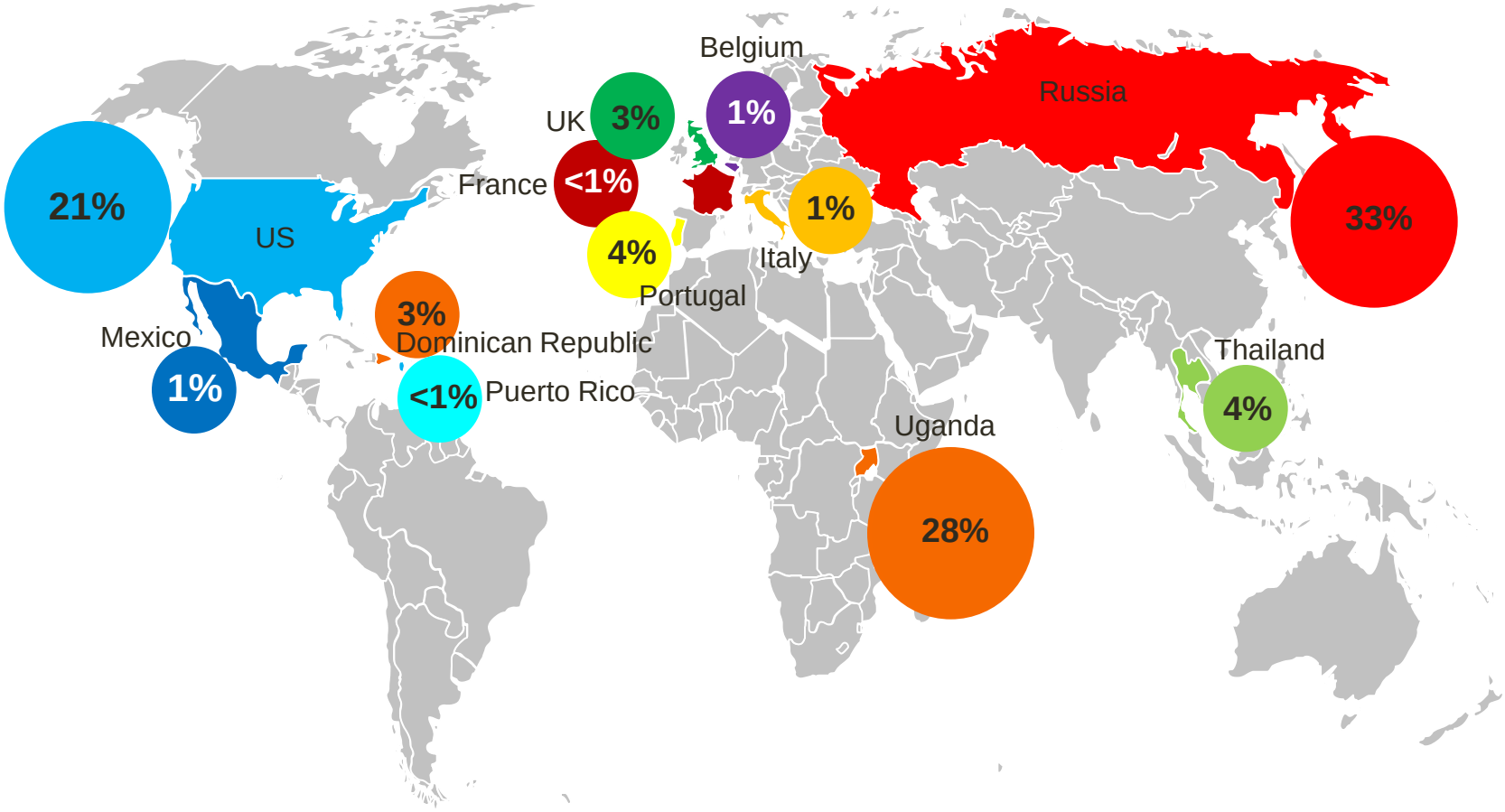
Key eligibility criteria:
HIV-1 RNA > 500 copies/mL
estimated GFR > 70 mL/min
no history of prior antiretroviral therapy
sensitivity to FTC, TDF, and ATV
Stratification by HIV-1 RNA (> / ≤ 100,000 copies/mL, (> / ≤ 400,000 copies/mL) and race (Black or non-Black)

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

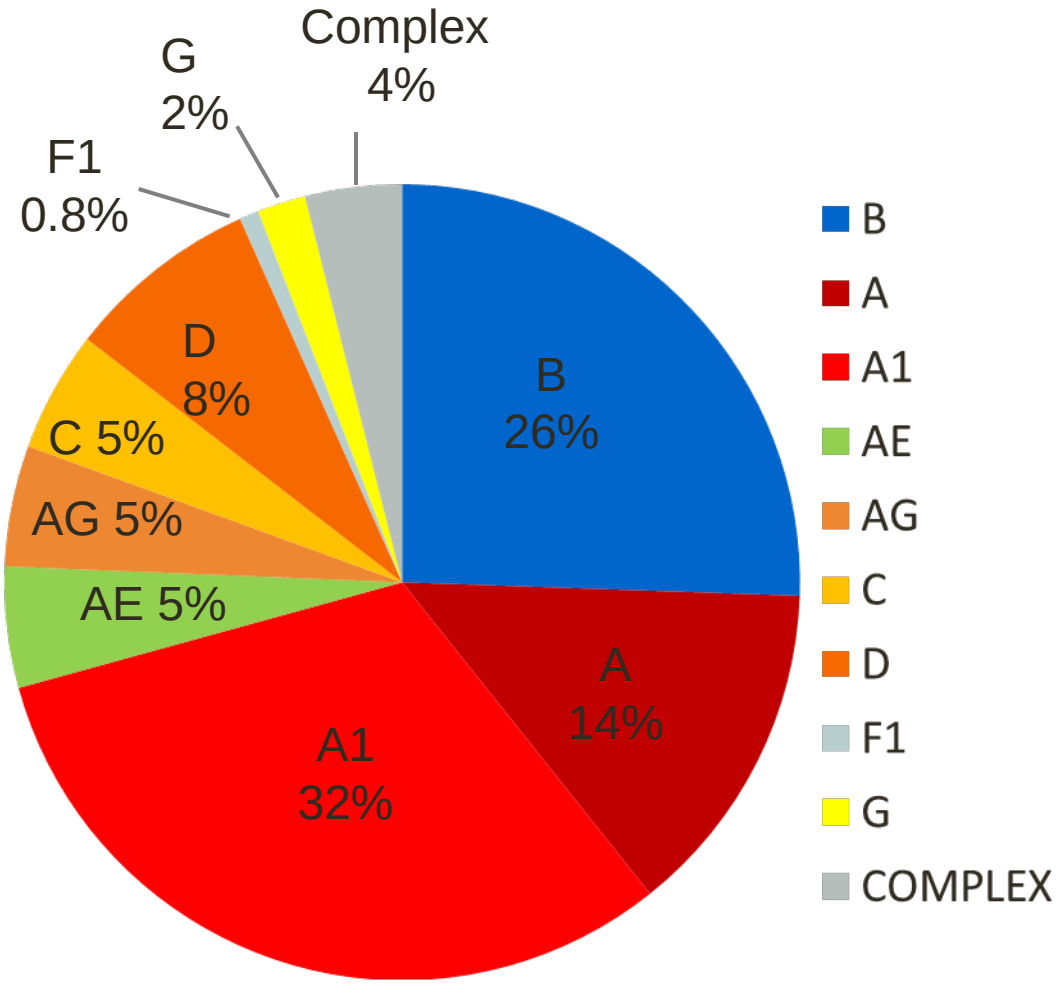
Methods

- Genotypic analyses of protease and reverse transcriptase genes were conducted
- Drug susceptibilities were predicted by Monogram Biosciences.
- Descriptive statistics are used and comparisons amongst various groups was conducted using Fisher's exact

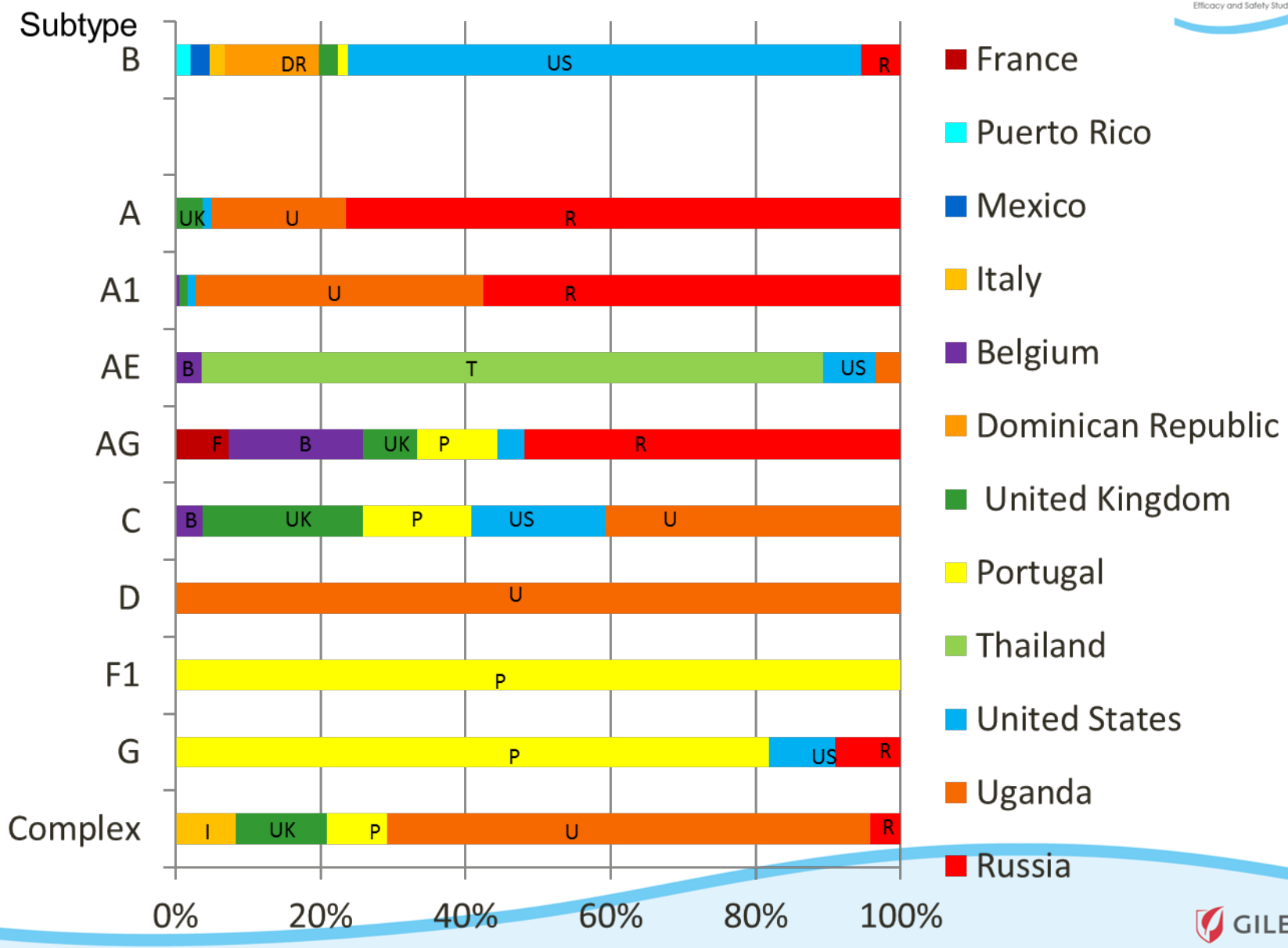
Distribution of WAVES Participants



Distribution of Patients by HIV-1 Subtype (n=575)



Global Subtype Distribution in WAVES



Predicted ARV Resistance at Baseline

Antiretroviral *	Prevalence of predicted reduced drug susceptibility (%)		
	All	B	Non-B
NRTI[a]	**1.0**	**1.4**	**0.9**
tenofovir	0	0	0
emtricitabine/lamivudine	0	0	0
abacavir	0	0	0
zidovudine	1.0	1.4	0.9
NNRTI	**11.3**	**12.9**	**10.7**
efavirenz	4.9	10.2	3.0**
etravirine	0.3	0.7	0.2
nevirapine	5.2	10.9	3.3**
rilpivirine	7.0	4.1	7.9
PI	**13.4**	**2.7**	**17.1****
atazanavir	0	0	0

- No genotypic on HIV-1 integrase was conducted at screening.
- ** P<0.01

Baseline Resistance Mutations by Subtype

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HIV-1 Subtype	Frequency of Resistance Mutations, n (%)		
	NRTI-R	NNRTI-R	PI-R
All Subtypes (n=575)	**115 (20.0%)**	**115 (20.0%)**	**10 (1.7%)**
B (n=147)	13 (8.8%)	24 (16.3%)	4 (2.7%)
Non-B (n=428)	102 (23.8%)	91 (21.3%)	6 (1.4%)
A (n=81)	34 (42.0%)	15 (18.5%)	1 (1.2%)
A1 (n=184)	60 (32.6%)	49 (26.6%)	2 (1.1%)
AE (n=28)	0	2 (7.1%)	2 (7.1%)
AG (n=27)	0	2 (7.4%)	0
C (n=27)	2 (7.4%)	6 (22.2%)	0
D (n=45)	4 (8.9%)	11 (24.4%)	1 (2.2%)
F1 (n=1)	0	1 (100.0%)	0
G (n=11)	0	1 (9.1%)	0
Rare/Complex (n=24)	2 (8.3%)	4 (16.7%)	0

NRTI resistance-associated substitutions (NRTI-R) are M41L, E44D, A62V, K65R, D67N, T69D, T69 insertions, K70E/R, L74I/V, V75I, F77L, Y115F, F116Y, V118I, Q151M, M184V/I, L210W, T215F/Y, K219E/N/Q/R in RT.
NNRTI resistance-associated substitutions (NNRTI-R) are V90I, A98G, L100I, K101E/H/P, K103N, V106A/I/M, V108I, E138A, V179D/F/T, Y181C/I/V, Y188C/H/L, G190A/S, P225H, M230L in RT.
Primary protease inhibitor resistance-associated substitutions (PI-R) are D30N, V32I, L33F, M46I/L, I47A/V, G48V, I50L/V, I54L/M, Q58E, T74P, L76V, V82A/F/L/S/T, I84V, N88S, L90M in protease.

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ARV Resistance Mutations by Country

Resistance	Frequency of Resistance by Country, n (%)		
	United States (n=119)	Russia (n=192)	Uganda (n=161)
NRTI-R	11 (9.5%)	85 (44.3%)	17 (10.6%)
A62V	0	78 (40.6%)	0
V118I	5 (4.3%)	7 (3.6%)	8 (5.0%)
K65R	0	0	0
M184V/I	0	0	0
NNRTI-R	23 (19.8%)	50 (26.0%)	31 (19.3%)
K103N	9 (7.8%)	2 (1.0%)	4 (2.5%)
V106A/I/M	3 (2.6%)	1 (0.5%)	3 (1.9%)
E138A/G/K/Q/R	7 (6.0%)	16 (8.3%)	11 (6.8%)
V90I	2 (1.7%)	31 (16.1%)	8 (5.0%)
PI-R	4 (3.4%)	3 (1.6%)	1 (0.6%)

Conclusions

- WAVES enrolled 575 patients spanning 11 countries on 4 continents

- WAVES studies many HIV-1 subtypes
  - 74% non-B subtype HIV-1
  - 26% HIV-1 subtype B

- Pre-existing genotypic NRTI resistance substitutions were common
  - NRTI-R was most prevalent in subtypes A and A1; A62V in Russia
  - No impact on sensitivity to nucleoside(tide) agents used in study
  - Future impact on A62V on treatment outcomes will be assessed

- Pre-existing genotypic NNRTI resistance mutations were common
  - NNRTI-R mutations were more frequent in subtype A1; V90I
  - Predicted resistance to EFV and NVP was present in 10% (subtype B) and 3% (non-B subtype); transmitted K103N

- Pre-existing genotypic PI resistance mutations were uncommon but 13% of patients had predicted genotypic resistance largely to uncommonly used agents.

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Special Thanks to

WAVES Participant

Waves Investigators

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