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| **Supplementary Table 1.** Additional Characteristics of Psychiatric Symptoms\* That Occurred During DTG Clinical Trials | | | | | | | | | | | | |
|  | **SPRING-2**  **ART naive**  **Double blind**  **96 weeks** | | **FLAMINGO**  **ART naive**  **Open label**  **96 weeks** | | **SINGLE**  **ART naive**  **Double blind†**  **144 weeks** | | **ARIA**  **ART naive**  **Open label**  **48 weeks** | | **SAILING**  **ART experienced**  **Double blind**  **48 weeks** | | **Total DTG**  **(n=1672)** | **Total comparator arms**  **(n = 1681)** |
| **Cases** | **DTG + 2NRTIs‡**  **(n=411)** | **RAL + 2NRTIs‡ (n=411)** | **DTG + 2NRTIs‡ (n=242)** | **DRV/r + 2NRTIs‡ (n=242)** | **DTG + ABC/3TC (n=414)** | **EFV/TDF/FTC (n=419)** | **ABC/ DTG/3TC (n=248)** | **ATV/r + TDF/FTC (n=247)** | **DTG + ISBR (n=357)** | **RAL + ISBR (n=362)** |
| **Insomnia, n (%) [number of events]** | **25 (6%) [25]** | **20 (5%) [21]** | **20 (8%) [22]** | **16 (7%) [17]** | **71 (17%) [80]** | **52 (12%) [55]** | **10 (4%) [10]** | **8 (3%) [8]** | **12 (3%) [12]** | **14 (4%) [15]** | **138 (8%) [149]** | **110 (7%) [116]** |
| Serious (%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Resolved | 11/25 (44%) | 11/20 (55%) | 11/20 (55%) | 10/16 (63%) | 50/71 (70%) | 37/52 (71%) | 8/10 (80%) | 4/8 (50%) | 7/12 (58%) | 4/14 (29%) | 87/138 (63%) | 66/110 (60%) |
| Improved (recovering/resolving) | 2/25 (8%) | 0 | 0 | 1/16 (6%) | 3/71 (4%) | 2/52 (4%) | 1/10 (10%) | 0 | 1/12 (8%) | 0 | 7/138 (5%) | 3/110  (3%) |
| Not resolved | 12/25 (48%) | 9/20 (45%) | 7 /20 (35%) | 6/16 (38%) | 16/71 (23%) | 13/52 (25%) | 1/10 (10%) | 4/8 (50%) | 4/12 (33%) | 11/14 (79%) | 40/138 (29%) | 43/110 (39%) |
| Resolved with sequelae | 0 | 1/20 (5%) | 3/20 (15%) | 0 | 5/71 (7%) | 0 | 0 | 0 | 0 | 0 | 8/138 (6%) | 1/110 (<1%) |
| Fatal | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Anxiety, n (%) [number of events]** | **17 (4%)  [17]** | **23 (6%) [25]** | **13 (5%) [13]** | **9 (4%) [9]** | **28 (7%) [30]** | **30 (7%) [38]** | **5 (2%) [5]** | **8 (3%) [8]** | **5 (1%) [5]** | **6 (2%) [6]** | **68 (4%) [70]** | **76 (5%) [86]** |
| Serious (%) | 0 | 0 | 0 | 0 | 0 | 1 (3%) | 0 | 0 | 0 | 1 (17%) | 0 | 2/76 (3%) |
| Resolved | 7/17 (41%) | 12/23 (52%) | 6/13 (46%) | 2/9 (22%) | 14/28 (50%) | 23/30 (77%) | 3/5 (60%) | 6/8 (75%) | 0 | 3/6 (50%) | 30/66 (45%) | 46/76 (61%) |
| Improved (recovering/resolving) | 0 | 0 | 1/13 (8%) | 1/9 (11%) | 4/28 (14%) | 1/30 (3%) | 0 | 0 | 0 | 1/6 (17%) | 5/66 (8%) | 3/76 (4%) |
| Not resolved | 10/17 (59%) | 11/23 (48%) | 5/13 (38%) | 4/9 (44%) | 10/28 (36%) | 7/30 (23%) | 2/5 (40%) | 2/8 (25%) | 4/5 (80%) | 2/6 (33%) | 31/66 (47%) | 26/76 (34%) |
| Resolved with sequelae | 0 | 1/23 (4%) | 1/13 (8%) | 2/9 (22%) | 0 | 1/30 (3%) | 0 | 0 | 1/5 (20%) | 0 | 2/66 (3%) | 4/76 (5%) |
| Fatal | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Depression, n (%) [number of events]** | **29§ (7%) [30]** | **21 (5%) [21]** | **16 (7%) [19]** | **12 (5%) [13]** | **35 (8%) [42]** | **44 (11%) [52]** | **9 (4%) [9]** | **11ǁ (4%) [12]** | **11 (3%) [15]** | **9 (2%) [10]** | **100 (6%) [115]** | **97 (6%) [108]** |
| Serious (%) | 0 | 1 (5%) | 1 (6%) | 1 (8%) | 0 | 4 (9%) | 0 | 0 | 2 (18%) | 0 | 3/100 (3%) | 6 /97 (6%) |
| Resolved | 11/28 (39%) | 6/21 (29%) | 8/16 (50%) | 7/12 (58%) | 21/35 (60%) | 29/44 (66%) | 3/9 (33%) | 7/11 (64%) | 3/10 (30%) | 5/9 (56%) | 46/98 (47%) | 54/97 (56%) |
| Improved (recovering/resolving) | 4/28 (14%) | 2/21 (10%) | 1/16 (6%) | 2/12 (17%) | 5/35 (14%) | 3/44 (7%) | 1/9 (11%) | 0 | 2/10 (20%) | 1/9 (11%) | 13/98 (13%) | 8/97 (8%) |
| Not resolved | 13/28 (46%) | 11/21 (52%) | 8/16 (50%) | 1/12 (8%) | 9/35 (26%) | 13/44 (30%) | 5/9 (56%) | 4/11 (36%) | 6/10 (60%) | 3/9 (33%) | 41/98 (42%) | 32/97 (33%) |
| Resolved with sequelae | 0 | 2/21 (10%) | 0 | 3/12 (25%) | 1/35 (3%) | 1/44 (2%) | 0 | 1/11 (9%) | 0 | 0 | 1/98 (1%) | 7/97 (7%) |
| Fatal | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Suicidality, n (%) [number of events]** | **4 (<1%) [4]** | **6 (1%) [8]** | **4 (2%) [4]** | **1 (<1%)**  **[1]** | **3 (<1%) [3]** | **7 (2%) [7]** | **3 (1%) [3]** | **4 (2%) [4]** | **6 (2%) [8]** | **2 (<1%) [3]** | **20 (1%) [22]** | **20 (1%) [23]** |
| Serious (%) | 2 (50%) | 6 (100%) | 4 (100%) | 0 | 3 (100%) | 5 (71%) | 0 | 1 (25%) | 5 (83%) | 2 (100%) | 14/20 (70%) | 14/20 (70%) |
| Resolved | 4/4 (100%) | 4/6 (67%) | 3/4 (75%) | 1/1 (100%) | 3/3 (100%) | 6/7 (86%) | 3/3 (100%) | 4/4 (100%) | 6/6 (100%) | 2/2 (100%) | 19/20 (95%) | 17/20 (85%) |
| Improved (recovering/resolving) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Not resolved | 0 | 1/6 (17%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1/20 (5%) |
| Resolved with sequelae | 0 | 1/6 (17%) | 0 | 0 | 0 | 1/7 (14%) | 0 | 0 | 1/6 (17%) | 0 | 1/20 (5%) | 2/20 (10%) |
| Fatal | 0 | 1/6 (17%) | 1/4 (25%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1/20 (5%) | 1/20 (5%) |

\*The PS category *insomnia* included *insomnia*, *initial insomnia*, *middle insomnia*, and *terminal insomnia*; *anxiety* included *anxiety* and *anxiety disorder*; *depression* included *depression*, *major depression*, *depressed mood*, *depressive symptom*, and *bipolar disorder*; *suicidality* included *suicide attempt*, *suicidal ideation*, *completed suicide*, *intentional self-injury*, and *self-injurious behavior*.   
†Double-blind phase occurred from initiation to Week 96 followed by an open-label phase from Week 96 to Week 144. ‡Background therapy was ABC/3TC and TDF/FTC. **§**Outcome was not reported for one case.   
**ǁ**One additional case of depression has been identified in the ATV/r treatment group following the primarily analysis of ARIA; additional details not currently available.  
ABC, abacavir; ART, antiretroviral therapy; ATV/r, atazanavir/ritonavir; DRV/r, darunavir/ritonavir; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; ISBR, investigator selected background regimen; 3TC, lamivudine; NA, not available; RAL, raltegravir; TDF, tenofovir disoproxil fumarate; TTO, time to onset (to first occurrence).

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| **Supplementary Table 2.** Baseline Characteristics of the OPERA Cohort | | | | | |
|  | **ART Regimens** | | | | |
|  | **DTG-containing**  **(n=2029)** | **EFV-containing (n=1608)** | **RAL-containing (n=963)** | | **DRV-containing (n=1747)** |
| **Backbone of regimen, n (%)** | | | | | |
| ABC + 3TC only | 1058 (52.1%) | 38 (2.4%) | 72 (7.5%) | | 5 (0.3%) |
| TDF + FTC only | 526 (25.9%) | 1464 (91.0%) | 486 (50.5%) | | 12 (0.7%) |
| AZT + 3TC only | 3 (0.1%) | 15 (0.9%) | 5 (0.5%) | |  |
| ABC + 3TC + r/c only | 3 (0.1%) |  |  | | 178 (10.2%) |
| TDF + FTC + r/c only | 2 (0.1%) | 2 (0.1%) | 4 (0.4%) | | 1199 (68.6%) |
| AZT + 3TC + r/c only | 0 | 0 | 0 | | 4 (0.2%) |
| All others | 437 (21.5%) | 89 (5.5%) | 396 (41.1%) | | 349 (20.0%) |
| **ART exposure** | | | | | |
| Naïve | 896 (44.2%) | 1080 (67.2%) | 426 (44.2%) | | 847 (48.5%) |
| Experienced | 1133 (55.8%) | 528 (32.8%) | 537 (55.8%) | | 900 (51.5%) |
| **Baseline viral load** | | | | | |
| Median (IQR), log copies/mL | 3.5  (1.3, 4.7) | 4.0  (1.3, 4.9) | | 1.8  (1.3, 4.4) | 4.1  (1.7, 5.0) |
| **Baseline CD4 count** |  |  | |  |  |
| Median (IQR), cells/µL | 454.0  (275.0, 665.0) | 445.5  (285.0, 656.0) | | 481.0  (272.0, 679.0) | 349.0  (143.0, 571.0) |
| **Age** |  |  | |  |  |
| Median (IQR), y | 42.7 (31.3, 51.7) | 41.0 (29.9, 49.5) | | 48.0 (38.7, 54.3) | 44.2 (34.0, 51.2) |
| **Sex** |  |  | |  |  |
| Male | 1722 (85.0%) | 1404 (87.5%) | | 779 (81.1%) | 1387 (79.4%) |
| Female | 305 (15.0%) | 201 (12.5%) | | 182 (18.9%) | 359 (20.6%) |
| **Race** |  |  | |  |  |
| African American | 759 (37.4%) | 664 (41.3%) | | 278 (28.9%) | 740 (42.4%) |
| Not African American | 1270 (62.6%) | 944 (58.7%) | | 685 (71.1%) | 1007 (57.6%) |
| **Ethnicity** |  |  | |  |  |
| Hispanic | 476 (23.5%) | 336 (20.9%) | | 181 (18.8%) | 395 (22.6%) |
| Not Hispanic | 1553 (76.5%) | 1272 (79.1%) | | 782 (81.2%) | 1352 (77.4%) |

ART, antiretroviral therapy; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; IQR, interquartile range; PSs, psychiatric symptoms; OPERA, Observational Pharmaco-Epidemiology Research & Analysis; RAL, raltegravir; r/c, ritonavir/cobicistat.

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| **Supplementary Table 3.** Characteristics of Psychiatric Symptoms in Spontaneously Reported Cases Among Patients Treated With Dolutegravir or Abacavir/Dolutegravir/Lamivudine through 29 February 2016 | | | | | | | | | | | |
|  | **INSOMNIA** | | | **ANXIETY** | | | **DEPRESSION** | | | **SUICIDALITY** | |
| **Cases\*** | **DTG**  **(n=162)** | **ABC/DTG/3TC (n=94)** | **DTG**  **(n=29)** | | **ABC/DTG/3TC (n=41)** | **DTG**  **(n=63)** | | **ABC/DTG/3TC (n=37)** | **DTG**  **(n=35)** | | **ABC/DTG/3TC (n=15)** |
| **Reported by HCP, n  (%)** | **138 (85%)** | **88 (94%)** | **26 (90%)** | | **37 (90%)** | **56 (89%)** | | **34 (92%)** | **32 (91%)** | | **15 (100%)** |
| Deemed serious | 10 (6%) | 3 (3%) | 1 (3%) | | 6 (15%) | 20 (32%) | | 14 (38%) | 35 (100%) | | 15 (100%) |
| **Cases reporting TTO, n** | **57** | **31** | **12** | | **16** | **22** | | **14** | **20** | | **9** |
| TTO <14 days, n (%) | 39  (68%) | 21 (68%) | 5 (42%) | | 11 (69%) | 5 (23%) | | 6 (43%) | 8 (40%) | | 3 (33%) |
| TTO 14 days to <28 days, n (%) | 12 (21%) | 5 (16%) | 1 (8%) | | 3 (19%) | 4 (18%) | | 4 (29%) | 2 (10%) | | 1 (11%) |
| TTO >28 days, n (%) | 6 (11%) | 5 (16%) | 6 (50%) | | 2 (12%) | 13 (59%) | | 4 (29%) | 10 (50%) | | 5 (56%) |
| **Cases reporting action taken with drug, n** | **115** | **72** | **23** | | **35** | **48** | | **28** | **26** | | **12** |
| Discontinued total, n (%) | 69 (60%) | 48 (67%) | 19 (83%) | | 28 (80%) | 30 (63%) | | 26 (93%) | 15 (58%) | | 10 (83%) |
| Discontinued, positive dechallenge, n (%) | 24  (21%) | 19 (26%) | 7 (30%) | | 16 (46%) | 15 (31%) | | 14 (50%) | 8  (31%) | | 6 (50%) |
| **Cases reporting outcome, n** | **78** | **37** | **12** | | **17** | **30** | | **18** | **21** | | **8** |
| Resolved/Resolving, n (%) | 54 (69%) | 24 (65%) | 9 (75%) | | 16 (94%) | 18 (60%) | | 15 (83%) | 16 (76%) | | 6 (75%) |
| Completed suicide, n (%) | NA | NA | NA | | NA | 0 | | 0 | 4 (19%) | | 1 (13%) |
| **Cases in which psychiatric history is known, n** | NA | NA | NA | | NA | **23** | | **11** | **17** | | **3** |
| Past psychiatric condition, n (%) | NA | NA | NA | | NA | 21 (91%) | | 10 (91%) | 14 (82%) | | 2 (67%) |

\*The PS category *insomnia* included *insomnia*, *initial insomnia*, *middle insomnia*, and *terminal insomnia*; *anxiety* included *anxiety* and *anxiety disorder*; *depression* included *depression*, *major depression*, *depressed mood*, *depressive symptom*, and *bipolar disorder*; *suicidality* included *suicide attempt*, *suicidal ideation*, *completed suicide*, *intentional self-injury*, and *self-injurious behavior*.   
ABC/DTG/3TC, abacavir/dolutegravir/lamivudine; DTG, dolutegravir; HCP, healthcare provider; TTO, time to onset (to first occurrence).