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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).