P052

Factors Associated With Weight Loss or Stable Weight After Continuing or Switching to a Doravirine-Based Regimen

Chloe Orkin[1]; John R. Koethe[2]; Princy N. Kumar[3]; Zhi Jin Xu[4]; Rebeca M. Plank[4]; Wayne Greaves[4]; Peter Sklar[4,a]; Rima Lahoulou[5]

[1]Queen Mary University of London, London, United Kingdom; [2]Vanderbilt University Medical Center, Nashville, TN, USA; [3]MedStar Georgetown University Hospital, Washington DC, USA; [4]Merck & Co., Inc., Rahway, NJ, USA; [5]MSD France, Puteaux, France

[a]An employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, at the time of the study.

Background

- Weight gain has become an important aspect in the management of HIV
  - Use of integrase strand transfer inhibitors (INSTIs) and tenofovir alafenamide (TAF) is associated with increased weight gain, compared with other classes of antiretroviral therapy (ART)[1-4]
  - Risk factors for weight gain with INSTI therapy include female sex, lower CD4+ T-cell count, and use in combination with TAF[1,5]
  - Weight gain can have numerous consequences, including development of cardiovascular disease, diabetes mellitus, dyslipidemia, and other metabolic disorders[6-8]
- Minimal weight gain has been observed with doravirine (DOR)–based regimens as first-line therapy and in virologically suppressed adults switching therapy
  - In the DRIVE-FORWARD and DRIVE-AHEAD studies of first-line therapy in adults living with HIV-1, median weight gain in participants who were randomly assigned to receive DOR and who continued DOR in the study extension phase (up to week 192 or ~4 years of follow-up) was 1.9 kg in DRIVE-FORWARD and 2.0 kg in DRIVE-AHEAD,[9-11] similar to the average yearly increase observed among US adults without HIV-1[12,13]
  - In the DRIVE-SHIFT study, in participants who switched from a stable antiretroviral regimen to DOR with lamivudine (3TC) and tenofovir disoproxil fumarate (TDF) on day 1 (immediate switch group) or at week 24 (delayed switch group), mean weight gain from the time of switch to week 144 was 1.4 kg and 1.2 kg, respectively,[14] which again is similar to the average yearly increase observed in US adults without HIV-1[12,13]
  - In the three phase 3 clinical trials of DOR-based regimens mentioned above, the majority of participants (~70%) experienced < 5% weight gain[12,14]

Objective

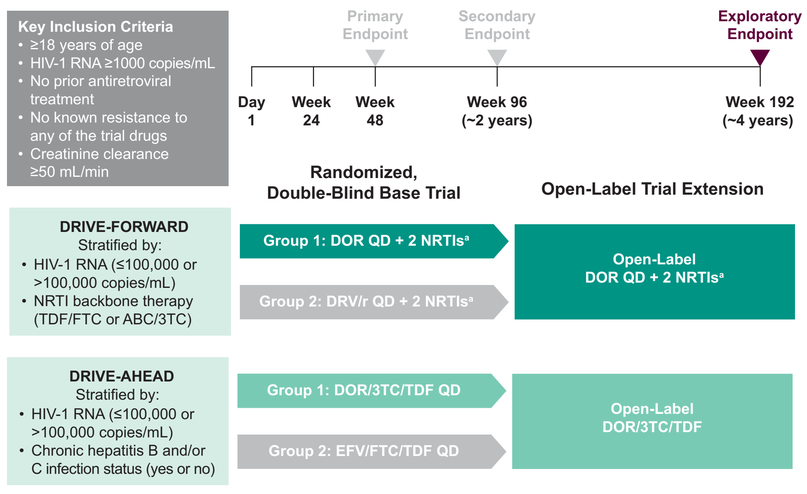
- To characterize predictive factors of participants who maintained or lost weight after continuing or switching to a DOR-based regimen in the DRIVE-FORWARD, DRIVE-AHEAD, and DRIVE-SHIFT phase 3 clinical trials

Methods

Study design

- DRIVE-FORWARD (NCT02275780) and DRIVE-AHEAD (NCT02403674) were randomized, double-blind, active-controlled, noninferiority studies of adults living with previously untreated HIV-1 (**Figure 1**)
  - Participants were randomly assigned to a DOR regimen (DOR with 2 nucleos(t)ide reverse transcriptase inhibitors (NRTIs) in DRIVE-FORWARD; DOR/3TC/TDF in DRIVE-AHEAD) or the comparator regimen (ritonavir-boosted darunavir [DRV/r] with 2 NRTIs or efavirenz [EFV]/emtricitabine [FTC]/TDF, respectively) for 96 weeks of double-blind treatment
    - DOR continued group: participants randomized to a DOR-based regimen continued that regimen for an additional 96 weeks
    - DOR switch group: participants randomized to a comparator regimen switched to the DOR-based regimen for 96 weeks
  - Participants who completed the double-blind phase, had derived benefit, and were clinically appropriate to continue treatment could enter an open-label study extension

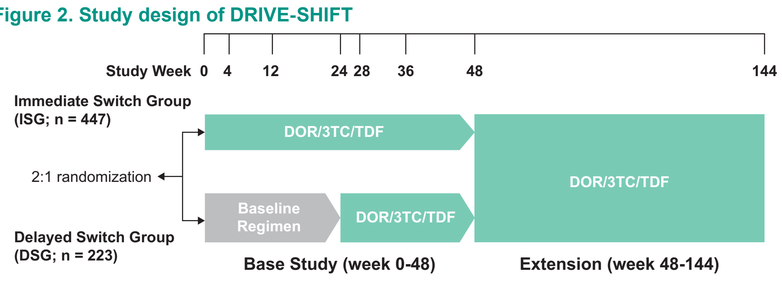
Figure 1. Study design of DRIVE-FORWARD and DRIVE-AHEAD



3TC, lamivudine; ABC, abacavir; DOR, doravirine; DRV/r, ritonavir-boosted darunavir; EFV, efavirenz; FTC, emtricitabine; NRTI, nucleos(t)ide reverse transcriptase inhibitor; TDF, tenofovir disoproxil fumarate; QD, once daily.
[a]NRTIs were TDF/FTC or ABC/3TC.

- DRIVE-SHIFT (NCT02397096) was a randomized, open-label, active-controlled, noninferiority study of adults who were virologically suppressed and on a stable antiretroviral regimen for ≥6 months before enrollment (**Figure 2**)
  - Participants were randomly assigned (2:1) to switch to DOR/3TC/TDF on day 1 (immediate switch group) or to continue their baseline antiretroviral regimen and switch to DOR/3TC/TDF at week 24 (delayed switch group)
  - Both groups continued DOR/3TC/TDF through study week 144

Figure 2. Study design of DRIVE-SHIFT



3TC, lamivudine; DOR, doravirine; DSG, delayed switch group; ISG, immediate switch group; TDF, tenofovir disoproxil fumarate.

Statistical analysis

- For DRIVE-FORWARD and DRIVE-AHEAD, percentage weight change was calculated based on the difference between week 96 and week 192

$$100 \times (\text{weight}_{[\text{week 192}]} - \text{weight}_{[\text{week 96}]})/(\text{weight}_{[\text{week 96}]})$$

- For DRIVE-SHIFT, percentage weight change was calculated based on the difference between week 24 and week 144

$$100 \times (\text{weight}_{[\text{week 144}]} - \text{weight}_{[\text{week 24}]})/(\text{weight}_{[\text{week 24}]})$$

- Participants with weight measurements at both time points were included in the analyses
- Weight change categories
  - Weight loss = percentage change ≤ –5%
  - Stable weight = percentage change > –5% and < 5%
  - Weight gain = percentage change ≥ 5%
- Odds ratios, 95% CIs, and *P* values for weight loss or stable weight versus weight gain were obtained from a generalized logistic model, with the status of weight change (loss, stable, and gain) as the outcome variable and the following explanatory variables:
  - DRIVE-FORWARD/DRIVE-AHEAD: prior ART (protease inhibitor [PI] vs non–nucleoside reverse transcriptase inhibitor [NNRTI]), sex, race (non-Black/Black), day 1 age group (<50 vs ≥50 years), week 96 body mass index (BMI) group (underweight/normal, overweight, and obese) and week 96 weight; interaction of sex and race not included because there were no Black females in the weight loss group
  - DRIVE-SHIFT: sex, race (non-Black/Black), interaction of sex and race, day 1 age group (≥50 vs <50 years), week 24 BMI group (underweight/normal, overweight, and obese), prior ART (PI, NNRTI, INSTI), NRTI in prior regimen (TAF, TDF, abacavir [ABC], or other), duration of prior ART (<1 vs ≥1 year), and week 24 weight
- At the time of switch to or continuation of DOR across the 3 trials, most participants were virologically suppressed (HIV RNA ≤50 copies/mL), and the median CD4+ T-cell count was >600 cells/mm^3; therefore, these variables were not included in the models

Results

DOR continued group: DRIVE-FORWARD (DOR + 2 NRTIs) and DRIVE-AHEAD (DOR/3TC/TDF)

- The combined DOR continued group consisted of 466 participants; 55 (11.8%) lost weight, 305 (65.5%) had stable weight, and 106 (22.7%) gained weight
- Participant characteristics were generally similar between the weight change categories; the weight loss group had a higher proportion of female participants than the stable weight or weight gain groups (**Table 1**)
- No clinical or demographic factors were associated with weight change from week 96 to week 192 among participants who continued DOR in DRIVE-FORWARD and DRIVE-AHEAD

Table 1. Participant characteristics by weight change category, DOR continued group, DRIVE-FORWARD and DRIVE-AHEAD

	Lost weight (change, ≤ −5%)	Stable weight (change, > −5% to < 5%)	Gained weight (change, ≥ 5%)
Participants in population, n	55	305	106
Sex			
Male	40 (72.7)	265 (86.9)	83 (78.3)
Female[a]	15 (27.3)	40 (13.1)	23 (21.7)
Age, median (range), years	34.0 (18-63)	33.0 (18-70)	33.0 (18-68)
Race			
American Indian or Alaskan Native	0 (0.0)	5 (1.6)	1 (0.9)
Asian	4 (7.3)	39 (12.8)	10 (9.4)
Black or African American[a]	10 (18.2)	44 (14.4)	22 (20.8)
Multiple	5 (9.1)	30 (9.8)	5 (4.7)
White	36 (65.5)	187 (61.3)	68 (64.2)
Week 96 weight, kg			
Median (range)	77.1 (52.0-136.1)	74.0 (41.4-135.0)	73.7 (48.0-134.5)
Week 96 BMI, kg/m^2			
Median (range)	26.2 (16.7-43.0)	24.6 (16.4-56.4)	24.7 (16.0-49.7)
Week 96 BMI group			
Underweight	2 (3.6)	9 (3.0)	7 (6.6)
Normal	23 (41.8)	155 (50.8)	52 (49.1)
Overweight	15 (27.3)	97 (31.8)	30 (28.3)
Obese	15 (27.3)	43 (14.1)	17 (16.0)

BMI, body mass index; DOR, doravirine. Values are n (%) unless otherwise noted.
[a]At week 96 for the DOR continued group (n = 550), the percentages of female, Black/African American, and Black/African American female participants were 16.9%, 18.2%, and 7.6%, respectively.

DOR switch group: DRIVE-FORWARD (DOR + 2 NRTIs) and DRIVE-AHEAD (DOR/3TC/TDF)

- The combined switch groups from DRIVE-FORWARD and DRIVE-AHEAD consisted of 423 participants: 40 (9.5%) lost weight, 243 (57.4%) had stable weight, and 140 (33.1%) gained weight
- The weight loss group had the lowest proportion of Black or African American participants: 7.5%, compared with 13.2% in the stable weight group and 22.1% in the weight gain group (**Table 2**)

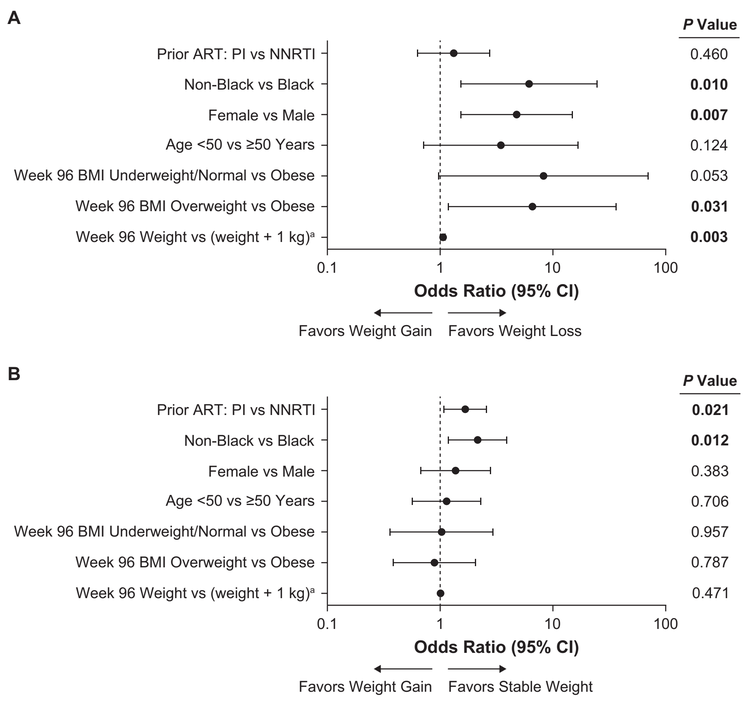
Table 2. Participant characteristics by weight change category, DOR switch group, DRIVE-FORWARD and DRIVE-AHEAD

	Lost weight (change, ≤ −5%)	Stable weight (change, > −5% to < 5%)	Gained weight (change, ≥ 5%)
Participants in population, n	40	243	140
Sex			
Male	33 (82.5)	211 (86.8)	121 (86.4)
Female[a]	7 (17.5)	32 (13.2)	19 (13.6)
Age, median (range), years	29.0 (19-56)	33.0 (19-67)	30.5 (18-69)
Race			
American Indian or Alaskan Native	0 (0.0)	4 (1.6)	0 (0.0)
Asian	7 (17.5)	22 (9.1)	22 (15.7)
Black or African American[a]	3 (7.5)	32 (13.2)	31 (22.1)
Multiple	3 (7.5)	23 (9.5)	12 (8.6)
Native Hawaiian/Other Pacific Islander	0 (0.0)	1 (0.4)	1 (0.7)
White	27 (67.5)	161 (66.3)	74 (52.9)
Week 96 Weight, kg			
Median (range)	75.0 (60.0-112.5)	74.0 (42.7-139.3)	72.7 (38.0-124.3)
Week 96 BMI, kg/m^2			
Median (range)	25.4 (20.2-38.8)	24.4 (14.9-48.0)	24.6 (16.6-44.6)
Week 96 BMI group			
Underweight	0 (0.0)	12 (4.9)	10 (7.1)
Normal	18 (45.0)	124 (51.0)	69 (49.3)
Overweight	19 (47.5)	76 (31.3)	46 (32.9)
Obese	3 (7.5)	30 (12.3)	15 (10.7)

BMI, body mass index; DOR, doravirine. Values are n (%) unless otherwise noted.
[a]At week 96 for the DOR switch group (n = 502), the percentages of female, Black/African American, and Black/African American female participants were 13.5%, 17.1%, and 5.8%, respectively.

- After switching to DOR, weight loss was more likely to occur than weight gain in non-Black participants compared with Black participants and in females compared with males (**Figure 3A**)
- Stable weight was more likely to occur than weight gain in non-Black participants compared with Black participants and after switch from DRV/r (prior ART: PI) compared with switch from EFV/FTC/TDF (prior ART: NNRTI) (**Figure 3B**)

Figure 3. Analysis of factors impacting the probability of (A) weight loss or (B) stable weight versus weight gain from week 96 to week 192, DOR switch group, DRIVE-FORWARD and DRIVE-AHEAD



ART, antiretroviral therapy; BMI, body mass index; NNRTI, non–nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.
[a]The odds ratio for week 96 weight versus (weight + 1 kg) is the ratio of the odds of 2 groups, one with weight X and another with weight (X + 1)

DRIVE-SHIFT (DOR/3TC/TDF)

- The combined switch group (immediate and delayed switch groups) in DRIVE-SHIFT consisted of 535 participants: 71 (13.3%) lost weight, 340 (63.6%) had stable weight, and 124 (23.2%) gained weight
- The weight loss group had a lower proportion of males and Black participants than the stable weight and gained weight groups (**Table 3**)

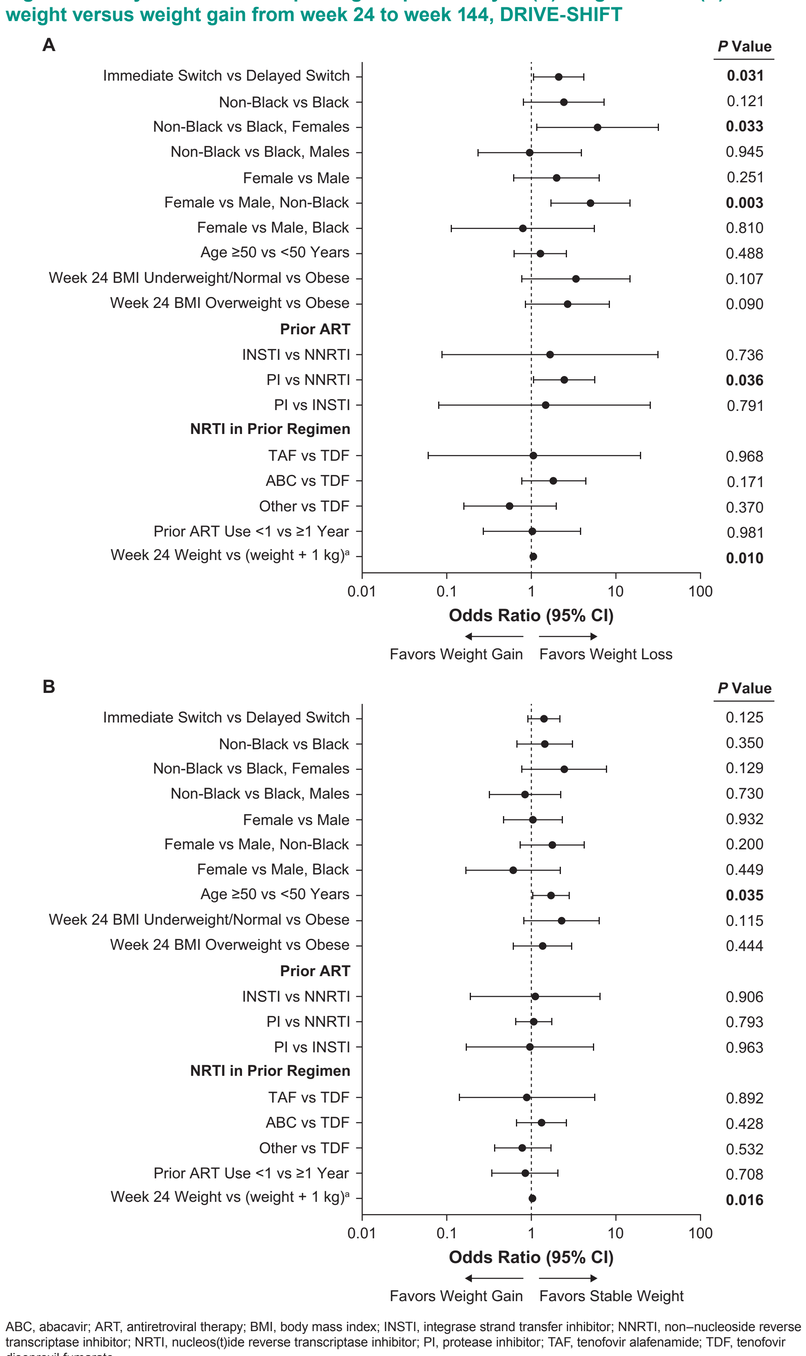
Table 3. Participant characteristics by weight change category, DRIVE-SHIFT

	Lost weight (change, ≤ −5%)	Stable weight (change, > −5% to < 5%)	Gained weight (change, ≥ 5%)
Participants in population, n	71	340	124
Sex			
Male	55 (77.5)	293 (86.2)	106 (85.5)
Female[a]	16 (22.5)	47 (13.8)	18 (14.5)
Age, median (range), years	44.0 (21-66)	44.0 (22-71)	41.0 (25-66)
Race			
American Indian or Alaskan Native	1 (1.4)	3 (0.9)	3 (2.4)
Asian	2 (2.8)	13 (3.8)	4 (3.2)
Black or African American[a]	7 (9.9)	36 (10.6)	15 (12.1)
Multiple	6 (8.5)	16 (4.7)	11 (8.9)
Native Hawaiian/Other Pacific Islander	1 (1.4)	0 (0.0)	0 (0.0)
White	54 (76.1)	272 (80.0)	91 (73.4)
Prior ART			
PI	59 (83.1)	235 (69.1)	84 (67.7)
NNRTI	9 (12.7)	86 (25.3)	33 (26.6)
INSTI	3 (4.2)	19 (5.6)	7 (5.6)
NRTI in prior regimen			
TAF	3 (4.2)	17 (5.0)	6 (4.8)
TDF	50 (70.4)	255 (75.0)	93 (75.0)
ABC	14 (19.7)	45 (13.2)	13 (10.5)
Other	4 (5.6)	23 (6.8)	12 (9.7)
Week 24 weight, kg			
Median (range)	78.1 (53.0-196.6)	78.0 (39.8-150.7)	76.2 (40.0-122.0)
Week 24 BMI, kg/m^2			
Median (range)	26.0 (19.0-50.1)	25.1 (16.4-54.4)	24.8 (14.2-36.6)
Week 24 BMI group			
Underweight	0 (0.0)	6 (1.8)	2 (1.6)
Normal	29 (40.8)	162 (47.6)	63 (50.8)
Overweight	30 (42.3)	111 (32.6)	42 (33.9)
Obese	12 (16.9)	60 (17.6)	17 (13.7)

ABC, abacavir; ART, antiretroviral therapy; BMI, body mass index; INSTI, integrase strand transfer inhibitor; NNRTI, non–nucleoside reverse transcriptase inhibitor; NRTI, nucleos(t)ide reverse transcriptase inhibitor; PI, protease inhibitor; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate. Values are n (%) unless otherwise noted.
[a]At week 24 for DRIVE-SHIFT (n = 670), the percentages of female, Black/African American, and Black/African American female participants were 15.5%, 13.4%, and 6.0%, respectively.

- Participants were more likely to have weight loss at week 144 if they immediately switched to DOR/3TC/TDF at day 1 than those who delayed switching to DOR/3TC/TDF at week 24 (**Figure 4A**)
- Non-Black females were more likely to have weight loss than non-Black males or Black females after switching to DOR/3TC/TDF (**Figure 4A**)
- Weight loss was also more likely to occur in participants who switched from PIs than in those who switched from NNRTIs (**Figure 4A**)
- Stable weight was more likely to occur in participants aged ≥50 years than in those <50 years (**Figure 4B**)

Figure 4. Analysis of factors impacting the probability of (A) weight loss or (B) stable weight versus weight gain from week 24 to week 144, DRIVE-SHIFT



ABC, abacavir; ART, antiretroviral therapy; BMI, body mass index; INSTI, integrase strand transfer inhibitor; NNRTI, non–nucleoside reverse transcriptase inhibitor; NRTI, nucleos(t)ide reverse transcriptase inhibitor; PI, protease inhibitor; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.
[a]The odds ratio for week 24 weight versus (weight + 1 kg) is the ratio of the odds of 2 groups, one with weight X and another with weight (X + 1)

Conclusions

- Weight loss or stable weight (< 5% change) was observed in the majority of participants who continued DOR or switched to DOR in the DRIVE-FORWARD, DRIVE-AHEAD, and DRIVE-SHIFT clinical trials
- In treatment-naive participants who were randomly assigned to and continued their DOR regimen in the extension phase in DRIVE-FORWARD and DRIVE-AHEAD, none of the factors examined had a significant association with weight loss or stable weight
- Among virologically suppressed participants who switched to DOR in the extension phase of the DRIVE-FORWARD and the DRIVE-AHEAD trials, and in the DRIVE-SHIFT trial, female sex, non-Black race, and switch from a boosted PI were associated with weight loss or stable weight
- Due to the low proportions of female and Black participants in these trials, further research is needed to better characterize the participant profile and mechanism for weight change with DOR

Acknowledgments

The authors thank all the individuals who participated in this study. The contributions of the investigators and their staff are also gratefully recognized. Medical writing support was provided by Kim M. Strohmaier, MPH, an employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Medical writing and/or editorial assistance was provided by Jared Cochran, PhD, and Andrea Humphries, PhD, of ApotheCom (Yardley, PA, USA). This assistance was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Funding for this research was provided by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

References

1. Sax PE et al. *Clin Infect Dis.* 2020;71(6):1379-1389.
2. Kouanfack C et al. *N Engl J Med.* 2019;381(9):816-826.
3. Venter WDF et al. *N Engl J Med.* 2019;381(9):803-815.
4. Calza L et al. *Infection.* 2020;48(2):213-221.
5. Hester EK et al. *Ann Pharmacother.* 2022;56(11):1237-1249.
6. Herrin M et al. *J Acquir Immune Defic Syndr.* 2016;73(2):228-236.
7. Mohammed SS et al. *J Acquir Immune Defic Syndr.* 2007;45(4):432-438.
8. Achhra AC et al. *J Acquir Immune Defic Syndr.* 2018;78(5):579-588.
9. Orkin C et al. Presented at: IAS 2021; July 18-21, 2021; Virtual. Accessed January 13, 2023. https://theprogramme.ias2021.org/Abstract/Abstract/709
10. Cahn P et al. Presented: at IDWeek 2021; September 29-October 3, 2021; Virtual. Accessed January 13, 2023. https://doi.org/10.1093/ofid/ofab466.824
11. Molina JM et al. Presented at: EACS 2021; October 27-30, 2021; Hybrid. Abstract BPD1/5. Accessed January 13, 2023. https://www.abstractserver.com/eacsabstractarchive/
12. Orkin C et al. *AIDS.* 2021;35(1):91-99.
13. Williamson DF. *Ann Intern Med.* 1993;119(7 pt 2):646-649.
14. Kumar P et al. *J Acquir Immune Defic Syndr.* 2021;87(2):801-805.

Presented at the British HIV Association Spring Conference 2023; April 24-26, 2023; Gateshead, United Kingdom