Fostemsavir in Heavily Treatment-Experienced Individuals Living with HIV-1: Insights from the Phase 3 BRIGHTE Study

Max Lataillade[1*], Peter Ackerman[1], Till Schoofs[2], Andrew Clark[3], Michael Kozal[4]

[1]ViiV Healthcare, Branford, CT, USA

[2]ViiV Healthcare, Brussels, Belgium

[3]ViiV Healthcare, Brentford, UK

[4]Yale University School of Medicine, New Haven, CT, USA

*Correspondence should be addressed to Max Lataillade; max.x.lataillade@viivhealthcare.com

Introduction

 Fostemsavir (Rukobia™, ViiV Healthcare, Research Triangle Park, NC), a prodrug of the first-in-class attachment inhibitor temsavir, was developed to provide a much-needed new therapeutic option for heavily treatment-experienced (HTE) people living with HIV-1 (PLWH) who are unable to form a suppressive regimen from remaining viable antiretroviral (ARV) agents because of multidrug resistance, contraindications, prior intolerance, or other safety considerations [1-4]. Effective treatment for this vulnerable population can be complicated by other challenges in addition to multidrug resistance, including low CD4+ T-cell counts, comorbidities, psychosocial factors, and non-adherence to complex regimens [4-9]. Regulatory approval of fostemsavir was based on results from the phase 3 BRIGHTE study (ClinicalTrials.gov, NCT02362503) showing that, in HTE adults who were failing their current ARV regimen with limited remaining treatment options, fostemsavir combined with optimized background therapy (OBT) was generally well tolerated and resulted in a distinctive trend of increasing virologic response rates (by intention-to-treat–exposed [ITT-E] Snapshot and observed analysis) and increases in CD4+ T-cell counts through 96 weeks [1,4]. In this commentary, we dig deeper into the rationale for the BRIGHTE study design, expand upon the remarkable patterns of virologic and immunologic response observed in BRIGHTE, and consider how these patterns may be related to the unique mode of action of fostemsavir (temsavir).

The BRIGHTE Clinical Study Design was Appropriate for HTE PLWH

 The design of clinical trials for HTE PLWH is complicated by the varying needs of this heterogeneous population with very few treatment options. Limitations of BRIGHTE include the inability to include a comparator group beyond the primary endpoint analysis and the confounder of highly individualized background therapies. These limitations are unavoidable and inherent to the treatment needs of HTE PLWH. Non-inferiority trials are not feasible because extensive multidrug resistance means that each study participant requires a highly individualized OBT and, thus, there is no appropriate active control to use for defining a non-inferiority margin. Long-term placebo-controlled comparisons are also not appropriate because continued use of an unmodified failed ARV regimen would increase the risk of emergent resistance to the investigational drug and progression of disease. The BRIGHTE study was designed to address these challenges in accordance with guidance on the development of ARVs for the HTE population [10,11]. Building on data from a phase 2b study (ClinicalTrials.gov, NCT01384734) that had demonstrated favorable efficacy, safety, and tolerability of fostemsavir in treatment-experienced PLWH [12,13], BRIGHTE aimed to further assess the efficacy and safety of fostemsavir and also to fulfill the crucial unmet medical needs of HTE PLWH. The study was designed with 2 cohorts: a Randomized Cohort of HTE participants with just 1 or 2 remaining fully active ARV agents that could be included in the OBT, and a compassionate-use Non-randomized Cohort of HTE participants with no remaining fully active, approved ARV options at study start [2,4].

The primary efficacy endpoint of the study was mean HIV-1 RNA decline over 8 days of treatment with fostemsavir (600 mg twice daily [BID]) or placebo added to the failing ARV regimen (ie, functional monotherapy) in the Randomized Cohort. After this short-term double-blind period, all Randomized Cohort participants received open-label fostemsavir (600 mg BID) in combination with a new individualized OBT.

In the Non-randomized Cohort, to facilitate the construction of an optimal background regimen to combine with fostemsavir, co-enrollment in other investigational ARV trials was permitted (eg, the phase 3 ibalizumab study). All participants in the Non-randomized Cohort received their new OBT in combination with fostemsavir (600 mg BID) from study Day 1.

BRIGHTE Recruited the Most Advanced HTE Population in HIV Clinical Trials

Results from BRIGHTE were particularly notable given the advanced disease state of the participants. Inclusion criteria regarding the level of treatment experience and multidrug resistance were the most restrictive to date among clinical trials conducted with treatment-experienced PLWH. Eligible study candidates had to demonstrate complete exhaustion of 4 of the 6 ARV classes (nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, integrase inhibitors, protease inhibitors, CCR5 antagonists, and fusion inhibitors) available at enrollment (February 2015 to May 2016) [2]. Complete exhaustion of an ARV class meant the elimination of all ARVs in that class as viable options for inclusion in OBT due to resistance, prior intolerance, contraindications, or unwillingness to use the twice-daily injectable enfuvirtide. This is quite different from previous clinical trials in PLWH with multidrug resistance, which only required resistance to 1 or more ARVs in at least 3 ARV classes [14-18]. Most participants in BRIGHTE had received ≥ 5 ARV regimens (85%) over >15 years of treatment (71%), 86% had a history of AIDS, and 75% had a baseline CD4+ T-cell count <200 cells/mm³ (30% <20 cells/mm³) [2-4]. The study population was also demographically diverse: 22% of participants were women, 22% were Black/African American, 29% were Hispanic or Latinx, and 44% were aged ≥ 50 years [2-4].

Fostemsavir Showed Consistent Antiviral Activity Over 8 Days of Functional Mono-therapy

In the Randomized Cohort, at Day 8, mean decrease in HIV-1 RNA was 0.79 $\log_{10}$ copies/mL in the fostemsavir group and 0.17 $\log_{10}$ copies/mL in the placebo group (between-group difference, −0.63 $\log_{10}$ copies/mL; 95% CI, −0.81 to −0.44; $P<0.001$) [2]. When interpreting these results, it should be noted that to ensure accessibility to HTE PLWH in need of new treatment options, BRIGHTE included participants with screening HIV-1 RNA ≥ 400 copies/mL. This cutoff is lower than the cutoff of >1000 copies/mL generally used in clinical trials involving participants with multidrug-resistant HIV-1 [14,17,18]. In the Randomized Cohort, 11% (31/272) of participants had baseline HIV-1 RNA <1000 copies/mL. These lower baseline viral loads restrict the range of viral decay kinetics that can be detected before reaching the lower limit of quantification (ie, <40 copies/mL). In BRIGHTE, this finding is illustrated by the larger Day 8 decrease in viral load seen in participants with baseline HIV-1 RNA >1000 copies/mL (median 1.02 $\log_{10}$ copies/mL with fostemsavir vs 0.00 $\log_{10}$ copies/mL with placebo) [2]. Because fostemsavir was added to a failing ARV regimen, with no other treatment changes during the first 8 days, these results demonstrate the antiviral potency and efficacy of fostemsavir. The decline in HIV-1 RNA was consistent with findings from the monotherapy sub-study of the phase 2b trial (conducted in generally treatment-experienced participants with temsavir 50% inhibitory concentration [IC_{50}] <100 nM) showing potent antiviral activity with median Day 8 decreases in plasma HIV-1 RNA of 0.7 to 1.5 $\log_{10}$ copies/mL across fostemsavir doses studied (400 mg BID, 600 mg once daily [QD], 800 mg BID, and 1200 mg QD) [19].

Fostemsavir Plus OBT Resulted in Increasing Rates of Virologic Response Over 96 Weeks

A remarkable and unique finding from BRIGHTE was the continuous increase in virologic response rates by Snapshot analysis in the ITT-E population from Weeks 24 through 96 in the Randomized Cohort. During the open-label study period, in which participants received fostemsavir combined with OBT, virologic response rates (HIV-1 RNA <40 copies/mL) in the Randomized Cohort were 53% (144/272) at Week 24, 54% (146/272) at Week 48, and 60% (163/272) at Week 96 [2,4]. These increases were not attributable to changes in OBT because such changes were counted as treatment failures in the Snapshot analysis. Notably, even in the Non-randomized Cohort, where participants generally had more advanced HIV disease than those in the Randomized Cohort and the contribution of OBT was significantly more compromised, virologic response rate by Snapshot analysis remained stable at 37% from Weeks 24 to 96 [4].

In a Snapshot ITT-E analysis, all randomized participants who receive ≥ 1 dose of study medication are included at all time points and any participants with missing data or change in OBT for efficacy reasons are counted as failures. Given the complexity and inevitable discontinuations seen in clinical trials involving HTE participants, this usually results in a gradual reduction in virologic response rates over time. For example, in the BENCHMRK trials

(which, like BRIGHTE, did not mandate discontinuation for participants with virologic failure), the percentage of participants with virologic response decreased from 62% at Week 16 to 57% at Week 96 [18,20]. In BRIGHTE, the absolute number of Randomized Cohort participants classified as virologic responders in the Snapshot ITT-E analysis went up by 19 from Week 24 (n=144) to Week 96 (n=163). This unique finding reflects the fact that 63 Randomized Cohort participants first achieved virologic response after Week 24 (n=44) or Week 48 (n=29) [3]. When we looked at the observed analysis, in which participants with missing data are excluded and changes in OBT are not counted as failures, this unprecedented efficacy trend was especially pronounced in the Randomized Cohort with virologic response rates increasing from 57% (141/246) at Week 24 to 62% (145/233) at Week 48 and 79% (170/214) at Week 96. Even in the Non-randomized Cohort, where fostemsavir was often the only fully active agent, virologic response increased from 42% (37/89) at Week 24 to 48% (40/83) at Week 48 and 59% (39/66) at Week 96. These data are more relevant to physicians treating HTE PLWH because they are more reflective of real-world clinical practice where small adjustments in the OBT will often be clinically necessary based on continuous evaluation.

Several hypothetical factors could contribute to the late responses seen in BRIGHTE. Firstly, the varying composition of the OBT among BRIGHTE participants may have led to differences in the rapidity of virologic response. An initial OBT including 1 or 2 potent ARVs with retained full activity might elicit a relatively rapid virologic response, while an initial OBT composed of ARVs with partial activity against a highly mutated and fitness-impaired viral population might result in a slow reduction in HIV-1 RNA. However, as noted above, similar increases in virologic response over time have not been reported in other clinical trials conducted in HTE PLWH [18,20]. Secondly, because temsavir binds to HIV-1 gp120 and prevents viral attachment to and entry into host CD4+ T-cells and other immune cells [21], virus particles are trapped in the extracellular space. This could result in persistent detectable levels of plasma HIV-1 RNA during earlier stages of treatment, particularly among participants with high baseline viral load. Thirdly, the gradual recovery of immune function in individuals with advanced disease may have contributed to a more gradual reduction in viral replication. The immune system, including CD4+ T-cells, is critical to HIV clearance. The low baseline CD4+ T-cell counts in many BRIGHTE participants could have hindered initial HIV-1 RNA reduction, with subsequent CD4+ T-cell recovery contributing to virologic response [2-4,22-24]. This is illustrated by the most profound increases in virologic response occurring among participants with the lowest baseline CD4+ T-cell counts (<20 cells/mm^3); in this group, the virologic response rate increased from 32% at Week 24 to 46% at Week 96. Lastly, the unique mechanism of action of temsavir may have some interesting consequences beyond preventing virus entry into host cells. Binding of temsavir to gp120 trimers on the surface of HIV-1 virions, near the CD4 binding pocket, locks the envelope into a fixed, closed conformation [21]. *In vitro* studies have shown synergy between temsavir and CD4-directed neutralizing antibodies [25]. It is possible that in individuals receiving a fostemsavir-based regimen, temsavir may augment the induction and/or binding of autologous neutralizing antibodies to virus particles and infected cells and, over time, enhance virus clearance via antibody-dependent cellular cytotoxicity [25-27]. This hypothesis is the subject of ongoing research.

Fostemsavir Plus OBT Resulted in Clinically Meaningful Increases in CD4+ T-cell Count

Another encouraging result from BRIGHTE was the clinically meaningful and robust increase from baseline to Week 96 in CD4+ T-cell count, including in participants who were most immunosuppressed at baseline. At Week 96, mean increase in CD4+ T-cell count was 205 cells/mm^3 in the Randomized Cohort (n=213) and 119 cells/mm^3 in the Non-randomized Cohort (n=65) [4]. Increases in the CD4/CD8 ratio were also observed (from a mean of 0.2 at baseline to 0.44 at Week 96 in the Randomized Cohort) [4]. This ratio is reported to be associated with a significantly lower risk of progression to both AIDS-related and non–AIDS-related morbidity and mortality, independent of CD4+ T-cell count [28].

In the Randomized Cohort, CD4+ T-cell increases were generally consistent across subgroups based on demographics and disease characteristics [3]. Notably, participants who were the most immunosuppressed at baseline (CD4+ T-cell count <20 cells/mm^3) achieved the greatest increases in CD4+ T-cell count at Week 96 (mean increase of 240 cells/mm^3) [4]. Among 71 participants with baseline CD4+ T-cell counts <50 cells/mm^3, 56% (n=40) had ≥ 200 cells/mm^3 at Week 96 [4]. This increase represents a life-changing response and a meaningful milestone for many PLWH and their healthcare providers, reducing the risk of opportunistic infections (and hence the need for prophylaxis), decreasing polypharmacy issues (eg, adherence, tolerability, toxicity), and ultimately reducing morbidity and mortality risks [5,29]. These CD4+ T-cell count increases are particularly impressive considering that low nadir CD4+ T-cell count and older age (2 common characteristics of HTE PLWH) are known risk factors for poor CD4+ T-cell recovery, even in cases of complete virologic suppression [7,8,30,31].

CD4+ T-cell count increases achieved in BRIGHTE are greater than expected based on results from previous studies in similar populations [15,17,20]. We speculate that the mode of action of temsavir could hypothetically play a role that goes beyond simply protecting CD4+ T-cells from *de novo* infection or re-infection. Several

gp120-mediated mechanisms have been described for the death of both infected and uninfected CD4+ T-cells in PLWH [32]. Studies with small-molecule mimetics of CD4 suggest that these molecules can protect uninfected bystander CD4+ T-cells from the attachment of soluble gp120 and subsequent antibody-dependent cytotoxicity. It is feasible that temsavir binding to soluble gp120 may have the same potential to interrupt bystander killing of uninfected CD4+ T-cells (a key contributing factor to CD4+ T-cell decline and subsequent immunosuppression seen in PLWH and advanced AIDS) [32], and this is the subject of ongoing investigations. We also plan to study whether adding fostemsavir to the ARV regimen of discordant responders, who have undetectable viral loads but poor immune responses (CD4+ T-cell counts <200 cells/mm^3) after years of treatment, can enhance CD4+ T-cell recovery and offer additional immune benefit.

Fostemsavir-Based Regimens Demonstrated a Favorable Safety Profile

A favorable safety profile is important for HTE PLWH who may have experienced previous intolerance and toxicity issues and who are more likely than treatment-naive or less treatment-experienced PLWH to be older and to have pre-existing comorbidities requiring concomitant therapies [7,31,33]. This is particularly challenging since the available treatment options are scarce and restricted by multidrug resistance.

The safety profile of fostemsavir-based regimens in BRIGHTE participants was consistent with previous reports from clinical trials in participants with multidrug-resistant HIV-1 [2,4,14,16,17,34]. Most (347/370; 94%) participants reported at least one adverse event (AE), most commonly diarrhea, nausea, upper respiratory tract infection, and headache [3,4]. Most AEs were mild or moderate in severity, self-limited, and resolved without interruption of study drug [4]. There were few drug-related serious AEs (12/370; 3%) and AEs leading to discontinuation (26/370; 7%) [3]. Most severe AEs (grade 3-4 AEs, serious AEs, and deaths) were related to complications of advanced HIV disease and acute infections and occurred disproportionately in participants who were the most immunocompromised at baseline and in Non-randomized Cohort participants [3,4]. Higher rates of severe AEs in Non-randomized Cohort participants can be explained by their more advanced baseline disease (median CD4+ T-cell count 41 vs 99 cells/mm^3 in the Randomized Cohort) and more compromised background therapy [2].

Fostemsavir is an Important Option for a Population with an Urgent Need for New Therapies

Heavily treatment-experienced PLWH have a variety of multidrug resistance patterns and experience with ARVs from most classes. It is therefore important that temsavir, the active component of fostemsavir, has shown no in vitro cross-resistance with other ARV classes and is active against HIV-1 virus regardless of tropism [35]. Importantly, recent data from clinical isolates have further confirmed that there is no cross-resistance between temsavir and ibalizumab and maraviroc [1,36,37]. A favorable drug–drug interaction (DDI) profile is also important for HTE PLWH to minimize constraints on their ARV options, particularly since many may rely on regimens that include pharmacologic enhancers, and because older PLWH frequently have multiple comorbidities requiring polypharmacy. Fostemsavir has a low dependency on the CYP3A4 metabolic pathway and, as a result, has few DDIs and can be administered with most drugs prescribed for the management of HIV-1 and associated comorbidities without dose adjustment [1,37]. This also means it is unlikely that fostemsavir will have any clinically significant DDIs with other novel agents currently in development for the treatment of multidrug-resistant HIV-1 in HTE PLWH.

These favorable safety and DDI profiles, coupled with the robust Week 96 efficacy and safety data, and last but not least the clinically significant CD4+ T-cell recovery seen in BRIGHTE, provide strong support for fostemsavir as an important treatment option for this vulnerable population both now and in the future. Future analyses will aim to identify baseline and on-treatment predictors of response to treatment with fostemsavir-based regimens.

Conflicts of Interest

Funding Statement

Acknowledgments

Author Contributions Statement

All authors contributed to the conception of the commentary; the collection, analysis, and interpretation of the information within; the drafting of the commentary; and critically revising the commentary for important intellectual content. All authors approve this commentary for submission.

References

1. ViiV Healthcare. Rukobia. Prescribing information [Internet]. Research Triangle Park, NC; 2020. Available from: https://viivhealthcare.com/content/dam/cf-viiv/viiv-healthcare/en_GB/files/Final_Rukobia_Prescribing_Information_NDA_212950.pdf

2. Kozal M, Aberg J, Pialoux G, Cahn P, Thompson M, Molina J-M, et al, for the BRIGHTE Trial Team. Fostemsavir in adults with multidrug-resistant HIV-1 infection. N Engl J Med. 2020 Mar 26;382(13):1232-43.

3. Ackerman P, Thompson M, Molina J-M, Aberg J, Cassetti I, Kozal M, et al. Long-term efficacy and safety of fostemsavir among subgroups of heavily treatment-experienced adults with HIV-1. AIDS. 2021 Jun 1;35(7):1061-72.

4. Lataillade M, Lalezari JP, Kozal M, Aberg JA, Pialoux G, Cahn P, et al. Safety and efficacy of the HIV-1 attachment inhibitor prodrug fostemsavir in heavily treatment-experienced individuals: week 96 results of the phase 3 BRIGHTE study. Lancet HIV. 2020 Nov;7(11):e740-51.

5. Niznik JD, He H, Kane-Gill SL. Impact of clinical pharmacist services delivered via telemedicine in the outpatient or ambulatory care setting: a systematic review. Res Social Adm Pharm. 2018 Aug;14(8):707-17.

6. Henegar C, Vannappagari V, Viswanathan S, DeKoven M, Clark A, Ackerman P, et al. Identifying heavily treatment-experienced patients in a large administrative claims database. Poster presented at: 10th IAS Conference on HIV Science; July 21-24, 2019; Mexico City, Mexico.

7. Pelchen-Matthews A, Borges AH, Reekie J, Rasmussen LD, Wiese L, Weber J, et al. Prevalence and outcomes for heavily treatment-experienced (HTE) individuals living with HIV in a European cohort. Poster presented at: 10th IAS Conference on HIV Science; July 21-24, 2019; Mexico City, Mexico.

8. Cutrell J, Jodlowski T, Bedimo R. The management of treatment-experienced HIV patients (including virologic failure and switches). Ther Adv Infect Dis. 2020 Jan 20;7:2049936120901395.

9. Priest J, Hulburt E, Gilliam BL, Burton T. Health care resource utilization and cost of heavily treatment experienced (HTE) people living with HIV (PLWH) in US commercial and Medicare Advantage health plans. Value Health. 2020 May 1;23(suppl 1):S176.

10. Mani N, Murray J, Gulick RM, Josephson F, Miller V, Miele P, et al. Novel clinical trial designs for the development of new antiretroviral agents. AIDS. 2012 May 15;26(8):899-907.

11. US Food and Drug Administration. Human immunodeficiency virus-1 infection: developing antiretroviral drugs for treatment. Guidance for industry [Internet]. Silver Spring, MD; November 2015. Available from: https://www.fda.gov/media/86284/download

12. Lalezari J, Latiff GH, Brinson C, Echevarria J, Treviño-Pérez S, Bogner JR, et al. Safety profile of HIV-1 attachment inhibitor prodrug BMS-663068 in antiretroviral-experienced subjects: week 24 analysis. J Int AIDS Soc. 2014 Nov 2;17(4 suppl 3):19530.

13. Thompson M, Lalezari JP, Kaplan R, Pinedo Y, Sussmann Peno OA, Cahn P, et al, for the AI438011 study team. Safety and efficacy of the HIV-1 attachment inhibitor prodrug fostemsavir in antiretroviral-experienced subjects: week 48 analysis of AI438011, a phase IIb, randomized controlled trial. Antivir Ther. 2017;22(3):215-23.

14. Akil B, Blick G, Hagins DP, Ramgopal MN, Richmond GJ, Samuel RM, et al, for the VIKING-4 study team. Dolutegravir versus placebo in subjects harbouring HIV-1 with integrase inhibitor resistance associated substitutions: 48-week results from VIKING-4, a randomized study. Antivir Ther. 2015;20(3):343-8.

15. Hardy WD, Gulick RM, Mayer H, Fätkenheuer G, Nelson M, Heera J, et al. Two-year safety and virologic efficacy of maraviroc in treatment-experienced patients with CCR5-tropic HIV-1 infection: 96-week combined analysis of MOTIVATE 1 and 2. J Acquire Immune Defic Syndr. 2010 Dec 15;55(5):558-64.

16. Castagna A, Maggiolo F, Penco G, Wright D, Mills A, Grossberg R, et al, for the VIKING-3 Study Group. Dolutegravir in antiretroviral-experienced patients with raltegravir- and/or elvitegravir-resistant HIV-1: 24-week results of the phase III VIKING-3 study. J Infect Dis. 2014 Aug 1;210(3):354-62.

17. Emu B, Fessel J, Schrader S, Kumar PN, Richmond G, Win S, et al. Phase 3 study of ibalizumab for multidrug-resistant HIV-1. N Engl J Med. 2018 Aug 16;379(7):645-54.

18. Steigbigel RT, Cooper DA, Kumar PN, Eron JE, Schechter M, Markowitz M, et al, for the BENCHMRK Study Teams. Raltegravir with optimized background therapy for resistant HIV-1 infection. N Engl J Med. 2008 Jul 24;359(4):339-54.

19. Lalezari JP, Latiff GH, Brinson C, Echevarría J, Treviño-Pérez S, Bogner JR, et al, for the AI438011 study team. Safety and efficacy of the HIV-1 attachment inhibitor prodrug BMS-663068 in treatment-experienced individuals: 24 week results of AI438011, a phase 2b, randomised controlled trial. Lancet HIV. 2015 Oct;2(10):e427-37.

20. Steigbigel RT, Cooper DA, Teppler H, Eron JE, Gatell JM, Kumar PN, et al, for the BENCHMRK Study Teams. Long-term efficacy and safety of raltegravir combined with optimized background therapy in treatment-experienced patients with drug-resistant HIV infection: week 96 results of the BENCHMRK 1 and 2 phase III trials. Clin Infect Dis. 2010 Feb 15;50(4):605-12.

21. Pancera M, Lai Y-T, Bylund T, Druz A, Narpala S, O'Dell S, et al. Crystal structures of trimeric HIV envelope with entry inhibitors BMS-378806 and BMS-626529. Nat Chem Biol. 2017 Oct;13(10):1115-22.

22. Fenwick C, Joo V, Jacquier P, Noto A, Banga R, Perreau M, et al. T-cell exhaustion in HIV infection. Immunol Rev. 2019 Nov;292(1):149-63.

23. Phetsouphanh C, Xu Y, Zaunders J. CD4 T cells mediate both positive and negative regulation of the immune response to HIV infection: complex role of T follicular helper cells and regulatory T cells in pathogenesis. Front Immunol. 2015 Jan 6;5:681.

24. Sant AJ, McMichael A. Revealing the role of CD4(+) T cells in viral immunity. J Exp Med. 2012 Jul 30;209(8):1391-5.

25. Zhang Y, Chapman JH, Ulcay A, Sutton RE. Neutralization synergy between HIV-1 attachment inhibitor fostemsavir and anti-CD4 binding site broadly neutralizing antibodies against HIV. J Virol. 2019 Feb 5;93(4):e01446-18.

26. Alvarez RA, Maestre AM, Law K, Durham ND, Barria MI, Ishii-Watabe A, et al. Enhanced FCGR2A and FCGR3A signaling by HIV viremic controller IgG. JCI Insight. 2017 Feb 23;2(4):e88226.

27. Munro JB, Gorman J, Ma X, Zhou Z, Arthos J, Burton DR, et al. Conformational dynamics of single HIV-1 envelope trimers on the surface of native virions. Science. 2014 Nov 7;346(6210):759-63.

28. Mussini C, Lorenzini P, Cozzi-Lepri A, Lapadula G, Marchetti G, Nicastri E, et al, for the Icona Foundation Study Group. CD4/CD8 ratio normalisation and non-AIDS-related events in individuals with HIV who achieve viral load suppression with antiretroviral therapy: an observational cohort study. Lancet HIV. 2015 Mar;2(3):e98-e106.

29. Panel on Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America [Internet]. Bethesda, MD; 2020. Available from: https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/Adult_OI.pdf

30. Negredo E, Massanella M, Puig J, Pérez-Alvarez N, Gallego-Escuredo JM, Villarroya J, et al. Nadir CD4 T cell count as predictor and high CD4 T cell intrinsic apoptosis as final mechanism of poor CD4 T cell recovery in virologically suppressed HIV-infected patients: clinical implications. Clin Infect Dis. 2010 May 1;50(9):1300-8.

31. Priest J, Hulbert E, Gilliam BL, Burton T. Healthcare resource utilization and cost of people living with HIV (PLWH) in US commercial and Medicare Advantage health plans. Open Forum Infect Dis. 2020 Oct;7(suppl 1):S539.

32. Richard J, Veillette M, Ding S, Zoubchenok D, Alsahafi N, Coutu M, et al. Small CD4 mimetics prevent HIV-1 uninfected bystander CD4 + T cell killing mediated by antibody-dependent cell-mediated cytotoxicity. EBioMedicine. 2015 Dec 9;3:122-34.

33. Pelchen-Matthews A, Ryom L, Borges ÁH, Edwards S, Duvivier C, Stephan C, et al, for the EuroSIDA study. Aging and the evolution of comorbidities among HIV-positive individuals in a European cohort. AIDS. 2018 Oct 23;32(16):2405-16.

34. Emu B, DeJesus E, Berhe M, Leider J, Creticos C, Weinheimer S, et al. Ibalizumab efficacy and safety through 48 weeks of treatment: results of an expanded access protocol (TMB-311). Open Forum Infect Dis. 2019 Oct;6(suppl 2):S303.

35. Li Z, Zhou N, Sun Y, Ray N, Lataillade M, Hanna GJ, et al. Activity of the HIV-1 attachment inhibitor BMS-626529, the active component of the prodrug BMS-663068, against CD4-independent viruses and HIV-1 envelopes resistant to other entry inhibitors. Antimicrob Agents Chemother. 2013 Sep;57(9):4172-80.

36. Rose B, Gartland M, Stewart E, Cockett M, Ackerman P, Lataillade M, et al. Reduced susceptibility to temsavir is not linked to IBA or MVC resistance. Presented at: Conference on Retroviruses and Opportunistic Infections; March 6-10, 2021; Virtual.

37. ViiV Healthcare BV. Rukobia. Summary of product characteristics [Internet]. Amersfoort, Netherlands; 2021. Available from: https://www.ema.europa.eu/en/documents/product-information/rukobia-epar-product-information_en.pdf