Switching to Elvitegravir/Cobicistat/Emtricitabine/ Tenofovir Alafenamide in Adults With HIV and M184V/I Mutation

Ignacio Perez-Valero, MD, PhD,a Josep M. Llibre, MD, PhD,b Antonella Castagna, MD,c Federico Pulido, MD,d Jean-Michel Molina, MD, PhD,e Stefan Esser, MD,f Nicolas Margot, MA,g Yongwu Shao, PhD,h Lauren Temme, PharmD, MBA,i David Piontkowsky, MD, JD,j Ian R. McNicholl, PharmD,k and Richard Haubrich, MDl

Background: The ability of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) to maintain virologic suppression in participants with M184V and/or M184I resistance mutations from historical genotypic reports when switching from a tenofovir disoproxil fumarate–based or abacavir (ABC)-based regimen was investigated.

Setting: Phase IIIb, 48-week, open-label, single-arm, multicenter, clinical trial (NCT02616029).

Methods: Virologically suppressed adults with HIV and documented M184V/I on historical genotypic reports switched to E/C/F/TAF from a tenofovir disoproxil fumarate–based or ABC-based regimen. The primary end point was HIV-1 RNA of <50 copies per milliliter at week 12 using pure virologic response (PVR). Secondary end points included HIV-1 RNA of <50 copies per milliliter at weeks 24/48 (PVR) and at weeks 12, 24, and 48 (Food and Drug Administration snapshot algorithm), and change in CD4+ count at weeks 12, 24, and 48.

Results: M184V alone was reported in 82.8% of 64 participants; 9.4% and 7.8% had M184I and M184V/I, respectively, and 43.8% had archived M184V/I (baseline DNA). All (62/62 with available data, 100%, 95% confidence interval 94.2% to 100%) participants maintained PVR at weeks 12, 24, and 48. By Food and Drug Administration snapshot algorithm, one participant had HIV-1 RNA of ≥50 copies per milliliter (week 12); confirmatory HIV-1 RNA was <50 copies per milliliter. No significant changes were observed in CD4+ cell count. Drug-related adverse events (AEs) were reported by 10 (15.6%) participants. Six (9.4%) and 5 (7.8%) participants had grade 3–4 AEs or serious AEs, respectively (none drug related).

Conclusions: The presence of the resistance mutations M184V/I did not jeopardize the efficacy of switching to E/C/F/TAF in virologically suppressed adults. High rates of virologic suppression were maintained throughout 48 weeks of therapy and treatment was well tolerated.

Key Words: M184V, switch, tenofovir, resistance, M184I

INTRODUCTION

M184V/I mutations are common nucleoside reverse transcriptase inhibitor (NRTI) resistance mutations,1–7 documented in

Received for publication July 30, 2020; accepted November 17, 2020.

From the 1Unidad VIH—Hospital Universitario La Paz, Madrid, Spain; 2Fundación Lucha contra el SIDA and Infectious Diseases, Hospital Universitari Germans Trias i Pujol, Barcelona, Spain; 3Vita-Salute San Raffaele University, IRCCS San Raffaele, Milan, Italy; 4Unidad VIH, Hospital Universitario 12 de Octubre, imas12, UCM, Madrid, Spain; 5Department of Infectious Diseases, Saint-Louis Hospital and University of Paris, Paris, France; 6University Hospital Essen, Essen, Germany; and 7Gilead Sciences, Foster City, CA.

I.P.V. has received honoraria for speaker bureaus, advisory boards, or travel grants from ViViV Healthcare, Gilead Sciences, Janssen-Cilag, and Merck. Sharp & Dohme. J.M.L. has received honoraria for speaker bureaus, participated in advisory boards, or received travel grants from Gilead Sciences, Janssen-Cilag, Merck, Sharp & Dohme, and ViViV Healthcare. A.C. has received honoraria for consultancy from Gilead Sciences, ViViV Healthcare, Janssen, MSD, and Theratechnologies. F.P. has received funding from Gilead, Janssen, MSD, and ViViV Healthcare. J.M.M. has participated in advisory boards for Aelix, Gilead, Merck, Sanofi, and ViViV Healthcare, and J.M.M.’s institution has received funding from Gilead. S.E. reports research funding, travel grants, advisory boards, speaker fees, and honoraria for speaker bureaus from Gilead; research funding, travel grants, consultancy fees, advisory boards, and speaker fees from ViViV; advisory boards from GSK; research funding, travel grants, advisory boards, and speaker fees from Janssen; research funding, travel grants, advisory boards, and speaker fees from MSD; travel grants, advisory boards, and speaker fees from AbbVie; and speaker fees from BMS, N.M., Y.S., L.T., D.P., I.R.M., and R.H. are employed by Gilead and own stocks in Gilead. The study was funded by Gilead Sciences, Inc., Foster City, CA.

N.M., Y.S., D.P., I.R.M., and R.H. were involved in the conception and design of the study. I.P.V., J.M.L., A.C., F.P., J.M.M., and S.E. were involved in acquisition of the data. All authors contributed to interpreting the data, drafting, and critically revising the manuscript. All authors provided final approval of the manuscript to be published.

Data sharing: Gilead Sciences shares anonymized individual patient data upon request or as required by law or regulation with qualified external researchers based on submitted curriculum vitae and reflecting non conflict of interest. The request proposal must also include a statistician. Approval of such requests is at Gilead Science’s discretion and is dependent on the nature of the request, the merit of the research proposed, the availability of the data, and the intended use of the data. Data requests should be sent to datarequest@gilead.com.

Correspondence to: Richard Haubrich, MD, Gilead Sciences, 333 Lakeside Drive, Foster City, CA 94404 (e-mail: Richard.Haubrich@gilead.com).

Copyright © 2020 The Author(s). Published by Wolters Kluwer Health, Inc. This is an open-access article distributed under the terms of the Creative Commons Attribution-No Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.
23%-80% of people living with HIV (PLWH) experiencing virologic failure.8-10 M184V/I mutations decrease virus susceptibility to lamivudine (3TC), emtricitabine (FTC),9,11 and abacavir (ABC)12,13 but increase susceptibility to tenofovir in vitro.9,11,14 Tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) exert anti-HIV activity via the tenofovir diphosphate (TFV-DP) active metabolite. TAF offers 4-fold to 7-fold higher activity via the tenofovir diphosphate (TFV-DP) active metabolite. TAF offers 4-fold to 7-fold higher activity in vitro and in vivo.15,16 In vitro results suggest that higher TDF-DP could translate to a higher resistance threshold with TAF, reducing the likelihood of viral escape.17,18 Thus, there is a rationale for switching from TDF to TAF.

The fixed-dose combination of TAF with elvitegravir, cobicistat, and FTC (E/C/F/TAF) demonstrates noninferior efficacy in virologically suppressed adults switching from TDF- or ABC/3TC-based regimens.19-21 To date, E/C/F/TAF trials have not included participants with known/archived resistance mutations or previous virologic failure.19-22 We investigated E/C/F/TAF to maintain virologic suppression in PLWH with a historical genotypic report of M184V/I when switching from TDF- or ABC-based regimens.

METHODS

Study Design

This phase IIIb, open-label, single-arm, multicenter, 2-part trial was conducted at 19 European and 3 US centers (NCT02616029). After screening (<42 days before baseline), participants switched from a stable antiretroviral regimen23 to receive single-tablet E/C/F/TAF (150 mg elvitegravir/150 mg cobicistat/200 mg FTC/10 mg TAF) orally, with food, for up to 48 weeks, at approximately the same time each day. Study visits included visit at weeks 4, 8, 12, 16, 24, 36, and 48 plus a 30-day follow-up visit.

The study was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonisation guidelines, and relevant national laws/regulations. Institutional review board/independent ethics committee approval was obtained at all centers. Written informed consent was obtained from all participants. E/C/F/TAF is not currently approved for the use under discussion (HIV-1 infection with known resistance mutations).

Study Population

Participants were adults with HIV and virologic suppression (HIV-1 RNA <50 copies per milliliter for ≥6 months before screening, measured at least twice using the same assay) who received a stable antiretroviral regimen (for ≥6 consecutive months before screening) containing FTC/TDF or ABC/3TC plus an allowed antiretroviral agent23 with documented M184V and/or M184I mutations (based on historical plasma genotypic assays [by Sanger sequencing]), without (part 1) or with (part 2) 1 or 2 thymidine analog-associated mutations (TAMs).23 Part 2 was initiated following an interim efficacy review by an Internal Data Monitoring Committee, after all part 1 participants had completed week 12 (>80% pure virologic response (PVR) required to initiate part 2).

Participants had estimated glomerular filtration rate per the Cockcroft-Gault formula (eGFRCG) ≥30 mL/min. Key exclusion criteria included presence of NRTI resistance mutations K65R, T69 insertion, K70E, or Q151M mutation complex and any primary integrase strand transfer inhibitor or protease inhibitor (PI) resistance mutations. Absence of mutations was confirmed at baseline by PBMC-HIV DNA analysis (GenoSure Archive assay; Monogram Biosciences, South San Francisco, CA). Individuals with previous virologic failure on a PI/ritonavir-based or integrase strand transfer inhibitor-based regimen (with/without resistance) were excluded. Participants could have prior virologic failure on a non-NRTI plus 2 NRTI-based regimen ≥6 months before the study.

Assessments and End Points

The primary end point was HIV-1 RNA of <50 copies per milliliter at week 12 using PVR. Secondary end points were HIV-1 RNA of <50 copies per milliliter at weeks 24 and 48 using PVR; HIV-1 RNA of <50 copies per milliliter at weeks 12, 24, and 48 using the Food and Drug Administration (FDA) snapshot algorithm24; emergence of new mutations in HIV-1 reverse transcriptase/integrase in any post-baseline sample with HIV-1 RNA of ≥50 copies per milliliter at 2 visits last visit); and change from baseline in CD4+ cell count at weeks 12, 24, and 48. Exploratory end points were sensitivity analyses for HIV-1 RNA <50 copies per milliliter at weeks 12, 24, and 48, which considered missing data as treatment failures (M = F) or excluded missing data (M = E). Safety and tolerability were evaluated by monitoring adverse events (AEs; coded using Medical Dictionary for Regulatory Affairs v22.0), laboratory tests, and eGFRCG.

Statistical Analysis

The target sample of 100 was calculated based on a 95% confidence interval (CI) width of ±5.9% for the primary end point, assuming an observed PVR rate of 90% (with large sample size approximation and binomial distribution). PVR analyses included participants who remained on study treatment and had no confirmed virologic rebound (HIV-1 RNA ≥50 copies per milliliter on 2 consecutive visits, or at any point during the study followed by premature study discontinuation) at the relevant time point. For the primary end point, 95% CIs were generated by normal approximation and exact methods. Sensitivity analyses of virologic failure used the FDA snapshot algorithm, M = F or M = E. The primary analysis population for efficacy analyses was the full analysis set, ie, all participants who received ≥1 dose of study drug and excluding participants who took E/C/F/TDF or F/TAF as part of the baseline antiretroviral therapy. The safety analysis set included all participants who received ≥1 dose of study drug. Statistical analyses used SAS version 9.4 (SAS Institute, Inc., Cary, NC).

RESULTS

Participants

The first participant was screened on December 17, 2015; the final study visit was on July 11, 2019 (overall, 120
PLWH were screened). Study accrual was closed before reaching 100 participants because of slow enrollment. Of the 66 participants enrolled (parts 1/2: n = 38/n = 28), 64 (n = 37/n = 27) received ≥1 dose of study drug; 60 (n = 34/n = 26) completed treatment. Four participants discontinued treatment; one each as a result of an AE, investigator discretion, protocol violation, and suicide. Two participants were excluded from the full analysis set, having received prohibited baseline antiretroviral regimens. Table 1 summarizes participant baseline demographics/disease characteristics.

**Efficacy**

All participants maintained a PVR at weeks 12 (primary end point), 24, and 48 (Fig. 1A). Sensitivity analyses consistently identified >90% of participants with HIV-1

| TABLE 1. Baseline/Disease Characteristics (Safety Analysis Set; N = 64) |
|-----------------------------------------------------------------------|
| **Parameter** | **Part 1 (n = 37)** | **Part 2 (n = 27)** | **Overall (N = 64)** |
|----------------------------------------------------------|------------------|------------------|------------------|
| Median (range) age, yr | 51 (22–76) | 55 (33–73) | 52 (22–76) |
| Female, n (%) | 8 (21.6) | 9 (33.3) | 17 (26.6) |
| Race/ethnicity, n (%) | | | |
| White | 27 (73.0) | 17 (63.0) | 44 (68.8) |
| Black or African descent | 7 (18.9) | 8 (29.6) | 15 (23.4) |
| Hispanic/Latino ethnicity | 6 (16.2) | 4 (14.8) | 10 (15.6) |
| Mean (SD) body mass index, kg/m² | 26.5 (5.31) | 26.5 (6.00) | 26.2 (5.57) |
| HIV risk factor categories, n (%) | | | |
| Heterosexual sex | 13 (35.1) | 15 (55.6) | 28 (43.8) |
| MSM | 18 (48.6) | 10 (37.0) | 28 (43.8) |
| Asymptomatic HIV disease status, n (%) | 30 (81.1) | 23 (85.2) | 53 (82.8) |
| Negative HCV antibody, n (%) | 31 (83.8) | 23 (85.2) | 54 (84.4) |
| HIV-1 RNA <50 copies/mL, n (%) | 37 (100) | 27 (100) | 64 (100) |
| Mean (SD) CD4⁺ cell count, cells/μL | 740 (319.6) | 665 (312.7) | 708 (316.4) |
| CD4⁺ cell count ≥500 cells/μL, n (%) | 29 (78.4) | 19 (70.4) | 48 (75.0) |
| CD4⁺ cell count <200 cells/μL, n (%) | 1 (2.7) | 2 (7.4) | 3 (4.7) |
| Median (range) eGFR<sub>CG</sub>, mL/min | 94 (36–215) | 96 (50–216) | 95 (36–216) |
| Screening regimen, n (%) | | | |
| NNRTI | 4 (10.8) | 3 (11.1) | 7 (10.9) |
| INSTI | 12 (32.4) | 10 (37.0) | 22 (34.4) |
| Protease inhibitor | 20 (54.1) | 14 (51.9) | 34 (63.1) |
| NRTI backbone was FTC/TDF | 20 (54.1) | 13 (48.1) | 33 (51.6) |
| Participants receiving a single-tablet regimen at baseline, n (%) | 7 (18.9) | 8 (29.6) | 15 (23.4) |
| Historical plasma genotype, n (%) | | | |
| M184V | 34 (91.9) | 19 (70.4) | 53 (82.8) |
| M184I | 2 (5.4) | 4 (14.8) | 6 (9.4) |
| M184V/I | 1 (2.7) | 4 (14.8) | 5 (7.8) |
| Archival DNA genotype, n (%) | | | |
| M184V | 13 (35.1) | 11 (40.7) | 24 (37.5) |
| M184I | 0 (0) | 0 (0) | 0 |
| M184V/I | 3 (8.1) | 1 (3.7) | 4 (6.3) |
| M184 wild type | 21 (56.8) | 15 (55.6) | 36 (56.3) |
| Baseline resistance, n (%) | | | |
| M184V/I only | 37 (100) | 16 (59.3) | 53 (82.8) |
| M184V/I + 1 TAM | 0 | 8 (29.6) | 8 (12.5) |
| M41L | 0 | 1 (3.7) | 1 (1.6) |
| K70R | 0 | 2 (7.4) | 2 (3.1) |
| T215Y/F | 0 | 4 (14.8) | 4 (6.3) |
| K219E | 0 | 1 (3.7) | 1 (1.6) |
| M184V/I + 2 TAMS | 0 | 3 (11.1) | 3 (4.7) |
| M41L + T215I/F | 0 | 3 (11.1) | 3 (4.7) |

*Two participants had a nonallowable third antiretroviral agent in their screening regimen (elvitegravir/cobicistat/emtricitabine/TDF and FTC/TDF + etravirine + raltegravir). eGFR<sub>CG</sub>, estimated glomerular filtration rate calculated by Cockcroft–Gault formula; FTC, emtricitabine; HCV, hepatitis C virus; INSTI, integrase strand transfer inhibitor; MSM, men who have sex with men; NNRTI, nonnucleoside reverse transcriptase inhibitor.
RNA of <50 copies per milliliter (Figs. 1B–D). No participant met the resistance analysis criteria. “Viral blips” (a single event of HIV-1 RNA ≥50 but <400 copies per milliliter) were experienced by 3 participants, all isolated events. At weeks 12, 24, and 48, the mean change from baseline in CD4+ cell count was −30 (SD 165.1), −10 (SD 187.4), and 9 (SD 126.8) cells per microliter, respectively.

Safety

Any AE, grade 3–4 AEs, and serious AEs (SAEs) were reported by 51 (79.7%), 6 (9.4%), and 5 (7.8%) participants, respectively, resulting in study drug discontinuation in 1 participant (1.6%) (nonserious muscle spasms). The most common AEs were asthenia, bronchitis, and nasopharyngitis, each occurring in 7 (10.9%) participants, followed by headache in 6 (9.4%), and back pain, cough, and diarrhea, each in 5 (7.8%) participants. Drug-related AEs were reported by 10 (15.6%) participants [all grade 1–2, asthenia (n = 2), fatigue (n = 2), headache (n = 2), diarrhea (n = 1), hypertension (n = 1), muscle spasms (n = 1), and skin burning sensation (n = 1)]. No participant experienced any Centers for Disease Control and Prevention Category C AIDS-defining events25 or treatment-emergent fracture AEs. Five urinary disorder AEs [polyuria (n = 2), hematuria (n = 1), micturition urgency (n = 1), proteinuria (n = 1)], and/or 4 renal AEs (n = 1 each for acute kidney injury, nephroangiosclerosis, renal cyst, and renal failure) occurred in 5 participants (7.8%). Three renal-associated SAEs occurred in 2 participants; 1 experienced acute kidney injury (on days 21–26) and renal failure (days 53–60), and the other had proteinuria (SAE; days 317–319). Both participants had a history of type 2 diabetes and abnormal renal test results at baseline. All renal-associated SAEs resolved without study drug interruption and were not considered study drug related. There were no notable changes from baseline in most renal
participants (87.5%) experienced laboratory abnormalities of lipids or glucose (data not shown), and minimal changes in renal tubulopathy, no clinically relevant changes in fasting lipids or glucose (data not shown), and minimal changes in body weight (mean, +0.7 kg [SD 4.30] at week 48).

DISCUSSION

In this study, 100% virologic suppression was maintained in participants with virologic suppression at baseline and with a historical genotypic report of M184V/I resistance (alone or with 1–2 TAMs), who switched to E/C/F/TAF from a stable antiretroviral regimen. All participants achieved HIV-1 RNA of <50 copies per milliliter using PVR at week 12 (primary end point) and maintained this at weeks 24 and 48. There were no virologic failures. No participant met the criteria for resistance testing. E/C/F/TAF was well tolerated, with no unexpected safety findings.

The proportion of participants with HIV-1 RNA of <50 copies per milliliter at week 48 (FDA snapshot) exceeded 90%, similar to previous phase III studies evaluating E/C/F/TAF. A similar proportion of participants maintained HIV-1 RNA of <50 copies per milliliter (FDA snapshot) at week 24 in this study compared with virologically suppressed individuals switching from ABC-3TC-based regimens to E/C/F/TAF (95.2% vs 93.4%). Unlike the current study, previous phase III studies excluded participants with documented resistance to the study drugs. Although all participants in this study, had a historical plasma genotypic report of M184V/I, archived M184V/I was detected in only 43.8% of participants at baseline. However, all participants met the primary end point, regardless of whether M184V/I was detected in their baseline proviral DNA genotype.

The discrepancy between historical genotype and archival PBMC-HIV DNA may result from differences in between-assay limits of detection or archiving (uneven archive, archive turnover, or mutation not archived). This highlights a limitation of PBMC-HIV DNA analysis to detect prior resistance in PLWH seeking to switch their regimen while suppressed. Using PBMC-HIV DNA testing to determine whether a participant has M184V/I mutation before choosing a switch regimen can be helpful if the test shows the mutation but might not detect existing mutations in all participants. Using E/C/F/TAF gives assurance that those harboring hidden M184V/I mutations can remain suppressed.

The primary end point was achieved by all participants in parts 1 and 2, suggesting that efficacy was similar for participants with or without TAMs in addition to M184V/I. The efficacy of the FTC-containing regimen may reflect partial antiviral activity of FTC despite the resistance conferred by M184V, rather like the beneficial effect of combining 3TC with boosted PI therapy for PLWH despite M184V mutation. The hypersensitivity of viruses with M184V to tenofovir and the high level of intracellular TFV-DP associated with TAF also likely contributed to the observed high efficacy.

E/C/F/TAF was well tolerated. Overall safety findings were consistent with the known safety profile identified in previous studies of virologically suppressed individuals switching to E/C/F/TAF from TDF and ABC regimens. No cases of proximal renal tubulopathy were reported, in line with previous findings for E/C/F/TAF. No renal-related AEs were considered study drug related, and there were no notable changes from baseline in measured renal function parameters. This favorable renal safety profile is anticipated based on the improved renal safety of TAF- versus TDF-containing regimens demonstrated in PLWH.

Study limitations include the open-label design and lack of a control group. Also, sufficient participants could not be enrolled to meet the target sample size, given the specific inclusion criteria (many PLWH with M184V/I have co-occurring mutations and/or virologic failure, making them ineligible). However, assuming a PVR of ≥95%, a sample size of 64 would have a 95% confidence CI width of ±5.3% or lower (ie, still high precision). However, exclusion of other NRTI resistance mutations meant that our findings are attributable to M184V/I mutation, alone or in combination with 1–2 TAMs. Because TAM-associated cross-resistance to tenofovir is mostly observed with 3 or more TAMs, the number of TAMs allowed in this study could be considered a limitation. Our findings may be limited by the under-representation of women and non-White participants.

In summary, M184V/I resistance mutation does not jeopardize the efficacy of a treatment change to E/C/F/TAF, with high rates of virologic suppression maintained throughout 48 weeks of treatment. These findings support E/C/F/TAF fixed-dose combination as a treatment option for virologically suppressed individuals with HIV and M184V/I mutation.

ACKNOWLEDGMENTS

Medical writing support, including development of drafts in consultation with the authors, assembling tables and figures, collating author comments, copyediting, fact checking, and referencing was provided by Beatrice Tyrrell, DPhil and Emma McConnell, MPHamb PhD CMPP at Aspire Scientific (Bollington, United Kingdom) and funded by Gilead Sciences, Inc. (Foster City, CA). The authors extend their thanks to the participants, their partners and families, and the additional study investigators: V. Abril López de Medrano, M. Andreoni, J.R. Arribas Lopez, L. Bernard, M. Bickel, M. Castaño Carracedo, D. Coulston, E. DeJesus, A. Di Biagio, C. Duivier, J. Gallant, M. Galli, D. Hagins, E. Lazaro, J. Mallois, A. Mills, C. Miralles Alvarez, O. Osiyemi, I. Poizot-Martin, T. Prazuck, D. Prelutsky, P. Pugliese, F. Raffi, M. Ramgopal, G. Richmond, D. Salmon-Ceron, J. Schattenberg, P. Sellier, P. Shalti, and H.J. Stellbrink.

REFERENCES

1. Martin-Odoom A, Brown CA, Odoom JK, et al. Emergence of HIV-1 drug resistance mutations in mothers on treatment with a history of prophylaxis in Ghana. Firo J. 2018;15:143.
2. Kiertiburanakul S, Chaisarwath R, Sirivichayakul S, et al. Comparisons of primary HIV-1 drug resistance between recent and chronic HIV-1 infection within a sub-regional cohort of Asian patients. PLoS One. 2013;8:e62057.

3. Wang Z, Zhang M, Zhang R, et al. Diversity of HIV-1 genotypes and high prevalence of pretreatment drug resistance in newly diagnosed HIV-infected patients in Shanghai, China. BMC Infect Dis. 2019;19:313.

4. Hamers RL, Sigaloff KCE, Wensing AM, et al. Patterns of HIV-1 drug resistance after first-line antiretroviral therapy (ART) failure in 6 sub-Saharan African countries: implications for second-line ART strategies. Clin Infect Dis. 2012;54:1660–1669.

5. Sivamalar S, Dinesha TR, Gomathi S, et al. Accumulation of HIV-1 drug resistance mutations after first-line immunological failure to evaluate the options of replacing NRTI drugs in second-line treatment: a study from South India. AIDS Res Hum Retrov. 2017;33:271–274.

6. Duani H, Alexio AW, Tupinambis U. Trends and predictors of HIV-1 acquired drug resistance in Minas Gerais, Brazil: 2002–2012. Braz J Infect Dis. 2017;21:148–154.

7. Li H, Zhong M, Guo W, et al. Prevalence and pattern variations of HIV drug resistance from 2010 to 2011 among ART-failure individuals in the Yunnan Province, China. PLoS One. 2013;8:e72630.

8. Bulletec N, Bans-Matharu L, Churchill D, et al. The emergence of drug resistant HIV variants at virological failure of HAART combinations containing efavirenz, tenofovir and lamivudine or emtricitabine within the UK Collaborative HIV Cohort. J Infect. 2014;68:77–84.

9. Miller MD, Margot N, Lu B, et al. Genotypic and phenotypic predictors of the magnitude of response to tenofovir disoproxil fumarate treatment for the treatment of human immunodeficiency virus type 1 in patients with suppressed HIV-1 RNA: a cohort study. Open Forum Infect Dis. 2017;4:e384–e392.

10. K65R, TAMs and tenofovir. AIDS. 2019;33:1455–1465.

11. Centers for Disease Control and Prevention. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Recomm Rep. 1992;41:1–19.

12. Margot N, Ram R, McNicholl I, et al. Differential detection of M184V/I mutation in sub-Saharan Africa (ANRS12 286/MOVIDIP): a multicentre, randomised, active-controlled, multicentre, open-label, phase 3, non-inferiority study. Lancet Infect Dis. 2016;16:43–52.

13. Hodder S, Squires K, Kiyo C, et al. Brief report: efficacy and safety of switching to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide (E/C/TAF) in virologically suppressed women. J Acquir Immune Defic Syndr. 2018;78:209–213.

14. Rizzardini G, Gori A, Miralles C, et al. Randomized study evaluating the efficacy and safety of switching from an abacavir/lamivudine-based regimen to an elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide single-tablet regimen. AIDS. 2019;33:1583–1593.

15. Squires K, Kiyo C, Hodder S, et al. Integrate inhibitor versus protease inhibitor based regimen for HIV-1 infected women (WAVES): a randomised, controlled, double-blind, phase 3 study. Lancet HIV. 2016;3:e410–e420.

16. NCT02616029: study to evaluate switching to elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/TAF) fixed dose combination (FDC) in virologically-suppressed HIV-1 infected adults harboring the archived isolated NRTI resistance mutation M184V/M184I. Available at: https://www.ncbi.nlm.nih.gov/trialshow/NCT02616029?term=NCT02616029&draw=2&rank=1. Accessed January 4, 2021.

17. US Food and Drug Administration. Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment Guidance for Industry. 2015. Available at: https://www.fda.gov/downloads/drugs/guidances/ucm355128.pdf. Accessed January 4, 2021.

18. Centers for Disease Control and Prevention. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Recomm Rep. 1992;41:1–19.