Advantages of switching to elvitegravir/cobicistat/emtricitabine/tenofovir therapy in virologically-suppressed people living with human immunodeficiency virus/acquired immune deficiency syndrome

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To the Editor: With recent advances in antiretroviral therapy (ART) regimens, many patients may benefit from switching drugs. The new combination drug, elvitegravir/cobicistat/emtricitabine/tenofovir (E/C/F/TAF), has been approved for use in people living with human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AID [PLWHA]) in China and has also been included within the scope of medical insurance. This single-tablet regimen provides a convenient, once-daily, treatment option for many PLWHA. E/C/F/TAF was shown to increase adherence to ART and decrease the risk of drug resistance and virological failure.[1-4] However, another study showed a higher level of several lipid parameters in patients with tenofovir alafenamide (TAF)-based therapy compared with tenofovir (TDF)-based therapy in treatment-naïve and -experienced adults.[5] In 2019, a phase IV clinical study of E/C/F/TAF was conducted at our Antiviral Treatment Center, allowing us to explore the virological and immunological responses during 12 months of follow-up after switching. We also explored the changes in renal function, liver function, and lipid parameters in PLWHA.

This study was conducted in compliance with the Declaration of Helsinki. Ethical approval was obtained from the Human Medical Ethics Committee of Tianjin Second People's Hospital (No. [2020]16). Written informed consent was provided by each recruited participant.

The study was conducted at Tianjin Second People's Hospital in Tianjin, China, a designated hospital for the treatment of HIV/AIDS. From January 1, 2019, to December 30, 2021, 605 HIV-infected patients with virological suppression switched from a stable antiretroviral regimen to E/C/F/TAF. The clinical characteristics of the participants are shown in Supplementary Table 1, http://links.lww.com/CM9/B378. Among the cohort, 70 patients received integrase strand transfer inhibitors (INSTIs)-based ART drugs (24 received dolutegravir (DTG)-based, 46 received raltegravir (RAL)-based), 82 received protease inhibitors (PIs)-based ART drugs (seven received darunavir/cobicistat-based, 75 received lopinavir/ritonavir-based), and 453 received non-nucleotide reverse transcriptase inhibitor (NNRTIs)-based ART drugs (22 received nevirapine-based, 431 received efavirenz-based). The median age of the participants was 34 (Q_1–Q_3: 28–47) years, and 581 cases (96%) were male. The median duration of previous treatment was 3.45 years (Q_1–Q_3: 1.91, 5.04). The rates of successful virological suppression (HIV ribonucleic acid [RNA] <50 copies/mL) for NNRTIs-, PIs-, and INSTI-based ART were 93.3% (308/330), 93.3% (42/45), and 92.9% (52/56), respectively, at 12 months [Figure 1A]. During follow-up, eight patients showed low level viremia and 61 patients showed a "blip" in viremia. At 12 months, HIV RNA >1000 copies/mL was detected in three patients (among whom two patients had switched from TDF + lamivudine [3TC] + dolutegravir [TDG] and one patient had switched from TDF + 3TC + efavirenz [EFV]). No individuals had to discontinue E/C/F/TAF because of a "blip" in viremia. The trends in the levels of cluster of differentiation 4 (CD4) are shown in Figure 1B. No significant immunological differences were found after switching. Among the included participants, the proportions with hypertriglyceridemia and hypercholesterolemia before switching were 26.3% (112/426) and 5.9% (30/507), respectively. After 12 months' follow-up, the proportions with hypertriglyceridemia and hypercholesterolemia increased to

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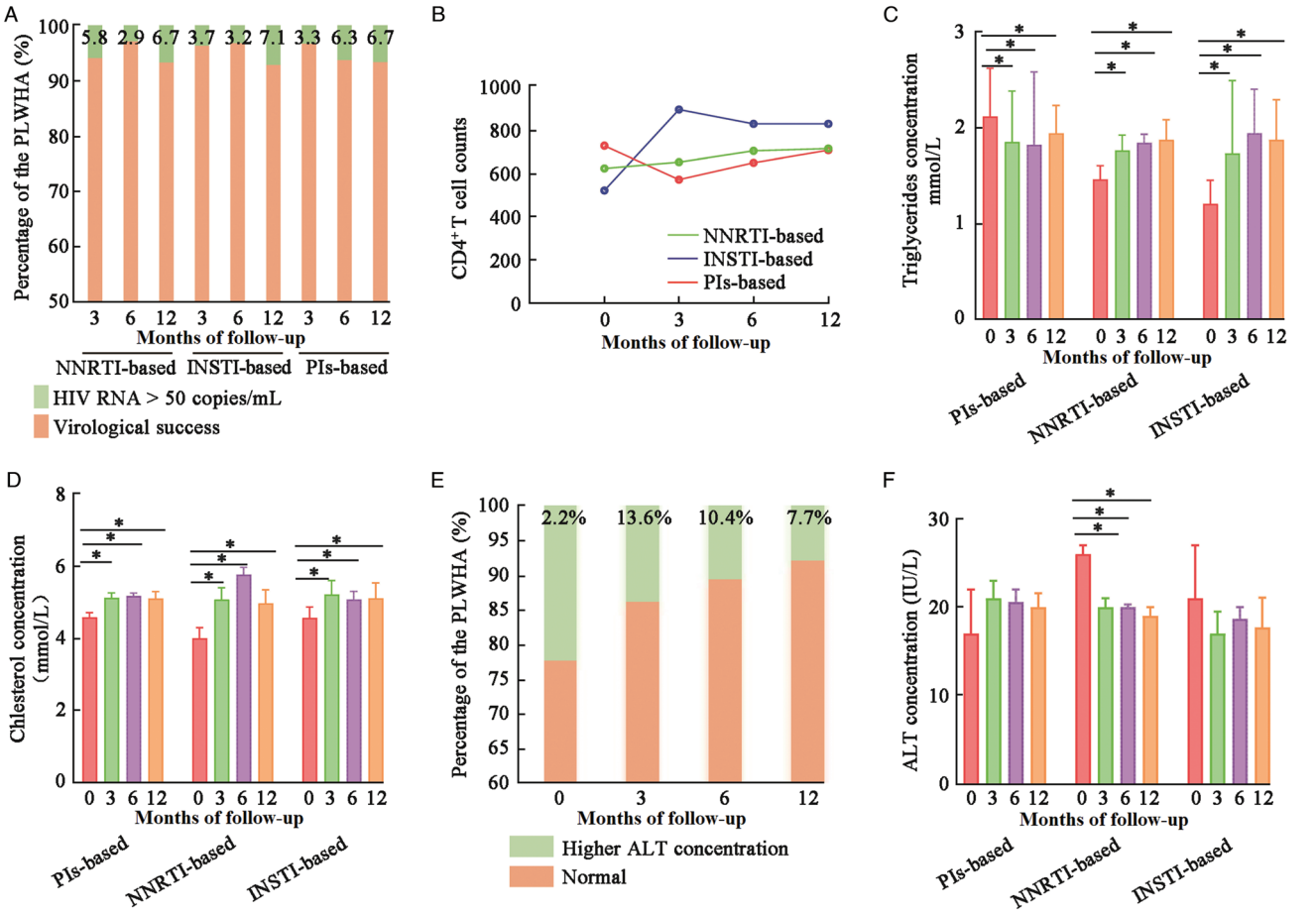

Figure 1: Changes in successful virological suppression, immunological recovery hyperlipidemia, and the proportion of higher transaminase during the 12 months after switching. (A) Successful virological suppression after switching to E/C/F/TAF. (B) CD4$^+$ T cell recovery. (C) Changes in the triglyceride concentration in three groups. (D) Changes in the cholesterol concentration in three groups. (E) Changes in the percentages of patients with higher ALT concentration. (F) Change in the ALT concentration in three groups. $^*P < 0.05$. Low-level viremia was defined as a patient with a plasma HIV RNA level between 50 copies/mL and 200 copies/mL. An increase in transaminase was defined as 1.25 × the upper normal level (AST: 40 mg/dL; ALT: 40 mg/dL). ALT: Alanine aminotransferase; ALT: Alanine aminotransferase; E/C/F/TAF: Elvitegravir/cobicistat/emtricitabine/tenofovir; INSTI: Integrase inhibitor; NNRTI: Non-nucleotide reverse transcriptase inhibitor; PIs: Protease inhibitors; PLWHA: People living with HIV/AIDS.

39% (124/314) and 20%(74/365), respectively. Patients who received PIs-based ART before switching had a higher triglyceride concentration than those who received INSTI- or NNRTI-based ART [Figure 1C] ($P < 0.001$). After 12 months' follow-up, the triglyceride concentration in PIs-based group had decreased significantly ($P < 0.001$). Furthermore, after 12 months' follow-up, a significant increase in the cholesterol concentration of PLWHA was detected after switching from INSTI-, NNRTIs-, and PIs-based ART regimens [Figure 1D]. The proportion of patients with a higher level of alanine transaminase (ALT) was 22% (107/376) before switching to E/C/F/TAF, which decreased to 13.6% (70/442) after 3 months, 10.4% (61/524) after 6 months, and 7.7% (34/406) after 12 months of follow-up [Figure 1E]. A decrease in the ALT concentration was observed after switching from NNRTI-based therapy to E/C/F/TAF [Figure 1F]. There was no significant change in the median aspartate transaminase concentration over the 12-month follow-up period after switching. The proportion of eGFR <60 mL · min^{-1}· 1.73 m^{-2} was 34.6% (187/354) before switching to E/C/E/T, and increased to 42.4% (214/296) after 3 months, 46.4% (271/313) after 6 months, and 49.2% (216/223) after 12 months. No significant difference between TDF-based and non-TDF-based therapy before switching was detected after follow-up. No patients discontinued E/C/E/T treatment as a result of adverse renal events.

This study provided the first real-world evidence on the safety and efficacy of E/C/F/TAF treatment in virologically suppressed PLWHA. Our findings demonstrated that E/C/F/TAF was effective in suppressing the viral load and increasing the number of CD4$^+$ T cells. With the exception of PIs based therapy, switching to E/C/F/TAF was associated with a significant increase in total triglycerides and cholesterol. An improvement in liver function was also found after switching to E/C/F/TAF.

In the STRATEGY-NNRTI study, patients were randomized, either switching to E/C/F/TAF or continuing with an NNRTIs regimen. After 48 weeks' follow-up, no viral drug resistance or improvement in neuropsychiatric symptoms was found in patients switching from NNRTIs

to E/C/F/TAF.[6] In our previous study, neuropsychiatric symptoms improved after switching from efavirenz.[7] In the present study, switching to E/C/F/TAF was associated with a lower proportion of hepatic insufficiency and increased triglyceride levels. E/C/F/TAF therapy thereby appeared safe and may alleviate toxicity, while also leading to improvements in symptoms.

With the exception of atazanavir, the other PIs have been reported to cause elevation of total cholesterol and triglycerides levels.[8] A previous study revealed that the prevalence of lipid derangement was 92.7%.[9] In the present study, no atazanavir-based ART combination was used in participants. However, we did detect a decrease in triglycerides in patients after switching to E/C/F/TAF from PIs-based therapy. This suggested that E/C/F/TAF may be a safe and effective alternative to continuing PIs-based therapy in PLWHA.

In summary, switching to an E/C/F/TAF regimen may ensure high viral suppression and immunological recovery, as demonstrated by our 12-month follow-up data. Switching from PIs-based therapy to E/C/F/TAF may be particularly relevant for patients with hypertriglyceridemia. The potential improvement in liver function was the main motivation for switching to an E/C/F/TAF regimen.

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Conflicts of interest

None.

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