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Clinical outcomes of HIV-1 infected patients switched from complex multi-tablet regimens to tenofovir alafenamide based single-tablet regimens plus a boosted protease inhibitor in a real-world setting

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ABSTRACT

Background: Multi-tablet regimens (MTRs) are associated with increased adverse events and non-adherence. Single tablet regimens (STRs) plus boosted protease inhibitors (PIs) are a simplification option for MTR-treated patients; however, data is needed to validate this therapeutic strategy.

Methods: This retrospective analysis included all HIV-1 infected patients seen at a single center from March 2016 to December 2017 who were switched from twice-daily (BID) regimens or regimens containing ≥ 3 pills daily to elvitegravir/cobicistat/emtricitabine/tenofovir-alafenamide (E/C/F/TAF) plus darunavir (DRV) or rilpivirine/emtricitabine/tenofovir-alafenamide (RPV/F/TAF) plus DRV boosted with ritonavir or cobicistat (DRV/r-c). Eligible patients had baseline HIV-1 RNA<200 copies/mL and were followed for 48 weeks. The primary endpoint was HIV-1 RNA≥50 copies/mL at Week 48. Adherence and safety data were recorded throughout the study.

Results: Of 61 patients included, median age was 53 years, the median number of pills taken daily (range) was 5 (3–9), 80% were taking BID regimens, 97% had baseline HIV-1 RNA<50 copies/mL, 56 (92%) were switched to E/C/F/TAF plus DRV and 5 (8%) to RPV/F/TAF plus DRV/r-c. At Week 48, 2 patients (3%) had HIV-1 RNA≥ 50 copies/mL, both were treated with E/C/F/TAF plus DRV and neither had evidence of treatment-emergent resistance. Fifty-nine (97%) had an HIV-1 RNA<50 copies/mL. Adverse drug reactions (ADRs) occurred in 3/61 (5%) (all Grade 2) leading to 3/61 (5%) ADR-related discontinuations.

Conclusion: In this real-world cohort of MTR-treated patients, switching to a TAF-based STR plus boosted PI maintained virologic control in 97% and was well-tolerated, supporting potential use of this strategy for regimen simplification.

Introduction

Complex, multi-tablet regimens (MTRs) are often used to achieve virologic suppression in HIV-1 infected treatment-experienced patients with prior virologic failures (VFs) or antiretroviral (ARV) resistance.[1] However, these regimens are often associated with an increased incidence of adverse events, drug-drug interactions, worsening polypharmacy, and greater risk of non-adherence. Any of these factors can ultimately lead to other complications including VF and drug resistance.[2] Data from a meta-analysis comparing treatment outcomes of HIV-infected patients treated with single tablet regimens (STRs) vs. MTRs demonstrated improved adherence, reduced time to virologic suppression, lower discontinuation rates and improved patient satisfaction in the STR cohort.[3] Current treatment guidelines recommend regimen simplification "whenever possible" given the association with improved care outcomes[4], however regimen simplification is often challenging in patients with a history of ARV resistance. Newer combination STRs provide opportunities for regimen simplification and are often combined with protease inhibitors (PIs) in clinical practice given the high genetic barrier to resistance of the latter. In a study by Huhn et al., 135 heavily

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treatment-experienced patients with multi-class resistance, who were virologically-suppressed at baseline were randomized to receive elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) plus darunavir (DRV) versus stay on a multi-tablet baseline regimen through 48 weeks. Virologic suppression was maintained in 94.4% of those receiving E/C/F/TAF plus DRV vs. 76.1% of those who remained on their baseline regimen at Week 48.[2] Hence, the strategy of combining an STR plus a boosted PI appears to be a promising treatment option for treatment-experienced patients seeking to simplify MTRs, however, further data from real-world cohorts are needed to validate this as a viable therapeutic strategy.

Methods

This was a single-arm, retrospective observational cohort study to describe the effectiveness, safety and tolerability of switching treatment-experienced patients on complex MTRs to tenofovir alafenamide (TAF)-based STRs plus a boosted PI through 48 weeks. Eligible patients included all HIV-1 infected patients seen at the Orlando Immunology Center who were switched from complex MTRs defined as twice daily (BID) regimens *or* regimens containing $\geq$ 3 pills daily to either E/C/F/TAF plus DRV *or* rilpivirine/emtricitabine/tenofovir alafenamide (RPV/F/TAF) plus DRV boosted with ritonavir or cobicistat (DRV/r-c) between 3/2016-12/2017 (which was the time from FDA approval of RPV/F/TAF to the date which allowed for at least 48 weeks of follow-up for each patient). Eligible patients had baseline HIV-1 RNA<200 copies/mL x 2 prior to switch with the caveat that virologic blips defined as a viral load between 50 and 200 copies/mL must have been preceded by two HIV-1 RNA values below 50 copies/mL This inclusion criteria was selected to allow patients with virologic blips to enter the study as blips are common among virologically-suppressed patients in real-world settings and values < 200 copies/mL are not typically associated with VF or consistent non-adherence.[4] Key exclusion criteria included patients on a fifth agent for HIV treatment in addition to the TAF-based STR plus boosted PI and patients with active hepatitis C infection. Informed consent was waived due to the retrospective observational nature of the study which utilized data collected as a part of routine clinical care.

Demographics, laboratory values and clinical parameters were extracted from the charts of all eligible patients through Week 48 of treatment with the TAF-based STR plus boosted PI. The primary endpoint of the study was the proportion of patients with plasma HIV-1 RNA$\geq$50 copies/mL at Week 48. Secondary endpoints included change in $CD4^+$ T cell count from baseline to Week 48, change in lipid parameters (total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides) from baseline to Week 48, and adherence to, safety of and tolerability of treatment with the TAF-based STR plus boosted PI. All laboratory abnormalities were graded using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events.[5]

Descriptive statistics (frequencies, proportions, and medians with range) were calculated for participant baseline demographic and clinical characteristics, virologic outcomes, adverse drug reactions (ADRs), adherence reports and discontinuations throughout the study. The Wilcoxon paired rank test was used to determine if there were any significant changes in $CD4^+$ T cell count or lipid parameters from baseline to Week 48. The Sterling Institutional Review Board determined that the study met IRB exemption criteria based on the observational nature of the study (Sterling IRB ID 7151).

Results

During the study period, 4096 treatment-experienced, HIV-1 infected patients received care at the Orlando Immunology Center. Of these, 61 (1.5%) were switched to a TAF-based STR plus boosted PI; 56/61 (92%) were switched to E/C/F/TAF plus DRV and 5/61 (8%) were switched to RPV/F/TAF plus DRV/r-c. The median age (range) of the sample was 53 (27–70) years, median baseline $CD4^+$ T cell count (range) was 510 cells/mm^3 (87–1798), 45 (74%) had previously used >2 nucleoside reverse transcriptase inhibitors (NRTIs), 36 (59%) had previously used $\geq$2 PIs and 56 (92%) were integrase strand transfer inhibitor (INSTI)-experienced (Table 1). The documented median duration of HIV infection (range) was 22 (4–33) years and the documented median duration on ARVs (range) was 14 (1–27) years. The median number of documented ARV regimens prior to switch (range) was 4 (1–10). Prior to switch, 49 (80%) patients were on BID regimens, the median number of pills taken daily (range) was 5 (3–9) and 23% were on $\geq$6 pills daily. The most common ARVs in regimens prior to switch were DRV or atazanavir in 85%, an INSTI in 82% and tenofovir disoproxil fumarate (TDF) or TAF in 69% (Table 1). Historical genotypic tests were available for 34 (56%) patients and revealed that 31 (91%) had some form of ARV resistance with 2-class resistance found in 28 (82%) patients and 3-class resistance in 17 (50%). NRTI resistance was most prevalent and occurred in 27 (79%) patients, PI resistance in 26 (76%) and 21 (62%) had non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance. Seventy-five percent of patients had a history of VF and the median number of prior VFs (range) was 1 (0–4). Reasons for switching to a TAF-based STR plus boosted PI included reducing pill burden (53/61), side-effect concerns from prior regimen (4/61) and 4/61 had no reason documented (Table 1). At baseline, the median total cholesterol was 176 mg/dL, median LDL cholesterol 101 mg/dL, median HDL cholesterol 47 mg/dL and median triglycerides 114 mg/dL.

At Week 48, 2/61 (3%) patients had HIV-1 RNA$\geq$ 50 copies/mL, and 59/61 (97%) had achieved virologic suppression. (Fig. 1). Both patients with HIV-1 RNA$\geq$ 50 copies/mL were treated with E/C/F/TAF plus DRV. One had baseline and Week 12 HIV-1 RNA<50 copies/mL but experienced an increase in HIV-1 RNA to 83 copies/mL at Week 48. At this visit, the patient reported 100% adherence with ARVs, and the provider suspected a virologic "blip". On historical genotypic testing, the patient had an M184 V/I and K65R mutation with no INSTI or PI resistance-associated mutations (RAMs). The patient was lost to follow up for 2 years after the Week 48 visit, however returned to clinic at Week 144 and was found to still be on E/C/F/TAF plus DRV. A subsequent archive genotype and HIV-1 RNA were obtained which demonstrated no new mutations and a viral load of 120 copies, respectively. The patient was continued on E/C/F/TAF plus DRV and has not yet attended additional follow-up visits. The other patient had baseline and Week 24 HIV-1 RNA<50 copies/mL but experienced an increase in HIV-1 RNA to 511 copies/mL at Week 36. At this visit, the patient endorsed suboptimal adherence and received adherence counseling. At the Week 48 visit, the patient had an HIV-1 RNA that had decreased to 88 copies/mL. Historical genotypic testing revealed no NRTI, PI or INSTI RAMs. At Week 96, the patient has continued E/C/F/TAF plus DRV and subsequently achieved an HIV-1 RNA<50 copies/mL; archive genotype testing performed at this visit demonstrated no new mutations.

Subgroup analyses revealed no difference in response at Week 48 based on number of historical NRTI, PI or INSTI RAMs. There was also no difference in response based on baseline viral load and $CD4^+$ T cell count (Fig. 1). There was no significant change in median $CD4^+$ T cell count from baseline to Week 48 (+14 cells/mm^3, 95% confidence interval (CI): [-50.5; 78.3].

There were significant changes in all lipid parameters from baseline to Week 48. Median total cholesterol increased by 15 mg/dL, 95% CI: [2.5; 28.5], median HDL cholesterol increased by 5 mg/dL, 95% CI: [2.5; 42.5], median LDL cholesterol increased by 13.25 mg/dL, 95% CI: [8; 30], and median triglycerides decreased by 24.5 mg/dL, 95% CI: [-89.5; −13.0]. Only 3 (5%) patients experienced ADRs throughout the study period; all 3 were treated with E/C/F/TAF plus DRV. One patient experienced a 10-pound weight gain over 48 weeks following switch and decided to discontinue treatment. A second patient reported tinnitus starting at Week 4 which continued and led to treatment discontinuation at Week 48. A third patient reported nausea with emesis starting at Week 8 following switch and discontinued treatment at Week 48. A fourth patient treated with E/C/F/TAF plus DRV also discontinued treatment

Table 1
Baseline demographic and clinical characteristics.

Characteristics	N = 61
Median age (range)	53 (27–70)
Sex	
Male, n (%)	47 (77)
Female, n (%)	14 (23)
Race/Ethnicity	
Caucasian, n (%)	20 (33)
Black, n (%)	15 (24)
Hispanic, n (%)	14 (23)
Other, n (%)	12 (20)
Median BMI (range)	26.7 (18.9–45.4)
Median baseline CD4$^+$ T cell count, cells/mm^3 (range)	510 (87–1798)
Median duration of HIV infection, years (range)[a]	22 (4–33)
Median duration on ARVs, years (range)[a]	**14 (1–27)**
Median duration of virologic suppression prior to switch, years (range)[a]	**5 (1–13)**
Prior ARV experience	
>2 NRTIs, n (%)	45 (74)
≥1 NNRTI, n (%)	39 (64)
≥2 PIs, n (%)	36 (59)
1 INSTI, n (%)	50 (82)
>1 INSTI, n (%)	6 (10)
Median number of ARV regimens prior to switch (range)	4 (1–10)
Complex MTR prior to switch	
BID regimen, n (%)	49 (80)
Median number of pills daily (range)	5 (3–9)
≥6 pills daily, n (%)	14 (23)
ARVs in regimen prior to switch	
TDF or TAF, n (%)	42 (69)
ABC, n (%)	10 (16)
ETR, n (%)	8 (13)
DRV or ATV, n (%)	52 (85)
Any INSTI, n (%)	50 (82)
Reasons for switch	
Simplification, n (%)	53 (87)
Side-effects, n (%)	4 (6.5)
None documented, n (%)	4 (6.5)
Historical genotypic resistance available, n (%)	34 (56%)
Prevalence of resistance[b]	
Any ARV resistance, n (%)	31 (91)
2-class resistance, n (%)	28 (82)
3-class resistance, n (%)	17 (50)
NRTI resistance, n (%)	27 (79)
NNRTI resistance, n (%)	21 (62)
PI resistance, n (%)	26 (76)
INSTI resistance, n (%)	4 (7)
Pattern of NRTI RAMs[b]	
K65R, n (%)	2 (3)
M184V/I, n (%)	17 (50)
M184V/I alone, n (%)	3 (9)
M184V/I+ 1 NRTI RAM, n (%)	3 (9)
M184V/I + > 1 NRTI RAM, n (%)	11 (32)
Other TAMs (excluding M184V/I and K65R), n (%)	10 (29)

Abbreviation: BMI body mass index; ARV, antiretroviral; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; INSTI, integrase strand transfer inhibitor; MTR, multi-tablet regimen; BID, twice-daily; TDF, tenofovir disoproxil fumarate; TAF, tenofovir alafenamide; ABC, abacavir; ETR, etravirine; DRV, darunavir; ATV, atazanavir; RAM, resistance-associated mutation

[a]Values for documented durations are reported and are likely underestimations given lack of complete ARV data for all patients.

[b]Total with available historical genotypes used as denominator.

due to provider decision to change the regimen as the patient continued to endorse non-adherence. Notably, this patient had an HIV-1 RNA<50 copies/mL at the time of discontinuation. Grade 1–2 laboratory abnormalities occurred in 38 (62%) patients and included LDL elevations in 17 (28%), glucose elevations in 17 (28%), triglyceride elevations in 13 (21%), liver function test elevations in 11 (18%), and creatinine elevations in 3 (5%). Grade 3–4 laboratory abnormalities occurred in 8 (13%) patients and included triglyceride elevations in 5 (8%), glucose elevations in 3 (5%), and LDL elevations in 1 (2%).

Discussion

In our study, switching patients with baseline HIV-1 RNA<200 copies/mL treated with complex MTRs to either E/C/F/TAF plus DRV or RPV/F/TAF plus DRV/r-c maintained virologic control in 97% of patients and was overall safe and well-tolerated. Previously, Huhn et al. demonstrated superior virologic efficacy of switching to E/C/F/TAF plus DRV versus continuation of a more complex baseline regimen in virologically suppressed adults with multi-drug resistant HIV-1 infection through 48 weeks in a randomized clinical trial setting.[2] E/C/F/TAF plus DRV was also found to be well-tolerated and associated with improved renal safety and higher treatment satisfaction compared to staying on baseline regimen in this study.[2] Though our study observations support these findings, there are some key differences of note. Our study is a single-arm cohort in which patients on complex MTRs were switched to TAF-based STRs plus a boosted PI in a real-world setting primarily due to a desire for simplification, whereas the Huhn study was a larger randomized clinical trial designed to evaluate the efficacy and safety of switching patients with a prior history of VF and documented ARV resistance to a once-daily simplified regimen. In this population, regimens prior to switch contained a median of 5 pills daily, were dosed BID in 65% and contained ≥6 pills daily in 39% of patients.[2] Though our inclusion criteria did not require a history of VF or documented ARV resistance, 75% of our cohort had a prior history of VF, and 82% of those with available historical genotypes had at least 2-class resistance. Prior to switch, the median number of pills taken daily was also 5, 80% were on BID regimens and 23% took ≥6 pills daily. These similarities suggest that despite key differences in design, both studies evaluated the efficacy and safety of switching to a TAF-based STR plus boosted PI in populations that are reflective of highly treatment-experienced patients on complex ARV regimens.

Our study included a small number of patients also switched to RPV/F/TAF plus DRV-r/c whereas the prior study only evaluated switching to E/C/F/TAF plus DRV. In our cohort, there were also 4/61 (7%) patients with INSTI RAMs and 12/61 (20%) with ≥1 DRV RAM, whereas the prior study excluded patients with baseline INSTI and DRV resistance. We conducted subgroup analyses to determine differences in virologic response based on pre-existing NRTI, PI and INSTI resistance though noting that only 34 (56%) patients had baseline genotypic testing available for evaluation, whereas the prior study only performed subgroup analyses based on age, sex and race. Our study contained a higher proportion of patients switched from BID regimens compared to the prior study, however we did not collect any patient-reported outcome data to evaluate treatment satisfaction with the switch, whereas the prior study was able to demonstrate significantly higher satisfaction and adherence with E/C/F/TAF plus DRV compared to staying on baseline regimen.[2]

Overall, both studies demonstrated high efficacy rates at Week 48 with no subjects discontinuing due to lack of efficacy. In the prior study, no subjects treated with E/C/F/TAF plus DRV met criteria for resistance testing as none experienced virologic rebound with an HIV-1 RNA>400 copies/mL.[2] In our study, 2 patients had HIV-1 RNA≥ 50 copies/mL at Week 48, both underwent subsequent archive genotypic testing which did not demonstrate evidence of treatment-emergent resistance. These findings in combination with the fact that 28/34 (82%) patients with available historical genotypes had at least 2-class resistance suggests that switching to a TAF-based STR plus boosted PI is a viable therapeutic strategyfor treatment-experienced patients with underlying ARV resistance.

In our cohort, switching to a TAF-based STR plus boosted PI was associated with significant lipid changes through 48 weeks; there was a significant increase in median total cholesterol, median LDL cholesterol and median HDL cholesterol, whereas median triglycerides significantly declined. However, the proportion of patients on lipid-lowering therapy remained the same at Week 48 compared to baseline suggesting that overall, these changes did not result in clinically meaningful differences in lipid outcomes. Notably, 40/61 (66%) patients switched from MTRs containing a PI plus ritonavir given BID, hence our switch strategy

resulted in lower cumulative PI and ritonavir exposure for most patients and this would have perhaps been expected to result in lipid benefits given the association between PIs and dyslipidemia.[6–9] This effect, however, may have been offset by the fact that approximately half of patients switched from TDF-containing regimens to TAF and likely lost the "lipid lowering effect" of TDF. Though studies have found that switching from TDF to TAF in a real-world setting has been associated with statistically significantly worsening lipid profiles,[10] a recently conducted post-hoc analysis of Gilead-sponsored studies evaluating switches from E/C/F/TDF to E/C/F/TAF demonstrated that the lipid changes with TAF do not substantially affect atherosclerotic cardiovascular disease risk (ASCVD) scores or statin eligibility.[11]

Switching to a TAF-based STR plus boosted PI was overall safe and well-tolerated in this cohort with only 3/61 (5%) patients reporting ADRs, all of which were Grade 2 and led to treatment discontinuation. Only 1 other discontinuation occurred, however this was in a virologically suppressed patient who was switched to another regimen because of continued non-adherence with the study treatment. There were no serious ADRs and a minority of patients (8/61) experienced Grade 3–4 laboratory abnormalities.

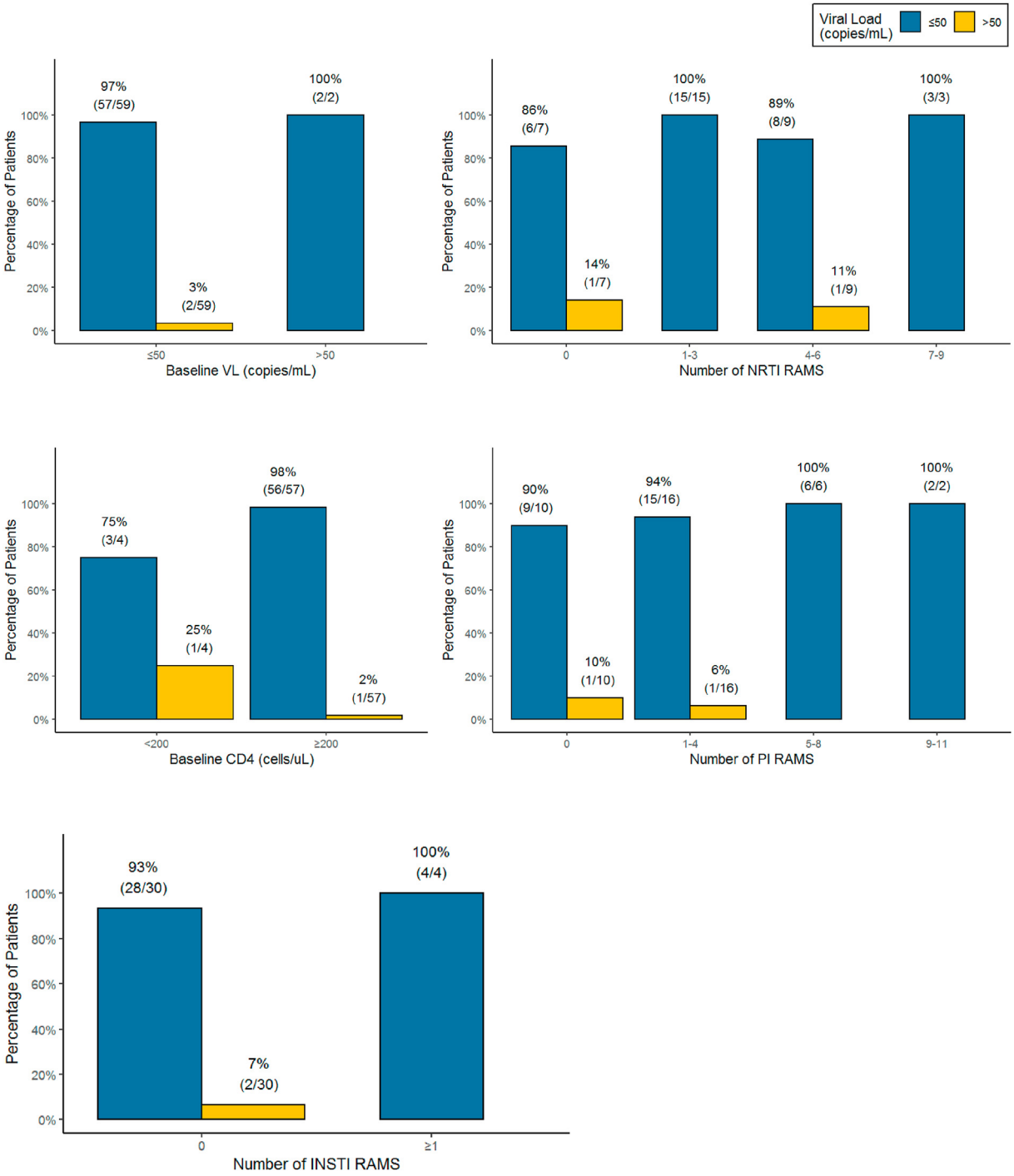

Fig. 1. Subgroup analysis of virologic outcomes at Week 48.
Abbreviations. VL, HIV-1 viral load; NRTI, nucleoside reverse transcriptase inhibitor; RAM, resistance-associated mutation; PI, protease inhibitor; INSTI, integrase strand transfer inhibitor.

There are several limitations to this study which include a small sample size, the retrospective nature of the analysis and the inability to control for other confounding factors. Another major limitation is the lack of accuracy and completeness of data documented in the electronic medical record, which is relevant for 56/61 (92%) patients in our cohort who received a portion of their HIV care at another practice. It is important to note that this likely results in a gross underestimation of several reported factors including the duration of HIV infection, ARVs and virologic suppression prior to switch, number of prior regimens, history of VF and prevalence of resistance. We also acknowledge that these data are from a single center in the Southeastern United States which limits generalizability to other populations.

In conclusion, the strategy of switching complex MTR-treated patients seeking simplification to a TAF-based STR plus boosted PI appeared to be effective at maintaining virologic control and was well tolerated in this small real-world cohort of treatment-experienced patients, many of whom had significant underlying NRTI and PI resistance.

Conflicts of interest and source of funding

There are no conflicts of interest for any author.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Yazdanpanah Y, Fagard C, Descamps D, et al. High rate of virologic suppression with raltegravir plus etravirine and darunavir/ritonavir among treatment-experienced patients infected with multidrug-resistant HIV: results of the ANRS 139 TRIO trial. *Clin Infect Dis*. 2009;49(9):1441–1449.
2. Huhn GD, Tebas P, Gallant J, et al. A randomized, open-label trial to evaluate switching to elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide plus darunavir in treatment-experienced HIV-1-Infected adults. *J Acquir Immune Defic Syndr*. 2017;74(2):193–200.
3. Clay PG, Yuet WC, Moecklinghoff CH, et al. A meta-analysis comparing 48-week treatment outcomes of single and multi-tablet antiretroviral regimens for the treatment of people living with HIV. *AIDS Res Ther*. 2018;15(1):17.
4. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. Department of Health and Human Services. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf. Section accessed 10/8/18.
5. U.S. Department of Health and Human Services NIoH. National institute of allergy and infectious diseases, division of AIDS. Division of AIDS (DAIDS) table for grading the severity of adult and pediatric adverse events.]. Available from: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdfpdf; 2017.
6. Echeverria P, Bonjoch A, Puig J, Ornella A, Clotet B, Negredo E. Significant improvement in triglyceride levels after switching from ritonavir to cobicistat in suppressed HIV-1-infected subjects with dyslipidaemia. *HIV Med*. 2017;18(10):782–786.
7. Kamara DA, Smith C, Ryom L, et al. Longitudinal analysis of the associations between antiretroviral therapy, viraemia and immunosuppression with lipid levels: the D:A:D study. *Antivir Ther*. 2016;21(6):495–506.
8. Ofotokun I, Na LH, Landovitz RJ, et al. Comparison of the metabolic effects of ritonavir-boosted darunavir or atazanavir versus raltegravir, and the impact of ritonavir plasma exposure: ACTG 5257. *Clin Infect Dis*. 2015;60(12):1842–1851.
9. Overton ET, Arathoon E, Baraldi E, Tomaka F. Effect of darunavir on lipid profile in HIV-infected patients. *HIV Clin Trials*. 2012;13(5):256–270.
10. Kauppinen KJ, Kivela P, Sutinen J. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide significantly worsens the lipid profile in a real-world setting. *AIDS Patient Care STDS*. 2019;33(12):500–506.
11. Huhn GD, Shamblaw DJ, Baril JG, et al. Atherosclerotic cardiovascular disease risk profile of tenofovir alafenamide versus tenofovir disoproxil fumarate. *Open Forum Infect Dis*. 2020;7(1):ofz472.