

# Comparative effectiveness of single versus multiple tablet antiretroviral therapy regimens in clinical HIV practice

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## Abstract

We determined risk of virologic failure (VF) in individuals initiating tenofovir/emtricitabine/efavirenz as single versus multiple tablet regimens (MTR). We found no significant difference in the risk of VF, though did observe a trend toward more VF and M184V mutations among persons initiating MTR. Temporal trends in care may have confounded results.

**Abbreviations:** ART = antiretroviral therapy, ARV = antiretroviral, CFAR = Center for AIDS Research, CNICS = CFAR Network of Integrated Clinical Systems, DHHS = Department of Health and Human Services, FTC = emtricitabine, HIV = human immunodeficiency virus, HR = hazard ratio, IAS-USA = International Antiviral Society United States of America, MTR = multiple tablet regimen, STR = single tablet regimen, TFE = tenofovir/emtricitabine (FTC)/efavirenz, US = United States, VF = virologic failure, VL = viral load.

**Keywords:** ART, atipla, comparative effectiveness, HIV, single tablet regimen

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MSS, SRC, TJ, and LR developed the study concept. DRD prepared the initial manuscript draft. AOW and SRC performed the data analysis. All authors reviewed and edited the manuscript.

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## 1. Introduction

Guidelines from the United States Department of Health and Human Services (DHHS) and the International Antiviral Society USA (IAS-USA) recommend treatment with combination antiretroviral therapy (ART) for all individuals infected with human immunodeficiency virus (HIV).<sup>[1,2]</sup> These recommendations have resulted in a dramatic increase in the number of persons in the United States (US) eligible for ART treatment compared with prior guidelines.<sup>[3,4]</sup> Two concurrent trends have accompanied the increase in patients eligible for treatment, which have the potential to increase the overall cost and success of expanded ART coverage: first, the introduction of fixed-dose combination or single-tablet regimens (STR) for the treatment of HIV and second the increase in the number of antiretrovirals (ARVs) that are now available as generic medications. Existing studies have shown that ART adherence is essential to the maintenance of viral suppression and prevents hospitalizations, AIDS, and death.<sup>[5–7]</sup> STRs may improve regimen durability<sup>[8]</sup> and adherence.<sup>[9,10]</sup> If clinicians are able to construct potent, durable, and tolerable regimens using generic medications, the potential for cost savings exists though this may also lead to more complex regimens that may impact adherence. We aimed to determine the risk of virologic failure (VF) in ART-naïve individuals starting a tenofovir/emtricitabine (FTC) /efavirenz (TFE) regimen as either an STR or multiple tablet regimen (MTR). To our knowledge this is the first study to compare ART-naïve patients starting an STR to those starting an MTR using the same component medications.

## 2. Methods

This study was conducted in the Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) cohort that contains clinical data on >30,000 HIV-infected patients

engaged in routine clinical care at 8 academic medical centers (Case Western Reserve University, Harvard Fenway, Johns Hopkins University, University of Alabama Birmingham, University of California San Diego, University of California San Francisco, University of North Carolina, and University of Washington) across the United States.<sup>[11]</sup> The CNICS repository systematically integrates demographic, laboratory, diagnosis, and medication data from electronic health records. Each site received local institutional review board approval to participate in CNICS and written informed consent was obtained from patients.

For this analysis, we identified ART-naive individuals initiating a TFE regimen from July 2003 to October 2012. Patients were divided into those that began TFE as an STR compared with an MTR. The outcome was VF that we defined in 2 distinct ways: first, in base model 1, VF was defined as a single HIV viral load (VL) >400 copies/mL at least 180 days after ART initiation; second, in the confirmed model 2, VF was defined as the date of the initial of 2 consecutive VL >400 copies/mL at least 14 days apart, at least 180 days after ART initiation. VL measurements prior to day 180 were ignored and individuals who died before 180 days excluded. Loss to follow-up was defined as a >210 day gap in care. Individuals were censored at the time of regimen change (including MTR to STR), last recorded VL, or date of last visit if they were lost to follow-up. We fit separate Cox proportional hazards regression models stratified by clinical site for each of the 2 VF models and compared persons who initiated an STR with those who started an MTR. Hazard ratios (HR) and 95% confidence intervals are reported. Each was adjusted for risk factors associated with VF: race, HIV transmission risk factor, and baseline CD4 (<200, 200–350, and >350 cells/mL) and continuous log<sub>10</sub> HIV VL.

In sensitivity analyses we examined the effect of treatment period to determine if changes in HIV treatment over calendar time could account for our results. Among VF patients we examined the frequency of common resistance mutations: K103N, M184V/I, K65R, and thymidine analog mutations.

### 3. Results

We observed 2258 patients who began a TFE regimen. Of these, 404 (18%) started an MTR (361 2-pill [89%] and 43 3-pill [11%]) and 1854 [82%] an STR. At baseline, individuals who started an STR had higher CD4 counts and lower HIV VL compared with MTR individuals (Table 1). Among MTR patients, 245 (61%) began between 2003 and 2005, 122 (30%) in 2006, and 37 (9%) between 2007 and 2012. STRs were started exclusively after 2005 with 87 (5%) starting in 2006 and 1767 (95%) starting between 2007 and 2012. Using model 1, 137 of 1854 (7%) individuals in the STR arm and 27 of 404 (6%) individuals in the MTR arm experienced an event. Using the stricter model 2, 42 of 1854 (2%) in the STR arm and 12 (3%) in the MTR arm had an event. Patients were censored for regimen change (45%), last viral load (30%), and lost to follow-up (31%).

In unadjusted analysis, using model 1 the HR of VF was 1.33 [0.87, 2.03] for MTR compared with STR, whereas in model 2 the HR was 1.93 [1.00, 3.72]. In adjusted analysis, using model 1 the HR of VF was 1.17 [0.76, 1.80], whereas using model 2 the HR was 1.54 [0.78, 3.04] (Supplemental Table 1, <http://links.lww.com/MD/B625>). In a sensitivity analysis looking at the effect of treatment era, the unadjusted hazard of VF in model 1 was 1.60 [1.00, 2.56] for the period of 2003 to 2006 and 1.07 [0.73, 1.56] for 2007 to 2009 compared with 2010 to 2012.

**Table 1**

**Baseline characteristics.**

	MTR (n=404)	STR (n=1854)
Mean age (SD)	38.9 (9.8)	38.4 (10.4)
Male sex, %	349 (86)	1629 (88)
Race/ethnicity, %		
Black	150 (37)	589 (32)
White	208 (52)	968 (52)
Other	46 (11)	297 (16)
HIV transmission risk factor		
MSM	234 (58)	1197 (65)
IDU	54 (13)	206 (11)
Other	116 (29)	451 (24)
Mean CD4 [cells/ $\mu$ L] (SD)	206 (148)	296 (198)
Mean log HIV VL [copies/mL] (SD)	5.0 (0.7)	4.7 (0.7)

IDU=injection drug user, MSM=men who have sex with men, MTR=multitabset regimen, SD=standard deviation, STR=single-tablet regimen.

Among the 164 patients with VF in model 1, we had genotypic resistance data available for 36 (29 STR, 7 MTR) patients. Of these, 25 (69%) had a K103N, 4 (11%) a K65R, 14 (39%) an M184V/I, and 7 (19%) had a thymidine analog mutation. While a trend was seen toward an increased likelihood of M184V mutations in the MTR group (5 out of 7) compared with the STR group (9 out of 29), it did not reach statistical significance. We found no other significant associations between the frequency of mutations in individuals on MTR compared with STR regimens.

### 4. Discussion

As the number of individuals treated with ART continues to increase, many important questions remain about the comparative and cost effectiveness of STR and MTR for the treatment of HIV infection. A recently published meta-analysis of clinical trial data showed that lower pill burden was associated with better adherence and viral suppression<sup>[12]</sup> in both once-daily and twice-daily subgroups. The included studies however tended to compare drugs of different classes which may have impacted results because of varying drug potency or adherence due to varying drug side effect profiles. Here, for the first time, we compared individuals taking the same medications as an STR with those taking them as an MTR to minimize bias resulting from variable potency or toxicity profiles of component medications.

In this analysis, we observed no significant difference in the development of VF between individuals started on an MTR compared with an STR TFE regimen though did see a larger hazard of VF in the MTR group; however, this difference was imprecise and the numerically higher rate of failure in the STR arm was likely due to longer duration of exposure in that arm. The overall number of VF events using either definition of VF was low which reduced the precision of our results, but the largest limitation of our study is that with the release of STR TFE in 2006, nearly all individuals initiating TFE after 2006 started an STR and those on an MTR nearly all switched to an STR truncating follow-up. As a result, the population of persons who started an MTR is heavily weighted to the pre-2007 period and we cannot exclude the possibility that unmeasured differences attributable to differing treatment era effects may have impacted our results.

Our study has a number of other limitations. Like all observational studies we cannot rule out unmeasured confounding. As CNICS is a cohort of patients seen for routine clinical care

at US academic medical centers, our findings may not be applicable in other settings, particularly in resource-limited settings. We had virologic resistance on only a small subset of patients who met our VF criteria and did not observe any significant associations comparing the frequency of specific resistance mutations between MTR and STR regimens. The suggestion of more M184V mutations in the MTR group is however intriguing and deserves further study. In addition because of the small number of persons with resistance data, it is possible that individuals may have met our definitions of VF due to poor adherence either due to pill burden or side effects without having developed genotypic resistance, though given that the component medications are the same, we do not believe that side effects should have varied between groups.

Our study also has a number of important strengths. It was conducted in a large and well-characterized cohort of HIV-infected individuals. We assessed 2 distinct definitions of VF because true clinical VF requires the treating clinician to assess detectable HIV VL in the setting of his or her assessment of a patient's adherence. As a result, no model of VF is perfect, though we believe that the confirmed model 2 likely represents individuals with more certain VF.

In summary, we did not find a significant difference in the development of VF for individuals treated with an STR versus an MTR TFE regimen, though this result may be confounded by the different treatment eras in which MTR and STRs were predominantly prescribed. While many studies have shown improved adherence and patient satisfaction with STR and ART adherence remains an important predictor of clinical outcomes in HIV-infected patients, important questions remain about the relative effectiveness of STR versus MTR. Future larger analyses should continue to focus on the development of virologic resistance.

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