Clinical Study

Single Tablet Regimen Usage and Efficacy in the Treatment of HIV Infection in Australia

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Single tablet regimens (STRs) for HIV infection improve patient satisfaction, quality of life, medication adherence, and virological suppression compared to multitablet regimens (MTRs). This is the first study assessing STR uptake and durability in Australia. This retrospective audit of all patients receiving an STR (n = 299) at a large Sydney HIV clinic (January 2012–December 2013) assessed patient demographics, treatment prior to STR, HIV RNA load and CD4 during MTR and STR dosing, and reasons for STR switch. 206 patients switched from previous antiretroviral treatment to an STR, of which 88% switched from an MTR. Reasons for switching included desire to simplify treatment (57%), reduced side effects or toxicity (18%), and cost-saving for the patient. There was no switching for virological failure. Compared to when on an MTR, patients switching to an STR had significantly lower HIV RNA counts (p < 0.001) and significantly higher CD4 counts (p < 0.001). The discontinuation rate from STR was very low and all patients who switched to an STR maintained virological suppression throughout the study duration, although the study is limited by the absence of a control group.

1. Introduction

Advances in the development of antiretroviral agents (ARVs) for the treatment of HIV have reduced morbidity and mortality from AIDS [1]. Over the past 2 decades, more potent, less toxic ARVs have been developed and treatment regimens of some 20 pills per day are now reduced to once-daily, single tablet regimens (STRs) incorporating 3 ARVs. STRs may improve adherence by reducing pill burden and thus prevent the development of drug-resistance mutations to individual ARVs in multitablet regimens (MTRs) [2].

There is also an association between ARV pill burden and risk of hospitalisation. Cohen et al. [3] note that patients receiving an STR had significantly better rates of adherence compared to those receiving MTRs, and this translated to lower rates of hospitalisation. Overall costs were higher with patients receiving MTRs due to higher pharmacy and inpatient related care costs [3]. A recent Italian study concluded that the STR not only resulted in better adherence, but added €4541.00 lower cost-effectiveness ratio per QALY in comparison with the MTR with a 17% lower cost in favour of the STR [4].

STRs are generally associated with better adherence and higher viral suppression [3, 5, 6] and patient-reported outcomes (i.e., better tolerability and satisfaction with the STR) are correlated with better quality of life [5, 7]. That said, adherence to ARVs is not necessarily improved by STRs where there are differences in access to care, for example, rural versus urban-based patient populations [8]. STRs also improve adherence in patients who have other chronic diseases requiring multiple treatments [9, 10]. Indeed, the World Health Organization (WHO) recommends STRs for the treatment of hypertension, tuberculosis, and HIV infection [11].

There are 4 STRs approved for use in Australia, that is (in order of approval), (1) tenofovir/emtricitabine/efavirenz (Atripla); (2) tenofovir/emtricitabine/rilpivirine...
(Eviplera/Complera); (3) tenofovir/emtricitabine/elongever- 
vir/cobicistat (Stribild); and (4) dolutegravir/abacavir/ 
lamivudine (Triumeq). The STRs “recommended” for initial 
therapy in current Australian HIV treatment guidelines 
include Atripla and the integrase based Strild and 
Triumeq, with Eviplera/Complera listed as “alternative” 
regimen in patients with HIV RNA < 100,000 copies/mL and 
patients whose CD4 count exceeds 200 cells/µL [12].

To our knowledge, no Australian study hitherto has 
compared the efficacy of STRs with MTRs, nor assessed the 
reasons patients switch from STRs to MTRs. Atripla and 
Eviplera/Complera were the only 2 STRs available when this 
study was conducted. Atripla is effective at achieving and 
maintaining virological suppression compared with MTRs 
[13]. In the STAR study, Eviplera/Complera was statistically 
noninferior to Atripla in relation to virological efficacy when 
baseline HIV RNA ≥100,000 copies/mL and statistically 
superior when baseline HIV RNA < 100,000 copies/mL [14].

2. Materials and Methods

Between 1 January 2012 and 31 December 2013, we conducted 
a retrospective audit of the medical and ARV dispensing 
records for all patients receiving an STR prescribed and man-
aged by a clinic doctor during the said period (patients who 
were dispensed medication prescribed by external doctors 
were excluded from the analysis). The study was conducted 
at Albion Centre, a WHO Collaborating Centre for Capacity 
Building and Health Care Worker Training in HIV/AIDS 
Care, Treatment and Support, and Australia’s largest public, 
multidisciplinary specialist HIV treatment centre, located in 
metropolitan Sydney.

Patients completed a brief questionnaire concerning 
demographics, current STR, and previous ARV regimen (if 
not treatment-naïve). They were asked to specify the main 
reason for switching to an STR according to the following 
predefined reasons: desire for an STR (convenience), once-
daily dosing, and improved toxicity, previously on a clinical 
trial (trial ended), or to state their own reason.

We established the number of Albion Centre patients 
receiving STRs including the proportion and reasons com-
enced on an STR as treatment-naïve patients, switched 
from an MTR to an STR, switched from an STR to another 
STR, and switched from an STR to MTR. We compared the 
HIV RNA and CD4 count of those on STRs to those on 
MTRs to deduce differences in relative virological efficacy 
and immune response.

Patients either initiated an STR as a treatment-naïve 
patient or switched from previous treatment to an STR 
before the study period; that is, all patients were receiving 
STRs during the study period and STR switches to an 
MTR “discontinuations” were then evaluated to calculate STR 
Survival (STR switch to an alternative STR was not classified 
as a treatment discontinuation for statistical purposes). Mean 
HIV RNA and CD4 count were obtained for the duration of 
previous therapy with MTR and STR from the medical 
record.

Data were analysed using SPSS version 22.0. Regarding 
statistical analyses, difference in mean HIV RNA 
during treatment with MTR versus STR was calculated using 
Wilcoxon’s Sign-Rank test; difference in mean CD4 count 
during treatment with MTR versus STR was calculated using 
a two-tailed paired t-test; difference in observed proportion 
of patient with HIV RNA > 20 copies/mL was calculated by 
McNemar’s test; and mean estimated STR survival during the 
24-month study period was calculated by means of a Kaplan-
Meier survival plot.

The postswitch HIV RNA and CD4 count were taken 
as the last available results in the medical record preceding 
31 December 2013. No patients were switched for reason of 
virological failure. Although the time from the initiation of 
STR until the end of study end-date varied for each patient, 
this was deemed the best indication of the efficacy of the STR 
for the purpose of our analysis. Ethics approval was obtained 
from the South Eastern Sydney Local Health District Human 
Research Ethics Committee.

3. Results

A total of 299 patients were receiving an STR during the 
study period. This represented approximately 25% of all ARV 
prescriptions dispensed through our pharmacy at the time. 
96% of patients were male and 4% were female. The cohort 
mean age was 42 years (range 19–73); 10% (29 patients) 
were hepatitis C antibody positive, 6% (18 patients) reported 
previous injecting drug use, and 5% (14 patients) were 
hepatitis B core antibody positive.

Two-thirds of patients (193) had previously received 
ARVs prior to enrolment and one-third (106 patients) were 
treatment-naïve. HIV RNA and CD4 counts obtained on the 
day of first prescription of an STR, if available, or immediately 
preceding the STR initiation, were used to define the “HIV 
RNA at switch” and “CD4 at switch” for the purpose of 
statistical analyses.

During the study period, 206 patients switched from their 
previous ARV regimen to an STR (14 previously treatment-
naïve, 192 previously treated). The details of previous ARV 
regimen and switch to an STR are shown in Table 1. Approx-
imately half the patients switched their previous treatment to 
Atripla and the other half to Eviplera/Complera. The majority 
(88%, 182 patients) had switched from an MTR, 11% (23 
patients) switched from an STR, and 1 patient, who had 
received an MTR but stopped treatment prior to the study 
period, was commenced on an STR (this patient was counted 
as a “switch” for the purpose of the analysis).

3.1. MTR Switch to STR. One hundred and eighty-three 
patients received an MTR as previous treatment for a mean 
duration of 6.25 years before switching to an STR; 56% 
(103 patients) requested the switch in order to simplify their 
ARV treatment (i.e., convenience of a single tablet, once-
daily dosing, cost reduction); 17% (32 patients) switched 
due to side effects or toxicity (e.g., hypercholesterolaemia, 
gastrointestinal symptoms); and 5% (10 patients) switched 
for some other reason (namely, immigration to Australia 
from countries with limited ARV access, initiation of hepatitis 
C treatment, reinitiation of ARV after prolonged interrup-
tion, and previous enrolment in a clinical trial). There was
no reason documented for the MTR switch for 21% of patients.

Seventy-four percent (136 patients) had HIV RNA <20 copies/mL at the commencement of the STR. Of the 95 patients who switched to Atripla, 70% (67 patients) were previously taking tenofovir/emtricitabine (Truvada) and efavirenz as 2 separate ARV tablets. Of the 82 patients who switched to Eviplera/Complera, 73% (60 patients) were previously receiving a Truvada backbone with either nevirapine (14/60 patients), or atazanavir plus ritonavir (21/60 patients), or lopinavir/ritonavir (Kaletra, 8/60 patients), or raltegravir (10/60 patients). Remaining patients received a variety of ARVs.

3.2. STR Switch to STR. Twenty-three patients receiving Atripla switched to Eviplera/Complera during the study period. 56% (13 patients) switched due to typical efavirenz toxicity (neurocognitive symptoms, rash, or lipid elevation) and 13% (3 patients) switched due to the convenience of taking their medication with meals. There was no reason for switching STRs documented for 8 patients. No patients switched from Eviplera/Complera to Atripla. Notably, 10% (30/299 patients) of all switches were from Atripla due to toxicity. This includes the 23 patients switching to Eviplera/Complera and 7 other patients who switched from Atripla to an MTR (discussed below).

3.3. STR Survival. The mean pretreatment HIV RNA as well as CD4 count for treatment-naive patients was 122,414 copies/mL and 414 cells/µL, respectively. Mean HIV RNA and CD4 count were calculated for duration of therapy with an MTR (i.e., before switch) and an STR (i.e., time from initiation for treatment-naive patients or switch for treatment-experienced patients). Mean HIV RNA and CD4 differed during treatment with MTRs and STRs. Mean HIV RNA during treatment with MTR was significantly higher compared to that during treatment with an STR, being 5454 and 1103 RNA copies/mL, respectively ($Z = -4.718; p < 0.001, Wilcoxon’s Sign-Rank test$). (Treatment-naive patients were not included in the pre- and postswitch analysis. Only those switching were analysed to obtain the aforementioned p values.)

Mean CD4 count during treatment with MTR was significantly lower than that with an STR, mean CD4 being 554 versus 332 copies/mL ($p < 0.001, 2$-tailed paired t-test). At the time of switch from an MTR to an STR, or an STR to an STR, the proportion of patients with HIV RNA >20 copies/mL was significantly higher with MTRs compared to STRs [69% (38 patients) versus STRs 58% (14 patients), resp. ($p < 0.001, McNemar’s test$)].

The benefits of convenience and improved adherence with STRs are meaningless if STRs cannot maintain virological suppression (durability) which is critical in preventing HIV disease progression and development of viral resistance. In terms of survival on an STR, all patients remaining on an STR maintained virological suppression throughout the duration of the study (HIV RNA < 20 copies/mL). The mean estimated survival time on an STR was 23.3 months calculated by Kaplan-Meier analysis (standard error = 0.204; 95% CI 22.95–23.75), whilst the STR discontinuation rate was low overall at 3% (10/299) (Figure 1).

Of the 10 patients who switched off an STR to an MTR during the study period, there were 7 Atripla switches due to efavirenz toxicity (neurocognitive symptoms, rash, lipid elevation, and abnormal liver function from hepatitis C coinfection) and 3 Eviplera/Complera switches due to declining eGFR, insomnia, rash, or abdominal pain. For those that switched from an STR to MTR, choices for regimens included a Truvada backbone plus either raltegravir or darunavir/ritonavir; or an abacavir/lamivudine (Kivexa/Epzicom); or zidovudine/lamivudine (Combivir) backbone plus rilpivirine.

4. Discussion

Atripla and Eviplera/Complera were the only STRs recommended by ARV guidelines and licensed in Australia at the
time this study was conducted. To our knowledge, this is the first study of STR uptake and durability conducted in Australia. Most patients (97%) remained on their STR over the 2-year observation period. Ten patients (3%) ceased their STRs, due to toxicity or tolerability issues: renal decline secondary to the tenofovir component of the STRs [15], abnormal blood lipid profiles, and for several patients complaining of drug-induced rash or insomnia, all known side effects of efavirenz [16–18]. Efavirenz was ceased in 3 cases due to viral hepatitis induced rash or insomnia, all known side effects of efavirenz.

In this study, Atripla and Eviplera/Complera were associated with improved CD4 counts and lower HIV RNA loads compared to MTRs. Once stabilised on an STR, there were few discontinuations and virological suppression was sustained. Most switches from an MTR to an STR were due to patient factors, such as pill burden, convenience, tolerability, and/or cost, whilst there were very few switches from one STR to another due to predicted side effects or dietary limitations. Our study suggests that once patients are initiated on an STR they are likely to remain on it over a medium term whilst maintaining virological suppression. As such, STRs are an effective option for many patients. The relative benefits of the newer integrase inhibitor based STRs may further extend these advantages, but this remains to be tested.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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