Brief Report



# Short Cycle Therapy with Bictegravir/Emtricitabine/Tenofovir Alafenamide in a Small Cohort of Virally Suppressed People Living with HIV: A Long-Term Follow-Up

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# Short Cycle Therapy with Bictegravir/Emtricitabine/ Tenofovir Alafenamide in a Small Cohort of Virally Suppressed People Living with HIV: A Long-Term Follow-Up

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**Abstract:** Short-cycle therapy has proven to be a safe and effective alternative to standard everyday antiretroviral treatment for virally suppressed people living with HIV. Here we report a favorable long-term virological and immunological outcome in 12 virally suppressed people on short cycle therapy with bictegravir/emtricitabine/tenofovir alafenamide administered five days a week (Monday to Friday).

**Keywords:** Antiretroviral treatment; short cycle therapy; HIV; virologically suppressed people; bictegravir

## 1. Introduction

In recent years, several strategies have been explored to reduce the exposure of people living with HIV (PLWH) to antiretroviral drugs and to improve their adherence and quality of life, while maintaining safety and virological suppression. Examples of this strategies are dual therapies (for example, dolutegravir and lamivudine or rilpivirine) and the recent introduction in clinical practice of long-acting injectable regimens (rilpivirine and cabotegravir). In a not-too-distant future, ultra-long-acting regimens, antiretroviral nano-formulations, microarray patches and broadly neutralizing antibodies will be available [1]. Meanwhile, the "intermittent" or "short cycle" therapy (SCT) has received considerable attention, especially in France [2]. This strategy allows PLWH to take their antiretroviral drugs at standard doses and in combination for a limited number of consecutive days (generally four or five) per week and to interrupt the treatment during the weekend (Friday to Sunday or Saturday to Sunday); non-nucleoside reverse transcriptase inhibitors, integrase strand transfer inhibitors, and boosted protease inhibitors have been used in this approach [3]. Integrase strand transfer inhibitors (INSTIs), due to their favourable forgiveness [4], are preferred.

Dolutegravir and bictegravir dissociate slowly from the INSTIs-DNA complex and their half-lives are approximatively 12 hours and 17 hours, respectively, and therefore longer than raltegravir and elvitegravir [5]. Thus, dolutegravir and bictegravir are the preferred antiretroviral drugs for intermittent dosing.

Here, we report the long-term virological outcome in 12 virally suppressed patients on short cycle therapy with bictegravir/emtricitabine/tenofovir alafenamide, administered five days a week (Monday to Friday).

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## 2. Case Series

In the Infectious Diseases Unit of Santa Chiara Hospital in Trento (Northern Italy), we regularly follow 629 PLWH. Among these, at the beginning of March 2022 twelve (three women) virologically suppressed individuals on a stable bictegravir/emtricitabine/tenofovir alafenamide antiretroviral daily regimen started a "short cycle" (Monday to Friday) therapy. All these people were selected after reporting that they often skipped a few doses of the drug compared to others (79), who were taking bictegravir/emtricitabine/tenofovir alafenamide regularly. All the individuals signed an informed consent form. In Table 1, people's characteristics at baseline are reported. The mean age was 55.9 years (range 25-75). Mean antiretroviral therapy duration was 18 years (range 4-32), mean duration of virological suppression was 12.5 years (range 4-25), and mean time from the diagnosis of HIV infection was 20 years (range 4-33). Most people had been on various antiretroviral regimens (mean number 6, range 1-13); however, they had not experienced any virological failure after starting their first regimen. All patients had plasma HIV RNA <20 copies/mL at the beginning of the short cycle therapy. Plasma HIV RNA was quantified one and three months after the switch, and every six months thereafter; blood samples were collected on Monday (more than 48 hours after stopping bictegravir/emtricitabine/tenofovir alafenamide and before restarting it). At the time of writing (end of May 2024), all patients are still aviremic and have a mean follow-up of 24.8 months (range 24-26). The mean CD4+ve cell count rose from 683/μL (at the beginning of the short cycle therapy) to 908/μL (at the last visit). The mean body weight was 72.1 Kg at the time of switch and 71.9 Kg at the last control.

**Table 1.** Baseline patients characteristics.

| | |
|---|---|
| **MEAN AGE (years)** | **55.9 (25-75)** |
| **GENDER (male; female)** | **9 males and 3 females** |
| **RISK GROUP (MSM, Heterosexual, Intravenous drug addiction)** | **7 MSM; 1 Heterosexual; 4 with a previous history of intravenous drug addiction** |
| **CDC STAGE** | **5 patients A1; 1 A3; 2 B2; 1 B3; 3 C3** |
| **MEAN WEIGHT AT SWITCH (Kg)** | **72.100 Kg** |
| **MEAN WEIGHT AFTER MORE THAN 24 MONTHS OF "SCT"** | **71.900 Kg** |
| **MEAN DURATION OF HIV INFECTION** | **20 years (4-33 years)** |
| **MEAN DURATION OF ANTIRETROVIRAL THERAPY** | **18 years (4-32 years)** |
| **MEAN DURATION OF VIROLOGICAL SUPPRESSION** | **12.5 years (4-25 years)** |
| **MEAN NUMBER OF ANTIRETROVIRAL REGIMENS BEFORE BICTEGRAVIR/EMTRICITABINE/TENOFOVIR ALAFENAMIDE** | **6 (1-13)** |
| **MEAN LYMPHOCYTE CD4 COUNT AT SWITCH (no./μL)** | **683/μL** |

## 3. Discussion

In our small cohort all people, on a stable bictegravir/emtricitabine/tenofovir alafenamide antiretroviral daily regimen and in virological suppression, have maintained a plasma viral load of less than 20 copies/mL for over 24 months and their CD4+ T cell count rose during follow-up.

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Various studies have shown the virological safety of a short cycle therapy, starting with the FOTO study in 2007 [6]. Subsequently, the BREATHER study ("BREaks in Adolescent and child THerapy using Efavirenz and two nRtis"), a multicentric, randomized, controlled, open-label phase 2/3 trial, demonstrated the non-inferiority of a 5-days-per-week SCT compared to standard 7-days-per-week schemes in 199 adolescents taking efavirenz-based ART [7]. More recently, the ANRS 170 QUATUOR, a randomized, open-label, multicentric, non-inferiority trial, demonstrated the non-inferiority of the 4days-on/3days-off strategy in a large cohort of virologically suppressed PLWH on different ART regimens over a 96- weeks follow-up period [3]. Small observational studies using as third agent bictegravir, doravirine or rilpivirine have confirmed the efficacy and safety of this strategy [8–10]. Some of the above studies have reported also the plasma concentrations of antiretrovirals [3,8,10]. In particular, in the ANRS 170 QUATUOR trial, the median concentrations of antiretroviral drugs were much lower in the intermittent arm than in continuous treatment [3]. Sellem and colleagues evaluated 85 virally suppressed PLWH switched to intermittent bictegravir/emtricitabine/tenofovir alafenamide treatment, administered 4 or 5 days a week [8]. Notwithstanding its limitations (observational nature and small number of people included), the study found a high level of virological success (100% at week 48 and 97.6% at week 96). Two people with poor adherence had a virological failure, without the development of resistance mutations at HIV genotypic testing [8]. Virological re-suppression was obtained after resuming daily bictegravir/ emtricitabine/tenofovir alafenamide treatment.

The authors performed a pharmacokinetics analysis in a subset of individuals; in 22 out of 38, the C trough of bictegravir was below the protein-adjusted $EC_{95}$ (162 ng/mL for the wild-type) [8].

Similarly, in 115 samples obtained after the three days off-treatment, to identify the lowest possible quantifiable concentration, we reported a plasma concentration of rilpivirine below the efficacy threshold of 50 ng/mL in 71.3% of the samples and below the 90% inhibitory concentration (IC90) of 12 ng/mL in 37.4% [10].

However, in all the above studies intracellular concentrations of antiretroviral drugs were not measured, hence not excluding the hypothesis of effective concentrations of the drugs inside PBMCs. Another possible explanation for the success of an intermittent strategy was put forward by Leibowitch and colleagues in the ICCARRE project; HIV rebound is observed after an eclipse phase of 1– 7 days or even more following the interruption of an effective therapy, this being particularly evident in PLWH with a long history of virological suppression, who have a reduced viral load, and whose lymphoid system is less activated and less favorable for HIV replication. In these conditions, lower concentrations of antiretroviral drugs are effective in controlling viral replication [11]. A 2010 study showed that the longer the viral suppression, the higher was the number of missed drug doses allowed without virological failure ensuing [12]. The proposed explanation was that lower levels of drug exposure are sufficient to prevent virological failure because the overall viral burden declines over time [12].

From a pharmacological point of view, bictegravir seems the most suitable INSTI for use in an intermittent antiretroviral therapy. The forgiveness of bictegravir and of other INSTI-containing regimens has been evaluated *in vivo* [13] and *in vitro* [14]. Maggiolo and Colleagues, in a retrospective study including 281 PLWH treated with bictegravir/emtricitabine/ tenofovir alafenamide, showed, through adherence measurement, an elevated forgiveness associated to a high rate of virological suppression [13].

Acosta and colleagues studied *in vitro* four INSTI-containing regimens (bictegravir/emtricitabine/tenofovir alafenamide, dolutegravir with emtricitabine/tenofovir alafenamide, dolutegravir/lamivudine, and dolutegravir/rilpivirine) [14], evaluating the time to *in vitro* virological breakthrough and emergence of resistance mutations (resistance barrier) at full or suboptimal treatment adherence levels. Bictegravir/emtricitabine/tenofovir alafenamide, when suboptimal treatment adherence level was tested, was the combination with the highest forgiveness and barrier to resistance [14].

In the same study dual therapy (dolutegravir/lamivudine and dolutegravir/rilpivirine combinations), was weaker, in terms of viral breakthrough and emergence of resistance mutations,

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than triple antiretroviral combinations for drug concentrations corresponding to having missed two or more consecutive doses (14).

Recently, a randomized, open-label, multicentric study ("ANRS 177 DUETTO"), evaluating a twodrug antiretroviral therapy (65.6% of participants were on a dolutegravir/lamivudine combination) taken four days a week rather than daily, found a similar rate of suppression but higher rates of treatment failure in the intermittent arm [15]. Six patients of the eight on virological failure were on dolutegravir/ lamivudine; interestingly, only two of the eight patients had a low plasma drug concentration.

## 4. Conclusion

Bictegravir/emtricitabine/tenofovir alafenamide seems the most appropriate for use in strategies of intermittent antiretroviral treatment, due to antiviral potency and forgiveness.

While waiting for new, potent long-acting drug formulations and different ways of delivery, oral short cycle antiretroviral therapies represent a feasible and valuable option for treatment optimization in selected individuals. This strategy can help to improve the quality of life, reducing pills fatigue and stigma, while also decreasing antiretroviral costs.

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