Real World Data on Forgiveness to Uncomplete Adherence to Bictegravir/Emtricitabine/Tenofovir Alafenamide

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Abstract

Background: forgiveness is the ability of a given regimen to maintain complete viral suppression despite a documented imperfect adherence. We explored forgiveness of bictegravir/emtricitabine/tenofovir alafenamide. Methods: drug refills were used to calculate the percent day covered (PDC) as a proxy of adherence. Forgiveness was calculated as the achieved rate of a selected HIV-RNA threshold by a given level of imperfect adherence. Results: 281 adult PLWH were followed for 343 patient/years. Adherence was very high with a median of 98% (IQR 95-100%). A PDC as low as 70% was sufficient to obtain 100% and maintain virologic suppression. According to probit analysis adherence was not related to the possibility to maintain an HIV-RNA TND or < 50 copies/ml. Conclusions: Long-term success of ART needs effective regimens that are the least intrusive of the patient’s lifestyle, an elevated forgiveness may be considered as an additional feature that can further improve long-term outcomes.

Keywords

forgiveness, adherence, B/F/TAF, cohort, INSTI, efficacy

Introduction

The issue of adherence to antiretroviral therapy (ART) came to the forefront in 2000 when Paterson et al1 showed that very high level of adherence were needed to achieve viral suppression in persons living with HIV (PLWH) mainly treated with un-boosted protease inhibitors. Additional studies lent support to this view2 leading to the conclusion that subjects should take at least 95% of the prescribed antiretroviral doses in order to control viral replication, and to an extreme emphasis on the need to achieve and maintain near perfect adherence in all PLWH on ART. This led to include a constant and aggressive monitoring of adherence into the management of ART.3 Successive studies, based on different adherence measures, different endpoints including viral suppression, but also resistance-inducing mutations selection and different therapeutic regimens based on boosted protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs), indicated that not all drugs acted the same and that some drugs could better tolerate moderate deviations from perfect adherence.4–7

The term “forgiveness” was consequently included into the lexicon of HIV management. When applied to ART, it refers to the ability of a given regimen to achieve and maintain complete viral suppression despite a documented imperfect medication adherence.8,9 In contrast with most pharmacological parameters, forgiveness lacks an established, quantitative measure, but, despite this, the medical community has embraced the concept that some regimens are more forgiving than others. Every day, in real world, substantial clinical and therapeutic choices that are made based on this concept. Although, generally judged as extremely potent and endowed of a high genetic barrier to resistance, very little is known about the forgiveness of modern integrase (INSTI) based regimens. We analyzed forgiveness of bictegravir/
emtricitabine/tenofovir alafenamide (B/F/TAF) in a single center unselected cohort.

**Methods**

In this retrospective study we included all PLWH of our cohort ever treated with B/F/TAF from January 2020 to March 2022. Patients with a minimum of 2 drugs refills were included irrespective of the length of their follow-up. Adherence was measured by means of percent day covered (PDC). The terminology used reflects that from ISPOR (Professional Society for Health Economics and Outcomes Research) Medication Compliance and Persistence Special Interest Group.10,11 PDC is the number of days with medication available divided by the number of days in a specified time interval. If excess medication is collected or refills are made early, the excess is applied toward subsequent absences of drugs. The denominator of PDC is typically a clinically meaningful number of days that in our case was the whole follow-up period. To calculate PDC a minimum of 2 refills are needed and PDC may be summarized as a continuous outcome or categorical. We obtained data to calculate PDC from the electronic data-base of the Hospital Pharmacy that reports date and quantity of any given refill. According to the Italian law, PLWH have to resupply for antiretroviral (ARV) drugs in the same center that follows them clinically. Usually the refill interval for ARV drugs is three months. As refills in other facilities are not allowed, the data-base of our hospital includes all medication dispensations of our cohort. We extracted and tabulated any drug refill of B/F/TAF. Similarly, demographic and clinical data were obtained from the electronic medical chart in use at the HIV outpatient clinic. All HIV-RNA measures from the beginning of the considered ARV regimen to the end of it or to the censoring date, last dispensing date (whatever came first) were extracted and tabulated as well.

To categorize patients, in terms of virologic response to ART, three different cut-offs were used:

- (a) Target not detected (TND), that is a value of HIV-RNA current standard methods do not detect and with no qualitative viral RNA detected. In our Center, the limit of qualitative detection is < 20 copies/ml.
- (b) HIV-RNA < 50 copies/ml as the gold standard to define therapeutic efficacy in clinical trials
- (c) HIV-RNA < 200 copies/ml as the value that prevents HIV transmission by sexual contacts

Finally, we evaluated forgiveness defined as the sensitive therapeutic success (eg selected HIV-RNA threshold) achieved rate under a given level of imperfect adherence.

The study was done in accordance with the 2008 Declaration of Helsinki under the approval of the Provincial Ethics Committee of the Bergamo Province (approval number 109/21-1588). All subjects signed an informed consent for the electronically based storage of their sensitive data and their use in aggregate anonymous way for cohort analyses.

Data were summarized as medians and interquartile range (IQR) if continuous or numbers and percentages if discrete. A probit model was applied to verify the impact of baseline variables and adherence on the virologic outcomes dichotomously defined according to the previously described cut-off values. All analysis were performed with SPSS 17.0.

**Results**

Our Hospital is a tertiary-level, urban, reference center for HIV infection that follows a cohort of more than 2880 PLWH. A total of 281 adult PLWH were treated with B/F/TAF and responded to the inclusion criteria of the study. All of them were included in the analysis. Most of the patients were males (75%); risk factor for HIV infection were heterosexual contacts in 50.2% of cases, while 29.8% of subjects were men having sex with men (MSM) and 19.2% intravenous drug users; a small percentage of subjects (0.7%) acquired the infection vertically.

The median age of the cohort was 49 years (IQR 43-58 years) and the median length of HIV infection was 8 years (IQR 5-16 years) indicating that most of the enrolled subjects were PLWH who switched to B/F/TAF from a previous ART. However for 50 PLWH B/F/TAF was the first ART regimen. The median nadir of CD4 cells was 342 cells/μL (IQR 83-573 cells/μL). The median cohort follow-up was 590 days (IQR 381-685 days) summing for a total of 343 patient/years of follow-up.

Overall, adherence, as calculated from PDC, was very high with a median of 98% (IQR 95-100%). Consequently, also the virologic response was sustained with 41.8% of PLWH with HIV-RNA < 200 copies/ml and with 96.8% of subjects with a HIV-RNA always < 200 copies/ml. Only 5 patients were non-responders and 37 subjects presented an isolated viral blip, 34 of which between 50 and 200 copies/ml.

As far as forgiveness is concerned, our data (Figure 1) indicates that a PDC as low as 70% is sufficient to obtain the desired virologic outcome irrespective of the considered cut-off ranging from a more demanding TND, to an HIV-RNA < 50 copies/ml or to a more comprehensive HIV-RNA < 200 copies/ml (Figure 1). Furthermore, probit analysis indicated that adherence variation was not related to the possibility to obtain and maintain an HIV-RNA TND or < 50 copies/ml, but that PDC significantly correlated with the threshold of < 200 copies/ml that differentiated patients truly non-responders from patients with eventual sporadic low-level viral blips (Figure 2). Adherence in non-responders was very low (median 67%; IQR 30-90%) compared to PLWH showing constant control of HIV replication (median 96%; IQR 95-100%), with a significant (P = 0.013) odds ratio of 1.11 (95%CI 1.02-1.22) (Figure 2). Interestingly, a marginally significant odds ratio (1.01, 95%CI 1.00-1.01; P = .004) was obtained for a lower CD4 nadir when the considered virologic outcome was TND.

**Discussion**

Antiretroviral medication adherence is an important predictor of virologic, immunological, and clinical outcomes in the
Adherence is a multifactorial variable whose correlates can be categorized as socioeconomic-related factors, patient-related factors, condition-related factors, health care team and system-related factors and therapy-related factors. Medication-related factors are also responsible for a given regimen’s forgiveness to less-than-perfect adherence. Medication half-life and antiviral efficacy are critical factors in forgiveness of non-adherence. These characteristics should be analyzed for the whole regimen focusing on the anchor drug as well as the antiretroviral components of the regimen. In general, a longer elimination half-life favors greater forgiveness. Under certain circumstances, however, a long half-life can confer a forgiveness disadvantage resulting, in the case of poor adherence, in de facto monotherapy (e.g., the ‘NNRTI tail’). The efficacy of a regimen at producing complete viral suppression, often referred to as ‘potency’ is another intrinsic drug characteristic that affects forgiveness. By definition, PLWH receiving less efficacious regimens are more likely to experience incomplete viral suppression at similar levels of adherence.

To calculate forgiveness, beside a precise desired outcome, an accurate adherence assessment is essential. No perfect adherence measures exist. Self-reported adherence measures have been widely used however, they allow to assess adherence over a short period, usually no longer than a month, and are influenced by recall bias as well as social desirability. Objective measures of adherence are generally more informing. Electronic monitoring devices often regarded as “gold standard” are expensive and difficult to implement in routine practice. Pharmacy refill is a valid alternative proxy of adherence measure focused on medication availability. Several studies in different chronic pathologies, including HIV infection, have shown that the performance of pharmacy refill and calculated PDC adherence measures was comparable to electronic adherence monitoring measures. Pharmacy refill records provide an objective yet inexpensive measure and, more relevant, they allow for adherence assessment over longer periods of time.

These considerations prompted us to use PDC as calculated from pharmacy refills to assess adherence and to apply these calculations to our cohort of PLWH receiving B/F/TAF as HIV treatment.

Modern therapies bring together high genetic barrier, extensive efficacy, low potential for drug-drug interactions or altered pharmacokinetics, good tolerability, and high convenience but very little is known of adherence to these therapies and even less is known about their forgiveness. Most current drug combinations are available as single tablet regimens (STRs), too.

In our study the overall median adherence (98%) was very high with the lowest interquartile level falling within the 95% limit. Interestingly, when more stringent outcome measures were considered, adherence level was not associated with the desired outcome. HIV-RNA levels between TND and 50 copies/ml may be regarded as a low level viremia (LLV). Several studies suggest that factors such as ART adherence difficulties could be the main cause of LLV in HIV patients. However, although LLV status does not seem to be a random biological phenomenon, its origin remains unclear and other causes/mechanisms such as viral reservoir size and clonal

![Figure 1](image.png)

**Figure 1.** Virologic response expressed as achievement and constant maintenance of different HIV-RNA thresholds according to the individual adherence level as calculated by means of PDC. Legend: PDC = proportion days covered; TND = target not detected.
expansion\textsuperscript{31} could be linked to this phenomenon. Of note, when a clinically relevant HIV-RNA cut-off discriminating true virologic failures (eg 200 copies/ml)\textsuperscript{32} was considered, adherence was significantly associated to the outcome. The high forgiveness of the studied ART regimen (70\%) is a possible alternative explanation to our findings. As a matter of fact, a high forgiveness could mask modest reductions of adherence rate.

Our findings indicate that most subjects had an optimal adherence supporting the idea that B/F/TAF is a friendly regimen, well accepted by patients. If this result is paramount for clinical practice it may represent a limit for the present study as only a few patients with much lower adherence rates did eventually not respond to ART. Another limit of our study is the single center setting. This does not allows to generalize results for different therapeutic strategies and organizations for HIV management, but, on the contrary induces a reduced number of potential biases linked to the caregiver attitude. The fact that most enrolled subjects had a long history of HIV infection and antiretroviral therapy does not allow us to differentiate chronically treated PLWH from subjects with a recent start of ART.\textsuperscript{33,34} The uncontrolled nature and retrospective design of our study may be seen as further limits. Finally, the decision to limit the enrollment period to the very recent years, reduced the potential amplitude of the casuistry, however, on the other hand eliminated the confounding bias of calendar year. As a matter of fact a recent study conducted in British Columbia revealed that the PDC rate necessary to obtain a 90\% success rate defined as a HIV-RNA level < 200 copies/ml was 64\% (95\% CI 50-77) in more recent years compared to an overall necessary rate of 93\% (95\% CI 90-96).\textsuperscript{34} The Authors concluded that these results could be attributable to the increased use of more potent ART drugs such as INSTIs.

Nevertheless, the limits of our study are tempered from the fact that we pointed our attention to the lower limits of adherence trying to define a forgiveness factor. B/F/TAF was very robust in forgiving lower adherence rates. Further, PDC, with the dispensing correction we adopted, could potentially overestimate adherence rates,\textsuperscript{34} as drug possession is not necessarily synonymous of effectively taking the drug, but cannot underestimate it (eg one cannot take a drug that does not have) though strengthening the meaning of our findings as the lower limits we observed could be even lower. Due to the nature of collected data, we cannot differentiate the real dynamics of bad adherence in terms of sporadic and repeated single days off versus prolonged drug holidays, as well as actual pill-taking behavior, including taking medication according to the prescriber’s instructions or on the prescribed time schedule. These aspects that go beyond our scopes could be argument for further studies.

Data derived from a cohort of PLWH using unregulated drugs\textsuperscript{34} support our results indicating that a lower adherence threshold (69\%; 95\% CI 45-92) was needed to maintain

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Box plot representation of PDC in PLWH achieving and maintaining a given virologic threshold compared to those that do not. Median adherence values and factors significantly associated with the outcome of interest according to probit analysis. Legend: PDC = proportion days covered; TND = target not detected.}
\end{figure}
HIV-RNA suppression in 90% of patients treated with integrase inhibitors compared to a level equal or superior to 95% to obtain the same results in PLWH treated with boosted PIs or NNRTIs. These results are slightly higher than those obtained by the Patient-centered HIV Care Model demonstration project that found an overall estimated adherence level necessary to achieve viral suppression in 90% of viral load tests of 82%, with high variation by regimen type, being sufficient for integrase inhibitor-based levels of 75%.35

These findings along with ours are likely a result of INSTIs’ higher potency and genetic barrier and improved pharmacokinetic profiles, which, in turn, may make them more forgiving to missed doses.36,37

In recent years therapeutic strategies using simplified two drug (2DR) regimens have become popular especially in therapeutic switch in virologically suppressed patients. Few data are available on adherence required to assure success of 2DR. An experimental model in vitro showed higher forgiveness of TAF-based triple therapy compared to 2DR, and consistent protection against emergence of drug resistance during simulations of short lapses in adherence,38 supporting the choice of this strategy in patients with suboptimal adherence.

A Spanish cohort, using PDC to evaluate adherence, reported high level of adherence in patients switched to 3TC/dolutegravir (DTG) 2DR, with median values 48 weeks after switch of 98% (95% CI 94–100) and a proportion of subjects with adherence levels < 90% limited to 14.2%.39 Our group, on the basis of PDC, in PLWH treated with 3TC/DTG estimated a very high adherence rate a median of 99% (IQR 95%–100%) that was associated to a sustained virologic response with 83.8% of PLWH never exceeding a HIV RNA of 50 copies/ml and 95.8% of subjects with a steadily HIV-RNA < 200 copies/ml. A PDC lower than 80% was however, always associated with a negative outcome irrespective of the HIV-RNA threshold considered.39 Even less is known about long-acting regimens. The customize study reported an high adherence rate (94%) in PLWH with injecting therapies as measured as the respect of the 7 days window to receive their injection.41

Long-term success of ART needs well tolerated, effective regimens that are the least intrusive of the patient’s lifestyle. In this context, an elevated forgiveness may be considered as an additional feature that can further improve long-term outcomes.

**Authors’ Contribution**

Maggiolo F: PI, protocol ideation, statistical analysis, manuscript writing
Comi L: database management, manuscript discussion and revision
Di Filippo E: database management, manuscript discussion and revision
Teocchi R: database management, data extraction
Valenti D: database management
Rizzi M: manuscript discussion and revision

**Declaration of Conflicting Interests**

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**Ethical Considerations**

The study was done in accordance with the 2008 Declaration of Helsinki under the approval of the Provincial Ethics Committee of the Bergamo Province (approval number 109/21-1588). All subjects signed an informed consent for the electronically based storage of their sensitive data and their use in aggregate anonymous way for cohort analyses.

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