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B/F/TAF forgiveness to non-adherence

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ABSTRACT

Background ART forgiveness is the ability of a regimen to maintain HIV-RNA suppression despite a documented imperfect adherence. We explored forgiveness of bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF).

Methods In this retrospective cohort study pharmacy drug refills were used to calculate the proportion of days covered (PDC) as a proxy of adherence. Forgiveness was defined as the possibility to achieve a selected HIV-RNA threshold by a given level of imperfect adherence. A logistic model was applied to verify the impact of baseline variables and adherence on the virologic outcomes.

Results We enrolled 420 adults. From them, 787 one-year time-periods were derived for a median cohort follow-up of 873 person/years.

Most of them were males (73.1%); the most frequent risk factor for HIV infection was heterosexual contacts (49.5% of cases), followed by 22.5% MSM and 22.5% intravenous drug users. The median age of enrolled persons with HIV was 51 years (IQR 45-57 years); the median duration of HIV infection was 7.9 years (IQR 4-18 years) and the median nadir of CD4 cells was 277 cells/mcL (IQR 100-513 cells/mcL).

Adherence showed a median of 0.97 (IQR 0.91-1.00), consequently only 17 time-periods (2.2%) in 17 different individuals (4.0%) showed HIV-RNA blood levels above 200 copies/ml.

A PDC of 0.75 was sufficient to obtain in > 90% of cases the virologic outcome for both 200 copies/ml or 50 copies/ml. An adherence value of 0.85 obtained a positive response in virtually all subjects either for a cut-off of 50 or 200 copies/ml.

Conclusions Long-term success of ART needs effective, well tolerated, friendly regimens. Adherence remains a crucial determinant of long-term success, but suboptimal adherence levels are relatively common. Given this, an elevated forgiveness plays a relevant role to further improve long-term outcomes and should be considered a fundamental characteristic of any antiretroviral regimen. B/F/TAF has been proved to have all of these characteristics.

WHAT IS ALREADY KNOWN ON THIS SUBJECT

⇒ In general, the minimum adherence rate to maintain virological success under antiretroviral therapy (a possible measure of forgiveness) is considered 95% of the prescribed doses. This value derives from studies performed with unboosted protease inhibitors. Forgiveness depends on the kinetic characteristics of drugs and on their potency; the real value of drugs other than protease inhibitors could be different. Nothing is known about second-generation integrase strand transfer inhibitors (INSTIs).

WHAT THIS STUDY ADDS

⇒ This study defines the value of forgiveness of bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) and adds further knowledge on the drivers that favour long-term success during INSTI therapy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The study should prompt researchers to study the relationship between suboptimal adherence and the virological response to therapy. In clinical practice, knowing the forgiveness value of B/F/TAF should reassure clinicians about the virological safety of the therapy even in the case of periods of incorrect adherence.

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INTRODUCTION

In recent years the use of second-generation integrase inhibitors has raised, in clinical trials, the proportion of long-term virological success both in naïve persons with HIV (PWH) starting first-line therapy[1] and in virologically suppressed PWH shifting to another regimen,[2] independently of gender[3] or age.[4] Such results would suppose a high level of treatment adherence as this variable has always been a major issue in antiretroviral therapy (ART). A landmark study with unboosted protease inhibitors indicated that >95% adherence was required to steadily control virological replication,[5] which led to the idea that only fully adherent PWH could present an undetectable HIV viral load. Successive studies indicated that moderate deviations from perfect adherence, could be tolerated by different drugs.[6–9] Chronic therapies are subject to suboptimal adherence. To ensure long-term success in HIV infection the ability to control HIV replication beyond the dosing interval because of imperfect adherence, is a crucial factor defined as forgiveness.[10–12] There is no established, quantitative measure for forgiveness, but the concept that some regimens are more forgiving may influence therapeutic choices.

Although bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) is considered an extremely potent antiretroviral with a high genetic barrier to resistance,[13] very little is known about adherence[14] to it and even less about its forgiveness.[15] The aims of the present study were to assess overall adherence in a cohort of PWH treated with B/F/TAF and to define the percentage of virological suppression

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achieved with different levels of adherence. Finally, variables associated with higher adherence and higher rates of virological suppression were explored.

METHODS

In this retrospective cohort study, all PWH treated with B/F/TAF between January 2020 and August 2022 and referring to two cohorts of Northern Italy were included. PWH with at least two drug refills were eligible. We extracted demographic and clinical data from the electronic medical chart in use at the corresponding HIV outpatient clinic, while data to calculate adherence were obtained from the database of the hospital pharmacy. In the latter, the quantity and date of any refill are reported. In Italy, PWH have to resupply for antiretroviral drugs in the same hospital that follows them clinically. Therefore the pharmacy database of each centre includes all medication refills of a person of the cohort. Data from either centre were, then, merged into a single database for analysis.

Adherence was measured according to the proportion of days covered (PDC). Methods have been extensively described elsewhere,[15 16] briefly, PDC is the number of days with available medication divided by the length (in days) of the time interval between two consecutive refills. PDC is a conservative method and by truncating oversupply at the end of follow-up cannot be greater than 1. To calculate PDC a minimum of two refills are needed. The denominator of PDC is usually a year.

The Pharmacy Quality Alliance, and the National Association of Specialty Pharmacy have recognised PDC as a preferred method for measuring adherence.[17 18]

To allow for standardisation of measures of adherence the follow-up of each patient was broken down into consecutive time periods (referred to as numbers in figures) of approximately 1 year in length. Each time period included at least one measure of HIV-RNA.

All HIV-RNA measures from enrolment to the end of follow-up or to the censoring date (whatever came first) were used.

We used three different cut-offs of HIV-RNA to define virological success. The first was target not detected (TND), defined as the value of HIV-RNA not detected by modern standard methods. The second was HIV-RNA<50 copies/mL, the current standard to define virological control in clinical trials, and finally HIV-RNA<200 copies/mL as the value that prevents sexual HIV transmission and that excludes low-level viral blips from failures.

Finally, we calculated forgiveness as the chance to reach and maintain one of the preset virological thresholds for any given level of imperfect adherence.

All subjects signed informed consent for the electronically based storage of their sensitive data and their use in an aggregate anonymous way for cohort analyses.

We summarised data as medians and IQR or mean and 95% CI if continuous or numbers and percentages if discrete. Univariate analysis of variance was applied to verify the impact of baseline variables (age, gender, geographical origin, risk factor for HIV, number of comorbidities, years since HIV diagnosis and CD4+T cells nadir) on adherence. A binary logistic regression model was used to verify the impact of the same baseline variables and adherence on the virological outcomes dichotomously defined as virological outcome reached or not reached according to the previously defined cut-off values. All analyses were performed with SPSS V.17.0.

RESULTS

Overall, 474 PWH potentially eligible for the present study were examined. 54 were excluded because they did not meet inclusion criteria (less than two drug refills or lack of virological data in the study period). The remaining 420 adults treated with B/F/TAF were enrolled. From them, 787 time periods were derived. Each person contributed with a median of 2 (IQR 1–3) time periods. The mean length of each time period was 393 (95% CI 388 to 397) days. Each time period included at least a measure of HIV-RNA, but the vast majority (725; 92%) had more than one measure. Consequently, the median cohort follow-up summed to 873 persons/years.

Most of the study participants were men (73.1%); the most frequent risk factor for HIV infection was heterosexual contacts in 49.5% of cases, followed by 22.5% men who have sex with men and 22.5% intravenous drug users; a few PWH (0.7%) acquired the infection vertically or through factor VIII transfusion.

The median age of the cohort was 51 years (IQR 45–57 years). Despite that 26 PWH were naïve on their first ARV therapy, the median length of HIV infection was 7.9 years (IQR 4–18 years) and the median nadir of CD4 cells was 277 cells/mcL (IQR 100–513 cells/mcL).

Adherence levels, according to, were very high with a median of 0.97 (IQR 0.91–1.00). As a reasonable consequence of this high adherence rate, the virological response was sustained, too. Only 17 time periods (2.2%) in 17 different individuals (4.0%) showed plasma HIV-RNA above 200 copies/mL and all of them were observed among PWH with lower levels of adherence (figure 1). Even measures over the HIV-RNA 50 copies/mL level were rare and observed in 48 PWH (11.4%) counting for 56 time periods (7.11%). In study participants with a steady HIV-RNA value below 50 or 200 copies/mL the mean adherence rate for B/F/TAF was 0.94 (95% CI 0.93 to 0.95).

According to the analysis of variance, adherence was significantly linked only to geographical origin (p=0.002), being PWH from Italy being more adherent (mean 0.93; 95% CI 0.92 to 0.94) than subjects born in a different country (mean 0.89; 95% CI 0.86 to 0.92). Age, gender, risk factor for HIV, time with HIV infection and number of comorbidities did not influence adherence.

For the forgiveness calculation, virological success, either for the 200 copies/mL or 50 copies/mL cut-off was obtained in >90% of cases for a PDC as low as 0.75. The same PDC value was sufficient in >60% of study participants for the TND target goal. An adherence value of 0.85 obtained a positive response in virtually all subjects, either for a cut-off of 50 or 200 copies/mL (figure 2).

According to logistic regression analysis, PDC was the most significant correlate for the threshold of <200 copies/mL (p<0.0001). Besides PDC a marginal significance (p=0.042) was obtained for geographical origin. Only PDC significantly correlated with the possibility of obtaining and maintaining an HIV-RNA <50 copies/mL. Finally, when the cut-off TND was selected, its achievement was influenced by PDC (p<0.0001), lower number of associated chronic pathologies (p<0.0001) and longer time with HIV infection (p=0.05).

DISCUSSION

The virological success rate in our cohort was very high. We observed only 17 HIV-RNA blood measures over the 200 copies/mL HIV-RNA threshold and 56 over the 50 copies/mL threshold over 873 persons/years. This fact testifies to the high efficacy of

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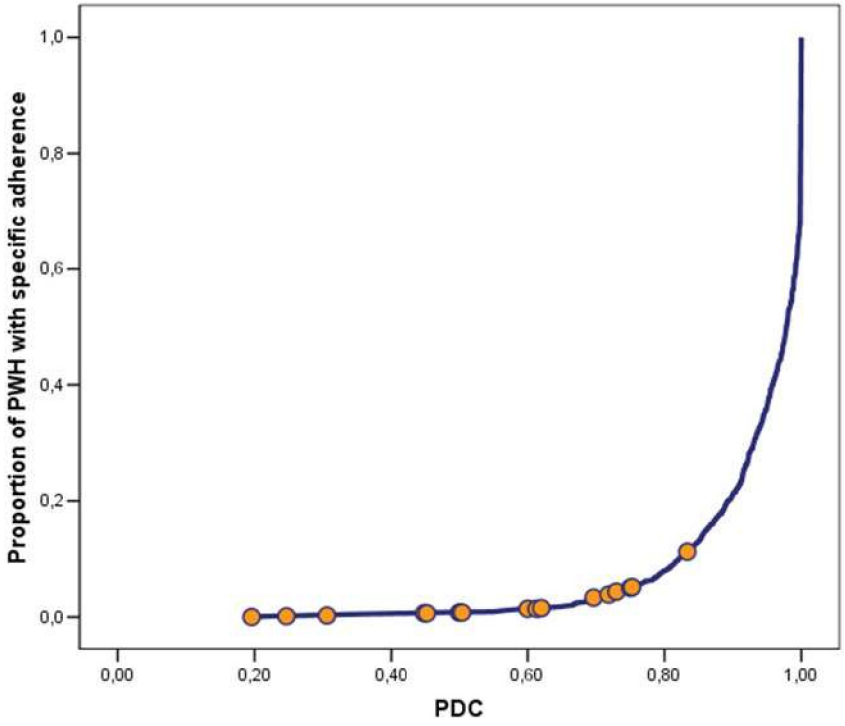

Figure 1 Proportion of subjects that for any given adherence cut-off reach and maintain a HIV-RNA level <200 copies/mL (dots indicate patients failing to obtain the objective). PDC, proportion of days covered; PWH, persons with HIV.

B/F/TAF, but, for the only sake of this analysis, may have introduced difficulties because of the scarcity of events.

The main goals of our analysis were to explore adherence and forgiveness of B/F/TAF. We used PDC as a proxy of adherence. The PDC does not calculate the actual pill-taking behaviour, but only how much time a person has access to medication. The PDC, therefore, could, potentially, overestimate adherence rates (eg, having a drug does not necessarily mean taking it). However, pharmacy refill data to calculate adherence has the advantage to exclude variables such as social desirability, recall bias or expense.[19]

In our cohort, the overall median adherence (97%) was very high. The lowest interquartile limit was above the 90% cut-off. The only variable significantly linked to adherence was the geographical origin. As a matter of fact, being immigrants, in our Country, is often associated with socio-structural determinants of health such as low education, low income, homelessness, food and work insecurity and socioeconomic marginalisation that are all known to substantially impact ART adherence.[20–22] Non-Italian origin, although not exclusive, may, therefore, be considered synonymous with a marginalised population.

Besides safety and tolerability that deeply influence adherence to treatment, the potency of the regimen and genetic barrier,[23] the number of viral mutations required to induce resistance, are the major pharmacological determinants of treatment success.

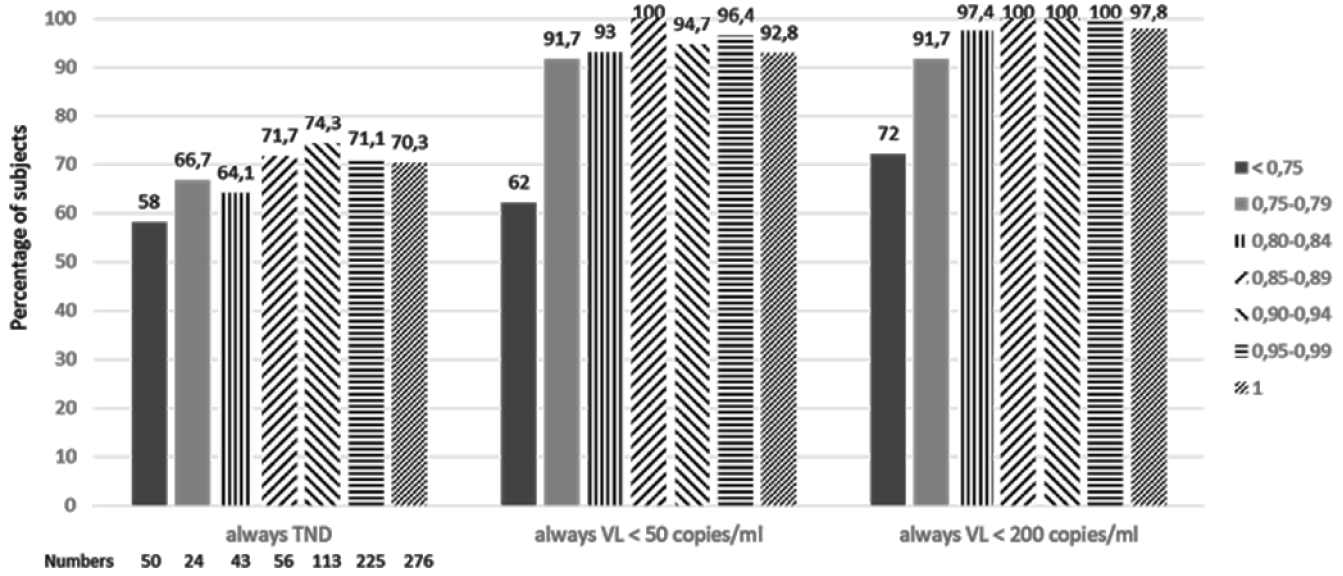

Figure 2 Treatment forgiveness as function of adherence level. TND, target not detected; VL, viral load.

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An ideal therapy combines all these characteristics at the maximum expression, even if the relevance of each one is different according to the various moments of ART. In a person starting ART, the goal is to suppress HIV RNA rapidly. This requires a high potency of ART, while the genetic barrier has an ancillary effect in preventing viral mutants while achieving complete virological suppression.[10] Once HIV RNA undetectability is reached, the goal of ART is to prolong this ideal situation. Long-term ART success is, surely, linked to tolerability and adherence, but another pharmacological characteristic raises in relevance. Over time, forgiveness becomes crucial, and more relevant than the potency or genetic barrier of the regimen.[10 15 16] There is an inverse relationship between adherence and forgiveness as factors that influence long-term therapeutic efficacy: higher adherence rates require less forgiveness. However, suboptimal adherence is relatively common, therefore forgiveness could play a crucial role to define long-term success. The regimen forgiveness is a function of the plasmatic and intracellular kinetics of drugs. Usually research about these factors and their relationship with virological outcomes focuses on the anchor drug of the regimen. However, the role of the other agents in the regimen should not be considered, too. The ideal regimen should include drugs with similar kinetic profiles, characterised by a long terminal half-life, which allows to overcome the occurrence of subinhibitory concentrations in the case of a missed dose and thus a high forgiveness.[23 24] A two drugs backbone, both with long intracellular half-lives responds to these concepts and supports the forgiveness of B/F/TAF.[25]

Host factors such as absorption, distribution, metabolism and elimination of drugs may affect the exposure of the virus to drugs[26 27] and hence have the potential to influence forgiveness.

Finally, HIV itself may influence forgiveness. The error-prone replicative system of HIV is a constant source of mutated viruses that could be prevalent because of the selective pressure exerted by subinhibitory levels of antiretroviral drugs. Resistance to one or more drugs of the regimen, independently of the adherence level,[6 8] increases the likelihood of virological failure and decreases forgiveness. Clades and subgroups of HIV may be other elements with an effect on forgiveness.

Considering all this, B/F/TAF was highly forgiving in our cohort. As shown in figure 1 all HIV-RNA blood measures >200 copies/mL clustered at very low levels of adherence where only a minority of study participants fell. A PDC of 0.75 was sufficient to obtain in more than 90% of cases the desired virological outcome for an HIV-RNA of 200 copies/mL or 50 copies/mL. Furthermore, a PDC lower than 0.75 obtained the desired outcome in over 50% of study participants irrespective of the considered virologic cut-off. On the other hand, the percentage of study participants failing to reach the TND threshold, in some cases even at the highest levels of adherence, could be an expression of the clonal expansion of T-cells with proviral expression contributing to residual viraemia rather than a marker of reduced forgiveness.[28] Furthermore, according to the definition of forgiveness, our results should be considered conservative as PDC, because of its nature, differently than for adherence, may only underestimate forgiveness but not overestimate it.

In our cohort, PDC was the most significant correlate for virological success at any virological threshold, confirming that adherence is a main variable for long-term ART success.

In evaluating our results, one should consider several limitations. First, The Italian Health Service offers free HIV care and ART for PWH, so cost was not a relevant variable influencing adherence in this study, this may be different for other healthcare systems without no-cost HIV care. Second, we cannot absolutely exclude that sporadic viral blips occurring far away from HIV-RNA testing were not captured. A further limit linked to this analysis is the high adherence rate we observed in our cohort. This resulted in a limited number of patients not obtaining the desired cut-offs for HIV-RNA, making more difficult to calculate a precise value for forgiveness. However, all measures of HIV-RNA not in line with the predefined cut-offs to define therapeutic success were observed for very low adherence rates strengthening, therefore, the reliability of our conclusions. Furthermore, forgiveness, as calculated by PDC, could be underestimated, but never overestimated, therefore our calculation should, at the most, be regarded as conservative. Finally, we cannot exclude that physicians' perception of B/F/TAF being a potent and reliable treatment did not induce them to treat most difficult subjects (or supposed such) with this regimen, but this would further strengthen our findings. However, our results are in line with previously described data. Our group[15] found a cut-off of adherence between 70% and 79% in PWH treated with B/F/TAF to maintain a viral load <200 copies/mL.[15] A cohort of PWH using unregulated drugs in British Columbia[29] reported a cut-off of adherence of 69% maintaining HIV-RNA <200 copies/mL in 90% of PWH treated with integrase inhibitors. The same Authors indicated that a lower adherence threshold was needed to obtain HIV-RNA suppression in PWH treated with integrase inhibitors compared with both protease inhibitors or non-nucleoside reverse transcriptase inhibitors. Finally, a collaborative American cohort[30] reported an adherence cut-off of 75% for the same outcome in PWH treated with any integrase inhibitor. The reproducibility of these results in different settings contributes to make them reliable.

In conclusion, well-tolerated, effective regimens that go along with people's lifestyles are needed for long-term success of ART. Nevertheless, adherence remains a crucial determinant of long-term success, it may vary over time and suboptimal adherence, at least temporary, to drugs is relatively common. Given this, elevated forgiveness plays a relevant role to further improve long-term outcomes and should be considered a fundamental characteristic of any antiretroviral regimen.

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