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Adherence to and Forgiveness of 3TC/DTG in a Real-World Cohort

Franco Maggiolo[1], Daniela Valenti[1,2], Rodolfo Teocchi[3], Laura Comi[1], Elisa Di Filippo[1], and Marco Rizzi[1]

Abstract

Background: adherence and forgiveness are key factors for virologic success. We evaluated them for 3TC/DTG. **Methods:** pharmacy refills were used to calculate the proportion of days covered (PDC). Forgiveness was calculated as the achieved rate of HIV-RNA threshold by a given level of imperfect adherence. **Results:** 240 PLWH were included. The median follow-up was 819 days (IQR 450-1459) for a total of 681 person/years of follow-up. Adherence was very high with a median of 99% (IQR 95%-100%). Consequently, the virologic response was sustained 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 associated with a negative outcome irrespective of the HIV-RNA threshold considered. **Conclusions:** The extensive virologic efficacy of 3TC/DTG demonstrated both in clinical trials and real-world experiences seems to rely more on its friendliness than on its forgiveness.

Keywords

forgiveness, adherence, lamivudine, dolutegravir, 3TC, DTG, cohort, INSTI, efficacy

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Introduction

Adherence is a major issue in antiretroviral therapy (ART) since the work of Paterson et al.[1] that in 2000 showed how very high levels of adherence were needed to achieve viral suppression in persons living with HIV (PLWH). The work was based mainly on the use of un-boosted protease inhibitors and along with additional experiences[2] lead to the" 95% rule", namely that subjects should take at least 95% of the prescribed antiretroviral doses in order to control viral replication. As a consequence, the need to achieve and maintain near perfect adherence in all PLWH was emphasized and aggressive monitoring of adherence was included into the management of ART.[3] Successive studies, using different ways of measuring adherence and various endpoints indicated that different drugs could better tolerate moderate deviations from perfect adherence.[4–7] These drugs were indicated as "forgiving" and the term "forgiveness", namely the ability of a given regimen to achieve and maintain complete viral suppression despite a documented imperfect medication adherence, become a relevant aspect of HIV management.[8,9] Despite the fact that forgiveness lacks an established, quantitative measure, the medical community has accepted the concept that some regimens are more forgiving than others and has based, on this assumption, therapeutic choices that are made every days in clinics.

In recent years the introduction into the HIV armamentarium of second-generation integrase inhibitors (INSTI) has induced clinicians to explore innovative drug regimens to control HIV replication both in drug-naïve[10] and experienced subjects.[11,12] Less drug regimens or dual-therapies (2DR) are generally judged as potent and endowed of a high genetic barrier to resistance,[10,12–15] but very little is known about adherence to these regimens[16] and even less about their forgiveness.

We analyzed adherence to and forgiveness of lamivudine/dolutegravir (3TC/DTG) 2DR in a single center unselected cohort.

[1] UOC Infectious Diseases, ASST Papa Giovanni XXII, Bergamo Italy
[2] FROM foundation, ASST Papa Giovanni XXII, Bergamo Italy
[3] Informatics department, ASST Papa Giovanni XXII, Bergamo Italy

Corresponding Author:
Franco Maggiolo, UOC Malattie Infettive, ASST Papa Giovanni XXIII, Bergamo, Italy.
Email: franco31556@hotmail.com

Methods

In this retrospective study we included all PLWH of our cohort ever treated with 3TC/DTG. Patients with a minimum of 2 drugs refills were included irrespective of the length of their follow-up. Adherence was measured by means of proportion day covered (PDC). PDC is the number of days with medication available divided by the number of days in a specified time interval. In the case that excess medication is collected or refills are made early, the excess is carried forward to cover subsequent absences of drugs. The denominator of PDC is a clinically meaningful number of days. We chose to use the whole follow-up period. To calculate PDC a minimum of 2 refills are needed. PDC may be summarized as a continuous or categorical outcome using defined cut-offs. We obtained data to calculate PDC from the electronic data-base of the Hospital Pharmacy that reports date and quantity of any given refill. As in Italy, PLWH must resupply for ARV drugs exclusively in the center that follows them clinically, the pharmacy database is absolutely indicative of the effective drug disposition. Usually the refill interval for ARV drugs is three months. We extracted and tabulated any drug refill of 3TC/DTG. 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 (whatever came first) were extracted and tabulated as well.

We chose three different cut-offs of HIV-RNA to define virologic response to ART. The first was target not detected (TND), that is the value of HIV-RNA current standard methods do not detect (usually < 20 copies/ml); the second was HIV-RNA < 50 copies/ml as the current gold standard to define therapeutic efficacy and finally HIV-RNA < 200 copies/ml as the value that prevents HIV transmission by sexual contacts and that allows to exclude low-level viral blips from failures.

Finally, we evaluated forgiveness defined as the possibility to reach and maintain one of the pre-defined virologic thresholds despite 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 71/17 1074). 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 descripted cut-off values. All analysis were performed with SPSS 17.0.

Results

A total of 240 adult PLWH were treated with 3TC/DTG and responded to the inclusion criteria of the study. All of them were included in the analysis. In accordance with the epidemics trends in our Country, most of the patients were males (75%). Heterosexual contacts was the most frequent risk factor for HIV infection (51.7% of cases), while 34.6% of subjects were MSM and 13.3% intravenous drug users; a small percentage of subjects (0.4%) acquired the infection by mother-to-child transmission.

The median age of the cohort was 52 years (IQR 43-58 years) and the median time from the diagnosis of HIV infection was 10 years (IQR 4-19 years). At diagnosis, the median of CD4 cells count was 351 cells/mcL (IQR 112-559 cells/mcL).

Most of PLWH (66%), beside HIV infection, presented at least a concomitant chronic pathology (up to 7). The most common of these, being present in more than 5% of PLWH were: hypertension (23%); gastro-enteric diseases (16%); cardio-vascular diseases (15%); dyslipidemia (14%); renal diseases, osteo-articular diseases, genitourinary diseases, neoplastic diseases (8% each); neurological and pulmonary diseases (7% each); psychiatric/psychological diseases and diabetes (6% each). Two subjects were HBV co-infected and took specific therapy (entecavir) for that reason. One patient died during the follow-up because of COVID-19 disease.

The median cohort follow-up was 819 days (IQR 450-1459 days) summing for a total of 681 person/years of follow-up.

Overall, adherence, as calculated from PDC, was very high with a median of 99% (IQR 95-100%). Consequently, also the virologic response was sustained with 38.3% of PLWH with HIV-RNA TND throughout the study period; while 83.8% of PLWH never exceeded a HIV RNA of 50 copies/ml and 95.8% of subjects with a steadily HIV-RNA < 200 copies/ml. Only 10 patients were non-responders and 29 subjects presented an isolated viral blip.

As far as forgiveness is concerned, a PDC lower than 80% was associated with a negative outcome irrespective of the HIV-RNA threshold considered. For PDC values over 80% there was a linear increment of response considering TND or a HIV-RNA < 50 copies/ml as goals, while we observed a plateau for PDC > 90% when the more comprehensive HIV-RNA < 200 copies/ml was considered (Figure 1). In the latter case the outcome was obtained by 95.5% of subjects with a PDC between 90% and 94% and by all PLWH with higher PDC values. Furthermore, probit analysis indicated that adherence variation was not related to the possibility to obtain and maintain an HIV-RNA TND, but was significantly ($P < 0.0001$) associated to the < 50 copies/ml or < 200 copies/ml thresholds (Figure 2). Adherence in non-responders was very low (median 78%; IQR 63-93%) compared to PLWH showing constant control of HIV replication (median 98%; IQR 97-98%), and the prognostic significance of adherence level was maintained in the multivariate probit analysis, too (Figure 2).

Discussion

Antiretroviral medication adherence is an important predictor of virologic, immunological, and clinical outcomes in PLWH.[17–19] Numerous co-variates may influence adherence ranging from socioeconomic-related, patient-related, condition-related factors, to health care team and system-related factors.[20]

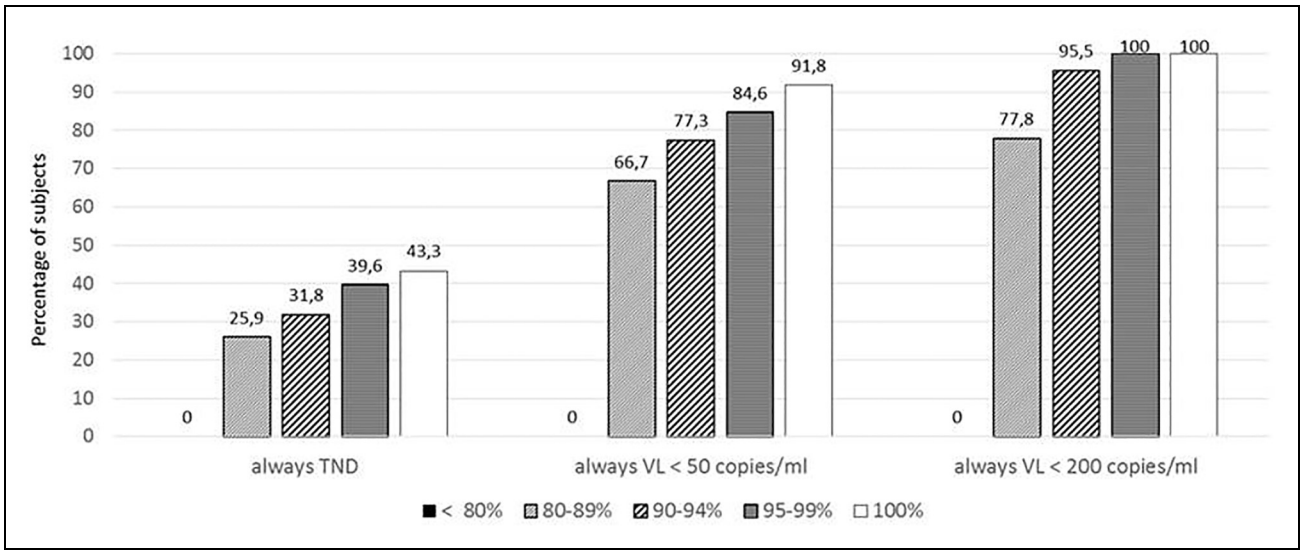
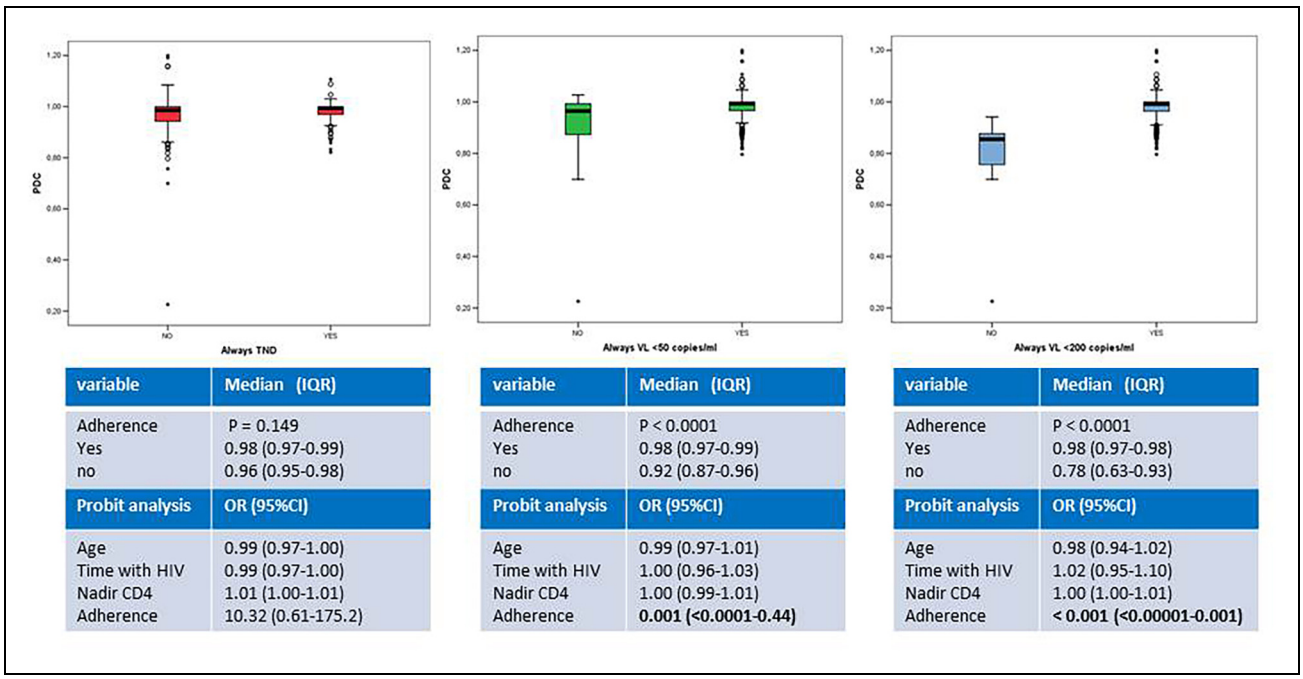


Figure 1. Virologic response expressed as achievement and constant maintenance of different HIV-RNA thresholds according to the individual adherence level as calculated by means of PDC.



variable	Median (IQR)
Adherence	P = 0.149
Yes	0.98 (0.97-0.99)
no	0.96 (0.95-0.98)
Probit analysis	**OR (95%CI)**
Age	0.99 (0.97-1.00)
Time with HIV	0.99 (0.97-1.00)
Nadir CD4	1.01 (1.00-1.01)
Adherence	10.32 (0.61-175.2)

variable	Median (IQR)
Adherence	P < 0.0001
Yes	0.98 (0.97-0.99)
no	0.92 (0.87-0.96)
Probit analysis	**OR (95%CI)**
Age	0.99 (0.97-1.01)
Time with HIV	1.00 (0.96-1.03)
Nadir CD4	1.00 (0.99-1.01)
Adherence	**0.001 (<0.0001-0.44)**

variable	Median (IQR)
Adherence	P < 0.0001
Yes	0.98 (0.97-0.98)
no	0.78 (0.63-0.93)
Probit analysis	**OR (95%CI)**
Age	0.98 (0.94-1.02)
Time with HIV	1.02 (0.95-1.10)
Nadir CD4	1.00 (1.00-1.01)
Adherence	**< 0.001 (<0.00001-0.001)**

Figure 2. 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.

Therapy-related and drug-related factors may influence adherence, too. A recent paper by Amor-Garcia et al has shown how DTG-based 2DR may positively influence adherence to a significant extent.[21] The same Authors indicated that some characteristics of the 2DR, namely lesser pills or single tablet regimen, and single daily dose were significantly associated to the adherence improvement. In our study adherence to 3TC/DTG was extremely high with a median of 99% and a lower bound of the interquartile range that was still above the 95% value that indicates nearly optimal adherence. The high tolerability of the combination, the lack of potential drug-drug interactions and the low intrusiveness in the daily life of PLWH[10,12,13,22–24] may play a relevant role in determining such high levels of adherence. Most relevant, our study demonstrates that high levels of adherence can be maintained over long periods of time in PLWH taking 3TC/DTG.

Therapy-related and drug-related factors are responsible of a given regimen forgiveness to less-than-perfect adherence, too.[25–27] Medication half-life and antiviral efficacy are critical factors in forgiveness of non-adherence. In general, a longer

elimination half-life favors greater forgiveness.[6] The efficacy of a regimen at producing complete viral suppression, often referred to as 'potency' is another intrinsic drug characteristic that affects forgiveness.[28]

To calculate forgiveness an accurate adherence assessment is essential. Existing measures of adherence have conceptual, practical and/or cost limitations. Self-reported measures, although widely used, assess adherence over a relatively short period, ideally a week or a month. Furthermore, they are affected by recall bias and memory and often influenced by social desirability.[29] Among objective measures, pill count is time consuming and usually limited to clinical trials,[16] while electronic monitoring devices may be considered the "gold standard" but they are expensive and difficult to implement in routine practice.[30–32] Pharmacy refill is a proxy of adherence measure based on medication availability. Some studies on chronic diseases including HIV infection have shown that the performance of PDC as calculated from pharmacy refill was comparable to electronic adherence monitoring measures.[31,32] Pharmacy refill records provide an objective and inexpensive measure and has the advantage to allow for adherence assessment over long periods of time.

Modern therapies bring together high genetic barrier, extensive efficacy, low potential for drug-drug interactions or altered pharmacokinetics, good tolerability, and high convenience but, so far, very few data are available comparing forgiveness of 2DR and triple-drug regimens. In vitro experimental models mimicking drug decay after missing successive doses showed a lower forgiveness for 3TC/DTC compared to a TAF-based triple therapy, having as an endpoint the emergence of drug resistance.[33] Clinically, a recent report described a relevant reduction of virologic efficacy (eg HIV-RNA < 50 copies at 48 weeks) in PLWH taking 3TC/DTG and having an adherence rate < 90% (69% with the desired outcome) compared to those subjects with higher adherence that suppressed the virus in 93% of cases.[16] The same study, however did not observe any difference comparing 3TC/DTG to a DTG-based triple therapy. Our study, considering the maintenance of HIV-RNA < 50 copies/ml for a very long period of time (up to 5 years) obtained very similar results as subjects with adherence < 90% reached the outcome in 66.7% of cases. However, for adherence rates < 80% in no case the desired outcome was obtained. And the linear relationship between adherence rate and positive outcome rate indicates that adherence is a relevant factor for 3TC/DTG efficacy. In other words, the forgiveness of this regimen although higher than that of therapies used in the early years 2000, may be lower than forgiveness of other more modern triple therapies[34,35] including DTG-based triple therapies for which none of the models considering adherence pattern parameters was significantly associated with HIV-RNA levels at six months.[36]

All together our findings indicate that most subjects had an optimal adherence supporting the idea that 3TC/DTG is a well-tolerated, friendly regimen and therefore well accepted by patients. Regarding the present study, however, an overall adherence value so high may constitute a limitation as results tend to plateau and only a few PLWH with truly adherence problems did eventually not respond to ART. Further limitations of our study are its single center nature that does not allows us to take into consideration different strategies and organizations for HIV management and the fact that we mostly enrolled subjects with a long history of HIV infection and antiretroviral therapy so being unable to differentiate chronically treated PLWH from subjects with short ART history.[37] The way we studied adherence offers lights and shadows, too. As we derived adherence from PDC we could overestimate adherence rates (eg possession of a drug does not necessarily means taking it), but we could not underestimate it (eg one cannot take a drug that does not have). The 80% limit we defined could be therefore even lower indicating better forgiveness. With regard to this, our results must be considered conservative.

3TC/DTG seems less robust in forgiving lower adherence rates than other INSTI- based regimens,[35,36] but apparently compensate this lower forgiveness with extremely high adherence rates in most of patients. Long-term success of ART needs well tolerated, effective regimens that are the least intrusive of the patient's lifestyle and therefore well accepted and well taken. The extensive virologic efficacy of 3TC/DTG demonstrated both in clinical trials and real-world experiences seems to rely more on its friendliness than on its forgiveness.

Conflict of interest

FM received research grants from Gilead, ViiV, Janssen and acted as member of advisory board for Gilead, ViiV, Janssen and Merck.

All other no conflict.

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

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: FM received research grants from Gilead, ViiV, Janssen and acted as member of advisory board for Gilead, ViiV, Janssen and Merck. All other no conflict.

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ORCID iD

Franco Maggiolo https://orcid.org/0000-0002-9791-0072

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