

Unexpected effects of COVID-19 outbreak: adaption of Anti-Retroviral Therapy (ART) delivery policies improved adherence in a population of People Living With HIV (PLWH)

Francesco Maria Fusco, Nadia Sangiovanni, Nunzia Papa, Valentina Mattera Iacono, Nunzia Cuomo, Rosaria Viglietti, Orsola Tambaro, Francesco Borrelli, Raffaella Pisapia, Maria Aurora Carleo, Viviana Rizzo, Micaela Spatarella, Vincenzo Esposito, Vincenzo Sangiovanni

Infectious Diseases Unit, "D. Cotugno" Hospital, AORN dei Colli, Naples, Italy

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SUMMARY

Background: Adherence to Anti-Retroviral Therapy (ART) is crucial for People Living With HIV (PLWH). In Italy, ART is delivered by Hospital Pharmacies, on a renewable prescription from the hospital physician. The measurement of package-refill (the rate of ART packages actually collected out of those to be collected in order to comply with therapy) is an effective tool to evaluate the adherence.

During COVID-19 outbreak, at "D. Cotugno" hospital in Naples, Italy, the ART delivery policies have been adapted, in order to reduce the number of patients' access. We analysed the impact of these changes on the pill-refill of ART in January-August 2020, compared with 2018-2019.

Methods: "D. Cotugno" hospital is a mono-specialistic Infectious Diseases hospital, caring for about 2500 PLWH. Since February 2020, the hospital was almost entirely dedicated to COVID-19 patients. All out-patient activities were interrupted, except for those dedicated to HIV/AIDS patients.

In this preliminary study we included all patients assigned to one of the three Medical Divisions dedicated to HIV, who were already under treatment since at least 2017. Rate of package-refill was obtained by the Hospital Pharmacy registry, demographic and clinical data were derived from clinical database.

During COVID-19, many measures were adopted in

order to increase safety of PLWH attending to hospital. Among these, medical prescription validity increased from 4 to 6 months, and number of packages to be collected increased from 2 to 4, adopting a multi-month dispensing strategy.

Package-refill is adequate if at least 95% of ART have been actually collected; partial and inadequate if 75%-94% or less than 75% of ART, respectively, have been collected. Package-refill was measured during the first year of COVID-19 (March 2020 - February 2021), compared to the same period in the two years before

Results: A total of 594 PLWH were included. PLWH with optimal pill-refill significantly increased in 2020-21 compared to 2018-2020 (62% vs 55%, p 0.013).

Discussion: Due to COVID-19, we would have expected a reduction in ART deliveries. Surprisingly, the opposite occurred. The increase of pill-refill rates may be due to different reasons, but we hypothesized that the adaption of delivery policies, with a higher number of packages allowed to be collected, strongly contributed to this result. This study suggests that multi-month dispensing policies may contribute to the improvement of adherence among PLWH.

Keywords: Antiretroviral Therapy; Adherence; Package-refill; HIV/AIDS; COVID-19; Multi-month dispensing.

Corresponding author

Francesco M. Fusco

E-mail: francescomaria.fusco@ospedalideicolli.it

■ INTRODUCTION

Adherence to antiretroviral therapy (ART) is crucial for People Living With HIV (PLWH). It is one of the major determinants of sustained HIV virologic suppression, restoration of immune system, prevention of drug resistance and reduced risk of HIV transmission [1, 2].

Adherence may be assessed through different methods, despite a “gold standard” for adherence measure does not exist [3]. In Italy, ART is delivered by Hospital Pharmacies, on renewable prescriptions from the hospital physicians. Therefore, adherence assessment through pharmacy-based measures is feasible and effective. Pharmacy-based measures include pill-refill count and/or package-refill count. These measures are based on the ratio between the number of pills/packages actually withdrawn compared to those that should have been withdrawn to ensure optimal adherence. These measures have several advantages: the assessment of pill/package refills is not expensive, easy to conduct, since data are already included in pharmacy records and may provide an overall long-term estimation of adherence [4]. Among these measures, the package-refill is easier to be assessed and has been already validated in the same setting: in a recent paper with a larger population, patients with inadequate adherence measured through measurement of package-refill have an increased risk for viral failure [5].

The COVID-19 pandemic had a relevant impact on management of PLWH. Reduction to access to counselling and testing sites, reduced resources for PrEP, PEP and other prevention policies, and difficulties for ART delivery have been widely reported [6-10]. On the other hand, some strategies may be implemented in order to overcome the barriers due to COVID-19 for PLWH.

During COVID-19 outbreak, at “D. Cotugno” hospital in Naples, Italy, the ART delivery policies have been modified, in order to reduce the number of patients’ access and to facilitate the access pathways. We analysed the impact of these changes on the package-refill of ART during the first pandemic year (March 2020-February 2021), compared with the same periods in 2018-2019 and 2019-2020.

■ PATIENTS AND METHODS

Study design

This is a retrospective observational study exploring the changes in ART adherence, measured by

package-refill, during the first year of COVID-19 pandemic, compared to the 2 previous years, in a large population of PLWH in care at “D. Cotugno” hospital, Naples, Southern Italy.

Setting

The study setting is the “D. Cotugno” hospital, a mono-specialistic infectious diseases referral centre sited in Naples, Campania, Southern Italy. Campania is the most populous region in Southern Italy, counting for 6 million of inhabitants. The “D. Cotugno” hospital has a long-term tradition in HIV/AIDS care and 3 Medical Units are mainly dedicated to in-patient and out-patient management of PLWH. A total of about 2500 PLWH are in care at “D. Cotugno” hospital, accounting for about 70% of PLWH in Campania Region.

Participants and data source

A sample of patients with HIV/AIDS in care at “D. Cotugno” hospital, those referring to one HIV/AIDS Unit caring for about 700 PLWH, were included in the study. Among the patients selected, only subjects already on care since 2017 and stably in care in the study period 2018-2021 were included. We defined as stably in care those patients with at least one access per year for laboratory assessment and at least one access per year for ART package withdraw. Data sources were represented by clinical electronic database for patients’ records, and by pharmacy electronic database for package-refill data.

Variables

The main outcome of the study is represented by ART adherence measured by package-refill. Package refill is calculated as the ratio between ART packages actually withdrawn, compared to the number of ART packages needed to regularly take the therapy. We considered adequate a package-refill $\geq 95\%$ of packages withdrawn in the study period, partial a package-refill of 70%-94%; inadequate a package-refill less than 70%.

Statistical methods

Package-refill have been calculated as the ratio between the number of packages of ART actually withdrawn in hospital pharmacy compared to the expected number of packages to be withdrawn (12 packages for each yearly period from March 2018 to February 2021).

Statistical differences were calculated with the Student's Chi-squared test, as appropriate, using a significance level of 0.05.

RESULTS

Adaption of hospital procedures during COVID-19 for PLWH

In the period March 2020-February 2021, almost all hospital activities were dedicated to the care of COVID-19 patients. Despite that, assistance to PLWH was never interrupted, but some adjustments were implemented.

Before COVID-19, periodical visits were performed every 2 or 4 months. Visit area were located near to Medical wards, inside the main hospital building. The medical prescription for ART was valid for 4 months, and the packages to be collected from the patients were at maximum 2. Access to hospital pharmacy for the withdrawn was located in the main hospital building.

During COVID-19, periodical visits were arranged less frequently every 4 or 6 months (despite specific clinical needs) and remote monitoring by mobile or email was encouraged, especially for stably well-being patients. Area for outpatient visits was re-organized, and moved in an area outside the main hospital building, with direct access from external. About ART delivery, medical prescription validity increased from 4 to 6 months, and number of packages to be collected (Multi-Months Dispensing, MMD) increased from 2 to 4. In order to reduce the presence of patients within the hospital, we built a dedicated external pathway for PLWH for access to Hospital Pharmacy, for the rapid and safe pick-up of ART. Finally, a service for the home delivery of ART for patients in isolation or quarantine was organized.

Effects of these measures on adherence

A total of 594 PLWH fulfilled the inclusion criteria and were included in the study. Their characteristics are summarized in Table 1: most were males, Italian, median age 48 years-old. The clinical profile of these patients is satisfactory, with a median CD4 during study period of 668 cells/ μ L, and 66% of them with HIV-RNA always less than 50 copies/ μ L during the entire 3-years-long study period. Obviously, ART regimens changed during study period, and 46% of patients underwent to at least one ART switch.

Table 1 - Demographical and clinical characteristics of 594 PLWH in care at "D. Cotugno" hospital, Naples, on ART at least since 2017.

Male sex (n; %)	517; 87
Age (median; IQR)	48; 40-54
Italian (n; %)	535; 90
Risk factor for HIV:	
Eterosex (n; %)	187; 31
MSM (n; %)	230; 39
IDU (n; %)	122; 21
Other/Unknown (n; %)	55; 9
Years from HIV diagnosis (median; IQR)	9; 4-15
Clinical data:	
CD4 nadir (median, IQR)	226; 81-363
Last CD4 in study period (median, IQR)	668; 483-939
HIV-RNA always <50 copies in study period (n; %)	393; 66
HIV-RNA at least one time 50-200 copies in study period (n; %)	123; 21
HIV-RNA at least one time >200 copies in study period (n; %)	69; 12
AIDS diagnosis in clinical history (n; %)	260; 44
Other comorbidities (n; %)	324; 55
ART:	
Single Tablet Regimen (STR) at beginning of study period (n; %)	338; 57
Single Tablet Regimen (STR) at end of study period (n; %)	469; 79
Number of patients with at least one ART switch (n; %)	276; 46
Total number of switches (n)	377
Triple regimen INI-based (n; %)	295; 50
Triple regimen PI-based (n; %)	108; 18
Triple regimen NNRTI-based (n; %)	95; 16
2-drug regimen (n; %)	59; 10
Other (n; %)	38; 6

The comparison of adherence measured as package-refill rates during pandemic period, compared with the 2 years before, is shown in Table 2. PLWH with adequate package-refill significantly increased in 2020-21 (62% vs 55%, p.013), while patients with inadequate package-refill significantly decreases in the same period (14% vs 19%, p.011). Overall adherence to ART in the study population improved during the first year of COVID-19 pandemic.

DISCUSSION

The impact of COVID-19 on services for PLWH is complex to estimate. The consequences of disrup-

Table 2 - Adherence to ART measured as package-refill in COVID-19 pre-pandemic and pandemic periods among 594 PLWH in care at “D. Cotugno” hospital, Naples, on ART at least since 2017.

	<i>Period March 2018 - February 2020 (pre-pandemic period)</i>	<i>Period March 2020 - February 2021 (pandemic period)</i>	<i>p</i>
Optimal pill-refill (95% or higher) (n; %)	328; 55%	371; 62%	.013
Partial pill-refill (75%-94%) (n; %)	152; 25%	142; 24%	.500
Inadequate pill refill (less than 75%) (n; %)	114; 19%	81; 14%	.011

tion of access to treatment and care services has been evidenced in several reports and will likely adversely affect outcomes of HIV patients [6, 7]. Particularly, access to ART is a critical public health priority during the COVID-19 pandemic. For healthcare settings caring for PLWH, to maintain adequate adherence to ART, despite the limitations posed by COVID-19 pandemic, is a challenge that requires flexibility and adaptability.

A decrease in the level of ART adherence was theoretically expected during the first pandemic year. Indeed, some factors could have adversely affected adherence: fear to attend to the COVID-19 hospitals and limitation of movement due to lockdown measures could have limited the access to PLWH to hospital for the withdrawn of ART. Surprisingly, the opposite occurred.

In the study population at “D. Cotugno” hospital, ART adherence significantly increased during the first year of COVID-19 pandemic compared with the same period in the two previous years. This increase of package-refill rates may be due to different reasons. The logistic changes, moving HIV services outside the main hospital building and assuring a direct access to hospital pharmacy, increased the sense of safety for PLWH. Similarly, the long-term tradition of “D. Cotugno” hospital in caring PLWH contributed to maintain patient confidence and ensured that they continued to access to HIV dedicated services.

But overall, we hypothesized that the adaptation of delivery policies, with a higher number of packages allowed to be collected, strongly contributed to this result. Multi-drug-dispensing (MDD) of ART is a strategy suggested by International Public Health bodies in order to improve adherence in limited resources countries [11, 12]. This approach has been advocated and successfully applied even during COVID-19 pandemic in African countries [13-14]. The effect of MMD on adherence has never been measured in high resource countries, but

COVID-19 gave the chance to apply it and to measure its effect: according to our data, MMD is a factor potentially contributing to improve ART adherence in high resource countries, too. Furthermore, during clinical practices we collected good feedbacks from patients about MMD, despite we didn't systematically assessed this positive feedback. For all these reasons, Hospital Pharmacy staff decided to maintain the MMD policy even after the end of limitations due to COVID-19 pandemic.

On the other hand, we cannot exclude that adherence increased for factors independent to COVID-19 pandemic and related measures. For example, the general improvement of new ART regimens, mostly in single tablet and with no toxicity, may cause an improvement in adherence, independently by the measures adopted during first year of COVID-19 pandemic. Further studies, involving more centres and prolonged in time, are needed in order to better assess the role of different factors, including MMD policies, in ART adherence in high resource settings. Moreover, we measured adherence only, with no correlation to virological improvements. On the other hand, increased adherence measured by package-refill is positively correlated with improvements in virological profile, as suggested by a recent study from our group [5].

In conclusion, several factors may have contributed to the improvement in ART adherence during the period March 2020-February 2021 compared to the previous two years. Among these, the adoption of an MDD strategy may have contributed more than others. In the light of these results, at the “D. Cotugno” hospital the MDD policy has been maintained even after the most acute phase of the pandemic was over.

Authors' contributions

FMF conceived the study, analyzed data, and drafted the paper; NS collected the data, contrib-

uted to draft the paper and to data analysis; NP, VMI, NC and MS contributed to data collection and analysis; RV, OT, FB, RP, MAC, VR contributed to data collection; VS and VE coordinated the study. All authors gave their contribute for important intellectual contents and all authors saw and approved the final version of the manuscript.

Conflict of interest disclosure

All authors declare to have not conflicts of interest about the contents of the study.

Data availability statement

The database of the study is available for review, if required.

Funding statement

No specific or dedicated funding have been used for this study.

Ethics approval statement

Due to the observational nature of the study and the presentation of anonymized aggregated data only, no specific ethic approval has been obtained.

Patient consent statement

For all patients, a generic authorization was obtained to use, exclusively anonymously and collectively, data deriving from clinical practice. This article presents overall data, completely anonymous, from which it is not possible in any way to trace the identity of the subjects involved. For this reason, we have not found it necessary to ask for specific consent.

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