Does Rapid Initiation of Antiretroviral Therapy At HIV Diagnosis Impact On Virological Response in a Real-Life Setting? A Single Centre Experience in Northern Italy

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Research

Keywords: antiretroviral therapy, new HIV diagnosis, rapid start, viral suppression, real life setting

Posted Date: October 18th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-966688/v1

Abstract

Background Rapid initiation of antiretroviral therapy (ART) has been largely proven efficacious and safe mostly through clinical trials. Further investigations are needed to better define feasibility and acceptability of rapid ART approach in real-life settings.

Methods We conducted a retrospective, observational study on newly HIV-diagnosed patients referred to Infectious and Tropical Diseases department of ASST Spedali Civili Hospital of Brescia from September 1st, 2015, to July 31st, 2019. All patients' baseline characteristics were anonymously extracted from medical records. According to the timing of ART initiation, we distinguished 3 groups of patients (rapid, intermediate and late group) and represented the trend of virological response during a 400 day-period. The hazard ratios of each predictor on viral suppression (HIV RNA < 50 copies/ml) were estimated through Cox proportional hazard model.

Results Median time from HIV diagnosis to first medical referral was 15 days and median time from first HIV care access to therapy start was 24 days. Three groups of patients were differentiated depending on ART initiation: within 7 days (rapid group, 37.6%), between 8 and 30 days (intermediate group, 20.6%) and after 30 days (late group, 41.8%). Longer time to ART start and higher baseline viral load were associated with a reduced probability of viral suppression. After one year, all groups showed high viral suppression rate (99%).

Conclusions In high-income setting as Italy, rapid ART approach seems to be useful to accelerate time to viral suppression. The latter tends to be great over time regardless the timing of ART initiation.

Introduction

Since the introduction of "treat all" recommendation by WHO in 2015, an emerging debate has focused on the best timing of antiretroviral therapy (ART) initiation in people living with HIV (PLWH) after a confirmed diagnosis. In 2017 WHO took a pass forward, recommending first the so-called "rapid ART initiation" [1], defined as start within seven days following a HIV diagnosis and clinical assessment, including the possibility of "same-day" initiation for people ready to be treated and without clinical contraindications. Actually, according to the latest WHO recommendations even among PLWH with signs and symptoms of tuberculous (TB) disease (except for meningitis) ART might be initiated cautiously while rapidly investigating for TB disease [2].

However, both benefits and concerns have to be considered when starting rapidly ART. On one hand, accelerated ART initiation may lead to undeniable benefits: faster time to virologic suppression [3, 4], higher therapy uptake [5, 6] together with durable viral control [4–8], reduction in HIV-related and non-HIV-related morbidity and mortality and decreased risk of HIV onward transmission [9–12]. On the other hand, it could be related to disadvantages as immune reconstitution inflammatory syndrome (IRIS), transmission of drug resistance according to a sub-optimal adherence and premature loss to care,

especially among those people who do not feel psychologically ready to accept the diagnosis and a lifelong treatment [5, 13–15].

To our best knowledge, most of clinical trials supporting rapid ART initiation strategy were conducted in resource-limited settings where large part of PLWH often experience disengagement from health services after diagnosis and ART initiation delays as result of complex socio-cultural factors and poor healthcare infrastructure [5–7, 13, 16, 17]. The generalizability of findings from these studies might be limited if adapted in high-income settings [15]. In this context little is still known about the best timing and the impact of rapid ART initiation beyond those circumstances where it is already considered essential (i.e. AIDS defining conditions, primary HIV infection, pregnancy, HBV and/or HCV co-infection) [17–19]. However, feasibility and acceptability of initiating ART as soon as possible after diagnosis in resource-rich countries was highlighted by Coffey and colleagues through the San Francisco RAPID ART program [8]. In addition, in recent years few more studies have been conducted in developed countries investigating potential benefits of accelerated ART but with non-univocal results. For example, both one cohort from London (UK) and one cohort from San Diego (CA, USA) of patients with recent HIV infection showed efficaciousness of rapid ART approach in reducing time to undetectable viral load and reaching high rate (90-99%) of viral suppression by 6 months of therapy [19, 20]. Differently, in 2019 an Italian experience from ICONA Foundation Study Cohort did not observe a clear utility of rapid ART initiation in terms of virological response and retention in care at 1 year of follow up [18]. Lastly, a prospective French cohort of newly HIV diagnosed patients even found that starting treatment rapidly (< 9 days) was negatively associated with care engagement after 1 year of follow-up [14].

In order to improve our knowledge about impact of an accelerated ART initiation in real-life practice in a high income country like Italy, with free-of charge access to care and good quality health system, we aimed to investigate rates and predictors of virological response among newly diagnosed HIV patients according to timing to ART initiation in a large HIV clinic in Brescia, Lombardy (Northern Italy).

Methods

A retrospective, observational, single center study was conducted in the Infectious and Tropical Diseases Department of the Azienda Socio Sanitaria Territoriale (ASST) Spedali Civili Hospital in Brescia, which represents the only tertiary referral center for HIV care of entire Brescia province (about 1,200,000 inhabitants). The Infectious and Tropical Diseases Department, following approximately 4,000 PLWH, is considered one of the largest outpatient clinics for HIV care in Italy.

We included all the newly HIV-diagnosed patients referred to our department from September 1st, 2015, to July 31st, 2019, both as hospitalized in our Infectious Diseases (ID) ward at time of HIV diagnosis (inpatients) and as outpatients, normally after receiving a positive HIV test in one of the community-based checkpoints or in private labs. We considered any clinical stage of HIV infection, including acute or early HIV infection (AEHI) defined according to Fiebig criteria [21] and AIDS presenters.

We retrospectively extracted data of patients from an electronic database (*NetCare*, Healthware Technology SpA, Salerno, Italy), generally used in our Department for everyday clinical activity and outpatients management. Thus, patients' baseline characteristics at the moment of linkage to our Clinic were collected in an anonymized database, including demographics (sex, age, nationality), the date and the modality of first HIV care access (as outpatient or inpatient), risk factor for HIV acquisition (heterosexual, male who have sex with male [MSM], bisexual, intravenous drug user [IVDU]), co-infections (HCV and HBV active infections), viro-immunological status (CD4+ T-cell count, CD4+/CD8+ T-cell ratio and HIV viral load), clinical stage of infection (primary HIV infection or AIDS), and time period occurred between the first HIV positive test and the first referral to our Clinic.

For patients starting ART, we recorded drugs chosen (reverse transcriptase inhibitors [NRTIs], non-nucleoside reverse transcriptase inhibitors [NNRTIs], integrase strand transfer inhibitors [INSTIs], boosted protease inhibitors [PIs]) as triple or dual regimen and the date of ART initiation. Assessment of viro-immunological profile (HIV viral load and CD4 T cell count) and execution of genotypic resistance test and HLA-B5701 normally precede ART initiation, which is selected by the treating physician based on the national and international HIV guidelines and own clinical experience and practice. Nevertheless, readiness of genotypic resistance test and HLA B5701 results is not mandatory to choose and begin initial ART regimen.

All patients were followed up for a total of 400 days from their very first referral at our Clinic and, independently from the start of ART, we recorded status of retention in care at 6th and 12th month (actively followed, lost to follow up [LTFU], transferred to another Center, deceased) and the rate of viral suppression (HIV RNA < 50 copies/ml) at the end of follow up period. We defined LTFU as any patient missing follow up visit and viro-immunological determination (HIV viral load and CD4+ T cell count) at 6th and/or 12th month from their first access without re-engagement in care.

Therefore, all newly HIV diagnosed out- and inpatients accepting to receive ART were divided in three groups according to the time of ART initiation from the first HIV care access (rapid start group [≤ 7 days], intermediate start group [between 8 and 30 days] and late start group [>30 days]) and followed up over time, assessing for each group rate of viral suppression at 1st, 3rd, 6th and 12th month. Inpatients initiating ART during hospital stay were followed up after their discharge as outpatients.

Statistical analysis

Baseline characteristics of all newly HIV diagnosed patients were summarized in a descriptive analysis calculating median, first and third quartile for continuous variables while counts and percentages were used for categorical variables.

For the survival analyses, we excluded patients not starting ART. Hazard ratios (HR) of viral suppression among continuous and categorical variables (gender, age, timing of ART initiation, antiretroviral pharmacological class, HIV viral load at baseline and CD4+ T cell count) were estimated through a Cox proportional hazard model and 95% confidence intervals (CI) were calculated. The difference in the effect

of ART initiation and viral suppression between in- and outpatients was tested through an interaction term between the two variables. The prediction obtained by the Cox model of the proportion of viral suppression depending by the time of follow up among three different groups of patients according to the time of ART initiation (rapid [1 -week initiation], intermediate [initiation between 8 and 30 days] and late [initiation >30 days]) was represented.

Results

Baseline characteristics of study population

A total of 320 newly HIV-diagnosed patients, including 206 outpatients and 114 inpatients, were initially selected for our study. All patients' baseline characteristics are summarized in Table 1.

Overall, the median age was 41.8 years (interquantile range [IQR] 32.0- 51.5), most participants were male (n=243, 75.9%) and Italian (n=215, 67.2%), while among foreign patients the majority was from Africa

Table 1
Patients' baseline characteristics

Characteristics	Outpatients (n=206)	Inpatients (n=114)	Total (n=320)	p value
Age, years, median (IQR)	39.3 (30.4-50.6)	46.3 (37.5-52.1)	41.8 (32.0-51.5)	0.002
Gender, n (%):	149 (72.3)	94 (82.5)	243 (75.9)	0.042
• Male	57 (27.7)	20 (17.5)	77(24.1)	
• Female				
Geographical origin, n (%)	137 (66.5)	78 (68.4)	215 (67.2)	0.392
Italy	29 (14.1)	19 (16.7)	48 (15.0)	
Foreign	14 (6.8)	11 (9.6)	25 (7.8)	
• Africa	13 (6.3)	3 (2.6)	16 (5.0)	
• East Europe	10 (4.9)	2 (1.8)	12 (3.8)	
• South/Central America	2 (1.0)	0 (0.0)	2 (0.6)	
• Asia	1 (0.5)	1 (0.9)	2 (0.6)	
• North America				
• Western Europe				
Risk factor for HIV acquisition, n (%)	119 (57.8)	82 (71.9)	201 (62.8)	0.090
• Heterosexual	80 (38.8)	27 (23.6)	107 (33.4)	
• MSM/bisex	7 (3.4)	4 (3.5)	11 (3.4)	
• IVDU	0	1 (0.9)	1 (0.3)	
• Unknown				
HCV co-infection, n (%)	10 (4.9)	6 (5.3)	16 (5.0)	0.913
HBV co-infection, n (%)	11 (5.3)	4 (3.5)	15 (4.7)	0.623
Baseline CD4+ T cell count, cells/uL	391.0 (247.6)	250.3 (270.6)	341.5 (264.2)	<0.001
mean (SD)	387.0 (199.0-556.0)		323.0 (103.5-520.5)	
median (IQR)		157.0 (30.0-369.0)		

MSM: men who have sex with other men; IVDU: intravenous drug user; AEHI: acute or early HIV infection

Characteristics	Outpatients (n=206)	Inpatients (n=114)	Total (n=320)	p value
Baseline CD4+ T cell count, %	20.4 (10.8)	16.4 (19.1)	19.0 (14.3)	<0.001
mean (SD)	20.9 (12.2-27.6)	12.7 (5.6-22.5)	18.4 (8.6-26.5)	
median (IQR)				
Baseline HIV RNA viral load, n (%)	143 (70.4)	49 (43.8)	192 (61.0)	<0.001
< 100000 copies/ml	60 (29.6)	63 (56.2)	123 (44.3)	
> 100000 copies/ml				
AEHI, n (%)	28 (13.6)	9 (7.9)	37 (11.6)	0.127
AIDS, n (%)	19 (9.2)	63 (55.3)	82 (25.6)	<0.001
Median time from HIV diagnosis to first referral, days (IQR)	19.0 (12.0-32.0)	10.5 (5.0-17.0)	15.0 (8.0-28.0)	<0.001
MSM: men who have sex with other men; IVDU: intravenous drug user; AEHI: acute or early HIV infection				

(n=48, 15.0%), followed by patients from East Europe (n=25, 7.8%), South/Central America (n=16, 5.0%), Asia (n=12, 3.8%), North America and Western Europe (n=2, 0.6%, each). Overall, the main risk factor declared for HIV acquisition was heterosexual exposure (n= 201, 62.8%).

Regarding the baseline viro-immunological profile, CD4+ T cell absolute and percentage mean counts were 341.5 cells/mmc and 19%, respectively, and patients with HIV RNA load <100.000 copies/ml were the majority (n=192, 61.0%). The inpatients' cohort showed a significantly worse status, having a lower CD4+ T cell count (mean absolute count 250.3 cells/mmc, mean percentage 16.4%) and HIV RNA viral load >100.000 copies/ml in more than one-half of cases (n=63, 56.2%) compared to outpatients.

Regarding the duration of infection at time of HIV diagnosis, overall, 25.6% of patients were found at AIDS stage, of whom just 19 were outpatients while the great majority (n=63) were inpatients, accounting for more than one- half of all inpatients (55.3%). A minority of patients (n= 37, 11.6%) was diagnosed as AEHI.

We observed a median time of 15 days (IQR 8.0-28.0) from the first positive HIV test to the first access to our Clinic.

ART initiation and regimens

Table 2. Characteristics of ART timing initiation and prescription

Patients starting ART	Outpatients (n=197)	Inpatients (n=114)	Total (n=311)	p value
Median time from first visit to ART start, days (IQR)	34.0 (9.0-44.0)	4.0 (0.2-17.8)	24.0 (2.5-41.0)	<0.001
Timing of ART start, n (%):	46 (23.4)	71 (62.3)	117 (37.6)	< 0.001
• rapid start	40 (20.3)	24 (21.1)	64 (20.6)	
• intermediate start	111 (56.3)	19 (16.7)	130 (41.8)	
• late start				
ART regimen chosen, n (%):	13 (6.6)	1 (0.9)	14 (4.5)	0.050
• PI:	18 (9.1)	14 (12.3)	32 (10.3)	0.010
ATV/booster	24 (12.1)	4 (3.5)	28 (9.0)	0.269
DRV/booster	66 (33.3)	50 (43.9)	116 (37.2)	0.004
• NNRTI (RPV)	65 (32.8)	28 (24.6)	93 (29.8)	
• NRTI:	64 (32.3)	35 (30.7)	99 (31.7)	
FTC/TAF	2 (1.0)	0 (0.0)	2 (0.6)	
FTC/TDF	119 (60.4)	88 (77.2)	207 (66.6)	
ABC/3TC	18 (9.1)	3 (2.6)	21 (6.8)	
3TC	8 (4.1)	7 (6.1)	15 (4.8)	
• INSTI:				
DTG				
ELV/cobicistat				
RAL				
Nine patients (all outpatients) never initiated ART. Characteristics of ART timing initiation and prescription are summarized in Table 2.				

Overall, among patients receiving ART (n=311) the median duration from the first access to our Clinic to ART prescription was 24 (IQR: 2.5-41.0) days, with a significant lower time interval (4 days, IQR: 0.2-17.8) registered in inpatients than in outpatients (34 days, IQR: 9.0-44.0). Therefore, we distinguished three groups of patients according to time of ART initiation from their first access to our clinic: 117 patients - 37.6% -, 46 outpatients (23.4%) and 71 inpatients (62.3%) started ART within 7 days (rapid start group). Sixty-four (20.6%) patients, 40 outpatients (20.3%) and 24 inpatients (21.1%) began ART between 8 and 30 days (intermediate start group). Lastly, 130 (41.8%) patients, 111 outpatients (56.3%) and 19 inpatients (16.7%) started ART after 30 days (late start group).

Regarding ART prescribing attitude, a three drug ART regimen was prescribed in all cases but two. The preferred 2 NRTIs back-bones were: emtricitabine/tenofovir alafenamide (FTC/TAF) (37.2%), abacavir/lamivudine (ABC/3TC) (31.7%) and emtricitabine/tenofovir disoproxil (FTC/TDF) (29.8%). Among pharmacological classes used as 3rd drug, INSTIs were used in 243 cases (78.1%), with dolutegravir (DTG) as preferred choice in 207 (66.6%) patients, boosted PIs (mostly darunavir) in 46 patients (14.7%) and NNRTI (only rilpivirine) in 28 cases (9.0%). Dual therapy containing DTG + 3TC was prescribed in only 2 cases.

Rates of retention in care and virological response during follow-up

As shown in Table 3, overall, median time to viral suppression was 84 days (IQR: 35.0-161.0). At the 6th month of follow up the great majority of patients (n=302, 94.4%) was still linked to care, while 4.7% were LTFU and just 3 patients had been transferred to another ID centre. By the 12th month 87.5% of patients were actively followed, 9.4% were LTFU and 10 subjects were transferred (n=5, 1.6%) or deceased (n=5, 1.6%).

Table 3
Median time to viral suppression and rates of retention in care during follow up

	Total (n=320)
Median time to HIV RNA < 50 copies/ml, days (IQR)	84 (35.0-161.0)
Status at 6th month of follow- up, n (%)	
LTFU	15 (4.7)
Followed up	302 (94.4)
Transferred	3 (0.9)
Deceased	0
Status at 12th month of follow-up, n (%)	
LTFU	30 (9.4)
Followed up	280 (87.5)
Transferred	5 (1.6)
Deceased	5 (1.6)
LTFU: lost to follow up	

Cox proportional hazard model was performed to investigate the association between ART start and virological response (HIV RNA < 50 copies/ml) adjusting for gender, age, being in- or outpatient, antiretroviral pharmacological class, HIV viral load at baseline and CD4+ T cell count (Table 4).

Table 4
Multivariable Cox Proportional Hazard model for Predictors of viral suppression

	HIV RNA < 50 copies/ml		
Predictors	Hazard ratios	95% CI	p
time (weeks) to start	0.96	0.93 – 0.99	0.016
Sex M vs F	1.01	0.73 – 1.38	0.966
Age	1.00	0.98 – 1.01	0.414
Inpatients vs Outpatients	0.86	0.65 – 1.15	0.320
PI vs INSTI based regimen	0.52	0.36 – 0.77	0.001
NNRTI vs INSTI based regimen	0.63	0.41 – 0.97	0.036
Log (HIV RNA at T0)	0.85	0.80 – 0.90	<0.001
Log (CD4 at T0)	1.18	1.04 – 1.34	0.008

Because of missing values among covariates, a total of 293 subjects were included in the model. We found that for each week awaiting initiation of therapy there was a 4% less probability to achieve HIV RNA < 50 copies/ml (HR 0.96, 95% CI 0.93-0.99, p 0.016). Starting ART with boosted PI or NNRTI-containing regimens was less likely associated with virological response overtime compared to INSTI-containing initial regimen (PI vs INSTI HR 0.52, 95% CI 0.36-0.77 p 0.001; NNRTI vs INSTI HR 0.63, 95% CI 0.41-0.97 p 0.036). Baseline viro-immunological status was a significant predictor of virological response: higher viral load showed a harmful effect reducing the probability of viral suppression (HR 0.85, 95% CI 0.80-0.90 p <0.001) while a high CD4+ T cell count was associated to a higher probability to achieve viral suppression (HR 1.18, 95% CI 1.04-1.34 p 0.008). When introducing an interaction term between time to ART start and being in- or outpatient we observed no difference in the role of time to ART start on viral suppression between the two patient categories (HR 1.03, 95% CI 0.97 – 1.10, p 0.280).

Figure 1 and Table 5show the predictions of the proportion of patients achieving HIV RNA below 50 copies/ml during a 400 day-time of follow up obtained by the Cox model setting initiation ART within 1 week, between 8th and 30th day and after 4 weeks (rapid, intermediate and late start, respectively). At 3 months of follow up the percentage of patients with virological success were 69.4%, 67.6% and 64.1% for rapid start, intermediate start and late start group, respectively. After 6 months these proportions

exceeded 90% in all groups (95.0% in rapid, 94.2% in intermediate, 92.5% in late start group) while at 12 months 99% of the patients in each group showed HIV RNA < 50 copies/ml

Table 5
Rates of viral suppression according to the ART initiation

months	Rapid start (%)	Intermediate start (%)	Late start (%)
1	20.7	19.8	18.2
3	69.4	67.6	64.1
6	95.0	94.2	92.5
12	99.6	99.5	99.2
ART: antiretroviral therapy			

Discussion

In this study, we observed that virological response was reached in the great majority of naïve PLWH patients (beyond 99%) by 12th month of ART, without being influenced by the timing of its initiation. This result is important considering that assessment of long-term efficacy and acceptability of rapid ART in the real-life practice remains challenging, especially in developed countries.

In our study the proportion of patients receiving rapid ART, as within 7 days from first HIV medical referral, was higher in inpatients' cohort (62.3%) rather than outpatients' one (23.4%). This observation might be due to the greater probability of inpatients to be diagnosed late with HIV namely in advanced stage of infection, as demonstrated by patients with AIDS defining events representing more than half (55.3%) of inpatients' group. These clinical conditions are already recognized by major national and international guidelines to require an immediate start of adequate therapy [22–25]. Recently, small cohorts from high-income settings also provided increasing evidence of safety and acceptability of rapid ART initiation in very early stage of infection out of clinical trials. For example, one cohort from London showed rapid viral suppression and high ART uptake by 24 weeks (99%) among those initiated ART at first medical appointment [19]. Similarly, another cohort from San Diego demonstrated increased ART uptake and higher likelihood to virally suppress (91%) by 24 weeks for participants initiating ART within 7 days [20].

Nonetheless, clear evidence that certain timing of ART initiation impacts or not on long-term care engagement and virologic suppression still lacks [15] and previous studies carried out in high-income settings sometimes highlighted discordant results. On one hand, researchers from ICONA Foundation Study Cohort did not observed any clear benefit of rapid ART start in term of virological success after one year of follow up [18]. On the other, one cohort study from France even showed that longer time between first medical visit and first ART prescription was associated with a better 1-year retention in care [14]. By contrast, a real-life world retrospective study in Taiwan demonstrated a higher rate of attrition from care together with lower rate of LTFU at 12 months in population receiving ART within 7 days [26].

Our Clinic follows around 4000 HIV-infected patients from the province of Brescia (Lombardy), which counts one of the highest incidences of HIV/AIDS diagnosis [27] and the fourth largest migrant population in Italy [28]. Another study carried out in our HIV Clinic during a 6-year-period (2012-2018) estimated a rate of 86.7% outpatients retained in care with a rate of viral suppression (HIV RNA < 37 copies/ml) more than 94% [29]. Although current study corroborates our previous findings, with low rate of LTFU (< 10%) and almost 90% (87.5%) of patients still linked to care after 1 year of follow up, we did not find a connection between time of ART start and likelihood of durable viral suppression over time. We observed a great rate of viral suppression (up to 99%) among people remained in care regardless of timing of ART initiation (rapid, intermediate and late).

Shortening time to ART initiation leads towards faster virologic suppression [3, 4, 14] with incontrovertible benefits regarding both individual patients' health and "community viremia", due to prevention of sexual and perinatal HIV-transmission [15, 30]. Indeed, although timing of ART initiation does not seem to be a successful guarantee of long-term retention in care [5, 13], one of the greatest goals of rapid ART start remains faster control of "community viremia" aimed at reducing time in which naïve HIV patients continue to be contagious. In our population each week spent waiting for therapy start brought to 4% less probability to reach undetectable HIV viral load (see Table 4). This finding might be concerning from a "public health" point of view if we consider that in our study the majority of patients (41.8%) still began ART after 30 days from their first medical encounter with, overall, almost 3 months as median time from ART prescription to first undetectable HIV RNA, clearly more than what observed by other cohorts [19, 20, 26]. Thus, in our real-life practice this time is still too wide and there is a room for improvement.

Obviously, fast initiation of treatment requires first removal of any cultural, financial and structural barriers which might prevent patients from diagnosis and care engagement [21, 31] and optimizing strategies able to guarantee easy prompt access to HIV care remains a crucial topic. Compared with published data [14, 18–20] and very far from WHO recommendations, in our Clinic time from HIV diagnosis to linkage to care tends to be still too long (around two weeks), as well as interval from first HIV referral to ART initiation is even wider, especially for outpatients who might have to wait for ART initiation up to 1 month (median time 34 days). As previously underlined by d'Arminio Monforte and colleagues, this lag time could be due not only to prescription policy of the Centre but also to the fact that HIV diagnosis often occurs outside hospital settings (i.e. private laboratories, community-based checkpoints) and the process to refer HIV positive patients to an ID Center might be delayed [18].

It is broadly recognized that predictors of virologic success include low baseline viremia, highly potent ART regimen, drug tolerability, convenience of the regimen and appropriate adherence to the treatment [15]. Thus, as shown already by other cohorts [4, 18–20, 26], in our study the achievement of viral suppression was more likely associated to patients' lower HIV RNA viral load and initial INSTI-containing regimens, the latter proven safe, non-inferior and less toxic in dual therapy for naïve HIV patients by GEMINI trials [32]. In our cohort, anyway, even though DTG turned out to be largely prescribed (66.6%), its use in dual therapy continues to lack, resulting paltry compared with its proportion in three-drug regimen.

Our study has several limitations. First, its single-centre retrospective, observational design might present bias related to retrospective data collecting as well as poor generalizability of findings to other settings. Second, these data may suffer from prescription habits of physicians from the same medical center and HIV care experience. Third, we did not characterize initial AIDS defining events, including eventual TB co-infections, which have probably influenced differently the choice of ART start timing. Therefore, we cannot draw precise conclusions regarding reasons behind clinician's decisions of ART timing initiation in such cases. Also, since September 2015, when the study period began, several aspects of our HIV continuum of care have changed. On one hand, bureaucratic procedures have been simplified, on the other national and international guidelines have progressed and our clinical practice in HIV care and ART prescription attitudes too, going beyond latest version of HIV care Italian guidelines from 2017 [25], which recommended clinicians offering rapid ART initiation primarily to those highly motivated patients; however, dual-therapy (DTG-based) in naïve patients has been implemented only in the last 24 months, due to the availability of single tablet regimen and according to the results of newer randomized clinical trials in this topic. Nowadays, main guidelines in HIV care share and strongly recommend offering rapid strategy in all but very few exceptions.

The strength of our study is mainly due to its perspective of "real -life" setting over 4-year period in a field of HIV care still deeply unexplored. Moreover, another point to be underlined is that, differently from most published studies, we included both in-and outpatients' cohorts reflecting our clinical practice even in severely ill patients.

Conclusions

Ensuring the best linkage to care and retention tools to guarantee access to ART initiation and an adequate adherence remain a priority regarding HIV continuum of care, in order to successfully pursue the "third 90" goal advocated by United Nations Program UNAIDS through its 90-90-90 slogan [33]. In a real-life setting of a high-income country like Italy, where a public national health system guarantees equal good-quality care and personalized health care are promoted, we may give priority to each patient's clinical and social conditions as guidance to establish the best individualized timing for antiretroviral therapy initiation.

List Of Abbreviations

ART: antiretroviral therapy

TB: tuberculous

PLWH: people live with HIV

IRIS: immune reconstitution inflammatory syndrome

ID: infectious diseases

AEHI: acute or early HIV infections

MSM: male who have sex with male bisexual

IVDU: intravenous drug user

NRTIs: reverse transcriptase inhibitors

NNRTIs: non-nucleoside reverse transcriptase inhibitors

INSTIs: integrase strand transfer inhibitors

PIs: boosted protease inhibitors

LTFU: lost to follow up

HR: hazard ratios

CI: confidence intervals

IQR: interquantile range

SD: standard deviation

FTC/TAF: emtricitabine/tenofovir alafenamide

ABC/3TC: abacavir/lamivudine

FTC/TDF: emtricitabine/tenofovir disoproxil

DTG: dolutegravir

RPV: rilpivirine

ATV: atazanavir

DRV: darunavir

ELV: elvitegravir

RAL: raltegravir

Declarations

Ethics approval and consent to participate

The present study was conducted in accordance with the rules of good clinical practice (GCP-ICH) and according to Declaration of Helsinki. The study was approved from the Ethical Board of the Brescia Province on October 1st 2020 and all efforts were made in order to obtain patient's written consent.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

EF received research Grants, consultancy fees and speakers honoraria from MSD, Gilead, Janssen and Viiv Healthcare. The remaining Authors have no conflict of interest to declare.

Funding

Not applicable

Authors' contributions

EQR, II, and EF contributed to study design, analysis, and data interpretation. SR and SC determined statistical methods and performed statistical analysis. NG. and GF contributed to data collection. NG and EF first drafted the article. EQR, EF and FC contributed to critical reviewing of the article. All authors reviewed the article, read and approved the final version of the manuscript.

Acknowledgments

We thank the participants who contributed to this study.

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Figures

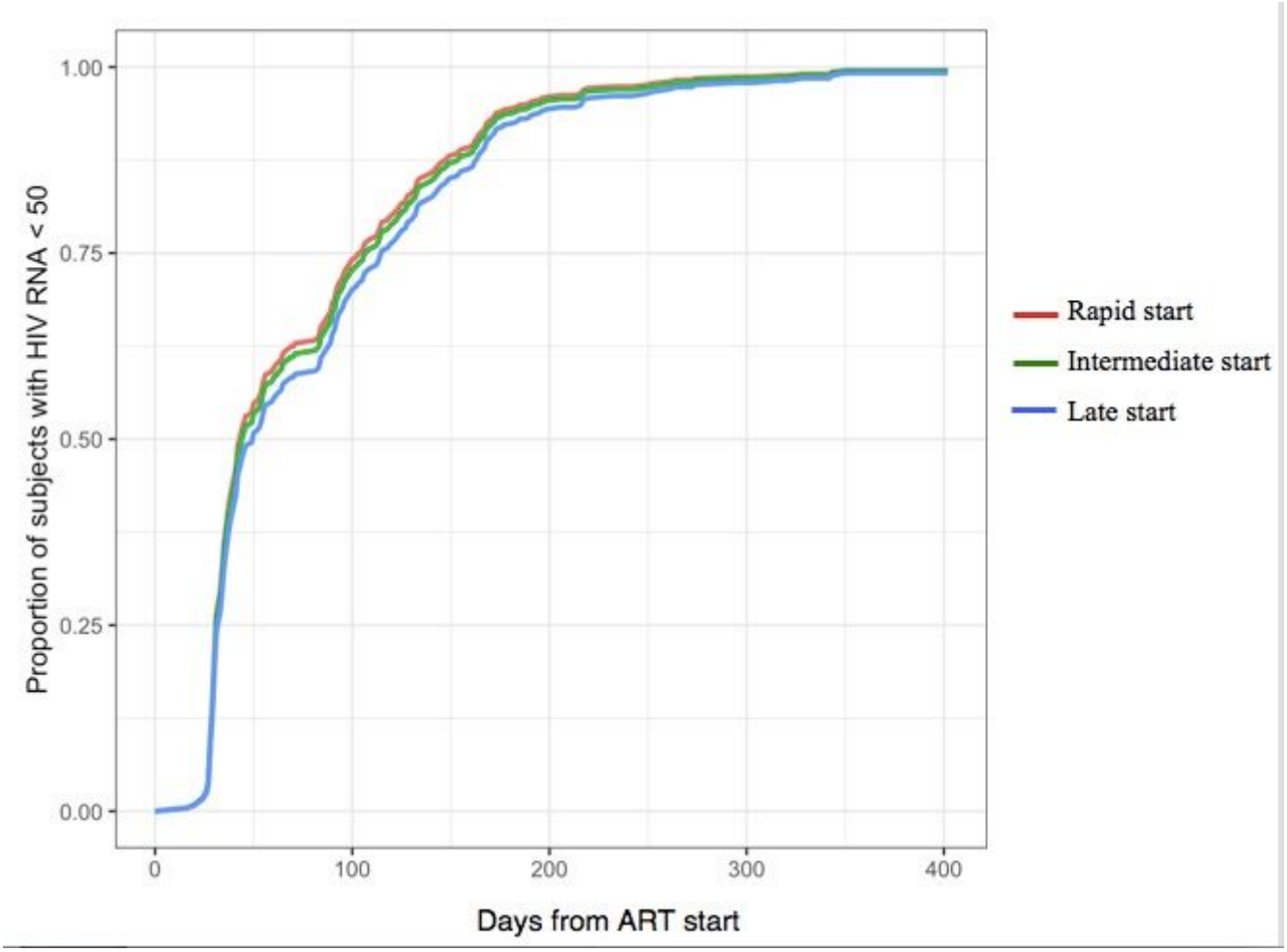

Figure 1

Time from ART start to virological response (HIV RNA < 50 copies/ml) according to different timing of initiation (rapid, intermediate and late)