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ORIGINAL RESEARCH

Comparison of Immunological and Virological Recovery with Rapid, Early, and Late Start of Antiretroviral Treatment in Naive Plwh: Real-World Data

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Background: Rapid initiation of antiretroviral therapy (ART) reduces the transmission of HIV infection in the community. This study aimed to determine whether rapid ART initiation is effective compared to standard ART treatment in our country.

Methods: Patients were grouped based on time to treatment initiation. HIV RNA levels, CD+4 T cell count, CD4/CD8 ratio, and ART regimens were recorded at baseline and follow-up visits for 12 months.

Results: There were 368-ART naive adults (treatment initiated at the time of HIV diagnosis; 143 on the first day, 48 on the second-seventh day, and 177 after the seventh day). Although virological suppression rates at 12th months were higher in all groups, over 90% on average, there were no statistically significant differences in HIV-1 RNA suppression rates, CD+4 T cell count, and CD4/CD8 ratio normalization in the studied months but in multivariate logistic regression analysis; showed a significant correlation between both virological and immunological response and those with CD4+ T <350 cells/mL at 12th month in total patients.

Conclusion: Our findings support the broader application of recommendations for rapid ART initiation in HIV patients.

Keywords: HIV, ART, antiretroviral, rapid start

Introduction

With the introduction of effective combination antiretroviral therapy (ART) for people living with HIV (PLWH) in 1996,[1] their life expectancy has now reached parity with that of individuals not infected with HIV, provided that they are diagnosed and treated upon infection.[2,3] Clinical guidelines for HIV treatment were updated after 2015 to recommend initiating ART in PLWH regardless of CD4+T cell count.[4–6] These updates were based on randomized controlled trials and observational studies in which ART was initiated at higher CD4+T cell counts (≥500 cells/mm^3).[7,8] This approach has reduced the risk of AIDS and non-AIDS events and the mortality rate for PLWH.

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Subsequent research has shown that initiating therapy on the first day or within a week of diagnosis results in the following outcomes: rapid and effective viral suppression, early immune system recovery, increased treatment adherence and persistence, improvement in quality and length of life, reduction in the development of HIV-related and noncommunicable diseases, prevention of complications, and, most importantly, reduction in the transmission of HIV in the community.[9–13]

While no standard for rapid ART has yet been established, it generally involves starting treatment within the first 24 hours of diagnosis.[5] However, the World Health Organization (WHO) defines it as starting ART within seven days of a diagnosis. In other research, it has been defined as starting ART within 14 days of a diagnosis.[5,9,11]

Until the initiation of ART, an individual diagnosed with HIV needs to make many hospital visits to arrange for counseling, laboratory tests, and other procedures, which can burden patients and delay the start of therapy.[4] This is most common in low-income countries, especially Sub-Saharan Africa.[9,11] In 2017, WHO advised that all persons living with HIV start rapid ART after a confirmed HIV diagnosis and clinical evaluation, to increase treatment adherence and follow-up by reducing lost to follow-up rates (LTFU).[5,14] Studies on rapid ART initiation were also performed in the United States (US). The time to reach viral suppression was found to be shorter, with higher viral suppression rates and lower LTFU.[15–18] This strategy has been recommended by several guidelines, including those issued by the US Department of Health and Human Services (DHHS), the International AIDS Society (IAS), and the European AIDS Clinical Society (EACS).[19–21]

HIV infections are officially reported in Turkey, and the number of cases is increasing every year. With the cumulative decrease observed in the last year due to the COVID-19 pandemic, a total of 25,745 adults were reported to be infected with HIV-1 as of the end of 2020, and the rate of patients receiving ART was 79%.[22,23] According to the Turkish Ministry of Health, the primary strategy to minimize HIV transmission in 2019 could be achieved via early detection, viral suppression, access to care, and retention in care.[24]

When a new case of HIV infection is diagnosed in Turkey, the average time to start ART after the initial visit is not exactly known. The first step is to select and prescribe an appropriate ART regimen. After the diagnosis, certain test results (such as CD4+T cell count, HIV viral load, genotypic viral resistance test results) are expected and counseling is provided to the patients if necessary. A team of health counselors, if available, also prepares the patient for ART. This process usually takes two to four weeks.

The rapid treatment initiation approach started to be used in our country after the studies were conducted when guidelines updated their recommendations to include rapid treatment. So far, there has been no published study on the rapid start of ART. This study aimed to determine whether rapid ART initiation is effective compared to standard ART initiation in Turkey.

METHODOLOGY Study Design

This study was a retrospective, multicenter comparative case series study conducted in 15 centers across Turkey. All eligible HIV-1 positive, treatment-naive patients were included between February 2, 2018, and December 28, 2020. A case report form was developed to collect age and gender data, HIV RNA levels, CD+4 and CD+8 T cell counts, and the ART regimens of the newly diagnosed patients. In total, 368 patients were included in the study, 143 in the rapid ART start group (RS) (38.8%), 48 in the early ART start group (ES) (13.2%), and 177 in the late ART start group (LS) (48%). The RS group was defined as those who initiated ART within the first 24 hours after admission to the clinic. The ES group was defined as those who started ART between the second day and the seventh day after arriving at the clinic. Those who began ART on Day eight and beyond were defined as the LS group.

The date of HIV diagnosis was determined as the first confirmed positive HIV antibody test, detectable HIV viral load, or the day the doctor made the diagnosis on the day of the first visit to the clinic. The time to start ART after diagnosis was defined as the time to treatment initiation.

The data were collected on-site by the treating physicians. The centers included in this study cover the Mediterranean, Marmara, Eastern Anatolia, Central Anatolia, Southeastern Anatolia, and Black Sea regions.

Patient records were analyzed retrospectively. Plasma HIV-1 RNA levels, CD4+ and CD8+ T cell counts were recorded at baseline and follow-up visits at Months 1, 3, 6, 9, and 12. At the same visits, the CD4/CD8 ratio was calculated by dividing the number of CD4+ T cells obtained by the number of CD8+ T cells.

For the demographic data of the three groups, age, sex, baseline HIV-1 RNA, CD4+ T cell count, CD4/CD8 ratio, and regimens used in ART were reported. ART regimens included dolutegravir (DTG) + tenofovir/emtricitabine (TDF/FTC), elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine (EVG/COB/TAF/FTC), bictegravir/tenofovir alafenamide/emtricitabine (BIC/TAF/FTC), dolutegravir/abacavir/lamivudine (DTG/ABC/3TC). Others were lopinavir/ritonavir + TDF/FTC, darunavir/ritonavir + TDF/FTC, efavirenz + TDF/FTC and DTG+3TC.

Laboratory Analysis

Plasma HIV-1 RNA detection and quantification levels were measured using real time- PCR (Abbott TagMan 2000, Illinois-Des Plaines USA) (lower limit as quantification, 10 IU/mL). CD4 and CD8+ T cell counts were analyzed with BD Simultest™ CD4/CD8 (Becton, Dickinson and Company BD Biosciences 2350 Qume Drive San Jose, CA 95131 USA).

Study Population

Patients older than 18 years of age, diagnosed with HIV, and receiving ART for at least 12 months were included in this study.

Study Endpoints

We analyzed the virological suppression (HIV-1 RNA ≤200 copies/mL) and immunological response (CD4+ T cell count and CD4/CD8 ratio) at Months 1, 3, 6, 9, and 12 for the three treatment groups.

Statistical Analysis

Statistical analysis was made using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY). Descriptive statistics were used to summarize baseline characteristics. Data were expressed as median (minimum-maximum) and percentage (%), and the continuous variables and categorical ones were compared with Mann Whitney U (or Student's *t*-test) where appropriate. A p value of <0.05 was set as the level of significance.

Age, gender, ART start time, initial HIVRNA level (Log10), initial CD+4 T cell levels identified as possible significant variables or confounding factors on virologic response (HIVRNA<200 copies/mL) and immunologic response (raise in CD4+T cell more than 150 cells/mL) at 12th month. Therefore, in this study, following the Hosmer–Lemeshow suggestion, variables with $p < 0.25$ in univariable analyses were included in the multivariable analysis.[25]

Results

Between February 2, 2018, and December 28, 2020; a total of 368 patients were investigated from the 15 centers' records, 143 in the rapid ART start group (RS) (38.8%), 48 in the early ART start group (ES) (13.2%), and 177 in the late ART start group (LS) (48%). Baseline (the time-point of HIV diagnosis) demographics and laboratory characteristics of the patients were comparable between arms. The median age of patients in the RS, ES, and LS groups were 34, 35, 35 (p=0.990), and the percentages of female patients was %12.6, %14.6, %13.0 (p=0.938) respectively. The median baseline CD4+ T cell count: 403, 413, 438 cells/mm^3 (p=0.761), median baseline CD4/CD8 ratio: 0.44, 038, 0.40 (p=0.522), median baseline HIV-1 RNA log10: 4.9, 6.0, 5.0 copies/mL (p=0.540) respectively. The three groups were balanced for all parameters except types of ART. The baseline characteristics of patients are summarized in Table 1.

Virological Response

There were no statistically significant differences in HIV-1 RNA suppression rates (<200 copies/mL) between the groups at Months 1, 3, 6, 9, and 12 (p>0.05) (Figure 1).

Table 1 Baseline Demographic and Laboratory Characteristics of the Study Patients

	Total n= 368	Rapid n= 143	Early n= 48	Late n= 177	*P**
Age, median years (range)	34.5 (18–83)	34 (18–83)	35 (20–61)	35 (18–72)	0.990
Gender (F), n (%)	48 (13)	18 (12.6)	7 (14.6)	23 (13.0)	0.938
Baseline **HIV-1 RNA** load, median log 10 (range)	5.0 (2.3–8.5)	4.9 (2.3–7.2)	6.0 (3.2–7.5)	5.0 (2.7–7.6)	0.540
Baseline **HIV-1 RNA** load groups, median copies /mL (range), n(%)					
< 100.000	174 (49.9)	71 (52.2)	22 (51.2)	81 (47.6)	0.806
100.000–500.000	90 (25.8)	31 (22.8)	10 (23.3)	49 (28.8)	
>500.000	85 (24.4)	34 (25.0)	11 (25.6)	40 (23.5)	
Baseline CD4+ T cell count, median (range)	427 (9–1886)	403 (9–1471)	413 (24–1368)	438 (12–1886)	0.761
Baseline CD4+ T cell count <350 n(%)	132 (37.0)	56 (40.6)	19 (40.4)	57 (33.1)	0.351
Baseline CD4/CD8 ratio, median (range)	0.41 (0.01–2.36)	0.44 (0.01–2.36)	0.38 (0.05–2.12)	0.40 (0.02–1.16)	0.522
ART Type n (%)					
TDF/FTC+DTG	110 (29.9)	40 (28.0)	17 (35.4)	53 (29.9)	0.002
EVG/COB/TAF+FTC	39 (10.6)	12 (8.4)	2 (4.2)	25 (14.1)	
BIC/TAF/FTC	174 (47.3)	82 (57.3)	25 (52.1)	67 (37.9)	
ABC/3TC/DTG	26 (7.1)	4 (2.8)	1 (2.1)	21 (11.9)	
Others	19 (5.2)	5 (3.5)	3 (6.3)	11 (6.2)	

Note: *Descriptive statistics were used to summarize baseline characteristics.
Abbreviations: ABC/3TC/DTG, dolutegravir/abacavir/lamivudine; ART, Antiretroviral treatment; BIC/TAF/FTC, bictegravir/tenofovir alafenamide/emtricitabine; EVG/COB/TAF+FTC, elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine; HIV-1 RNA, human immunodeficiency virus ribonucleotide acid; F, female; TDF/FTC+DTG, tenofovir/emtricitabine) + dolutegravir.

Changes in CD4+ T Cell Count and CD4/CD8 Ratio Normalization

No statistically significant difference was found in CD4+ T cell numbers and CD4/CD8 ratio normalization in the follow-up. Although there was no statistically significant difference between the groups, CD4/CD8 ratio was found to be higher

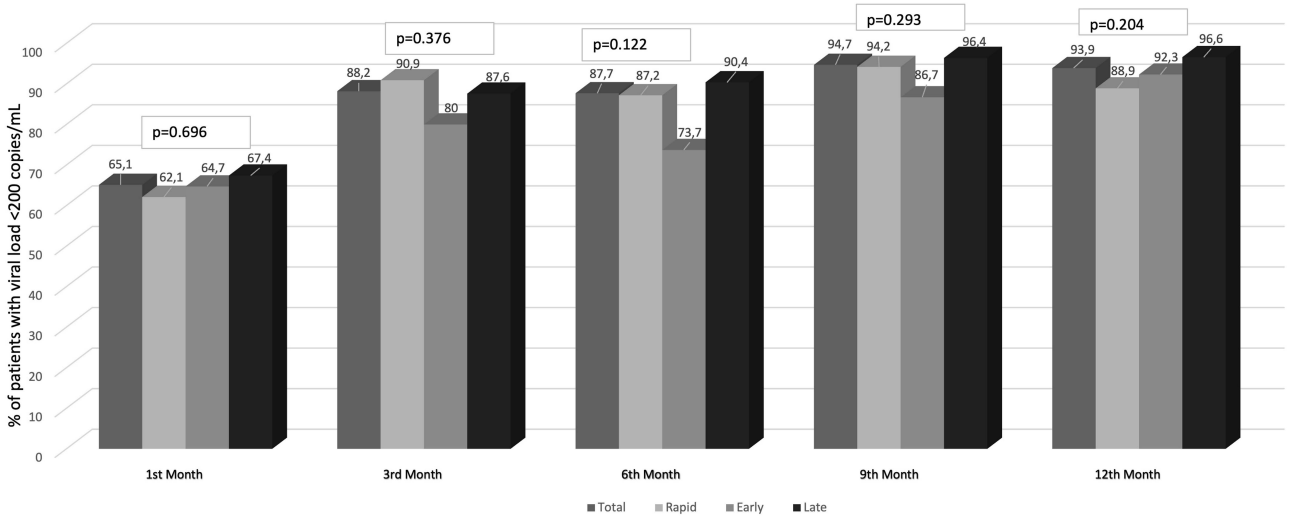

Figure 1 Proportional (%) HIV RNA<200 copies/mL of the patients (virological response).

in the RS group than others at Months 9 and 12. On the other hand, the LS group had higher CD4+ T cell counts, particularly in the last three months of the study (Figures 2 and 3).

Factors Associated with HIV Viral Load Suppression (< 200 Copies/mL); and CD4+ T Cell Count Increase (>150 Cells/mL) at 12th Month in Total Patients

Univariate analysis showed a significant association between virological response and those with late onset of ART, HIV RNA >5 log 10, CD4+ T <350 cells/mL, and between immunological response and CD4+ T <350 cells/mL (Table 2). In multivariate logistic regression analysis; showed a significant correlation between both virological and immunological response and those with CD4+ T <350 cells/mL (Table 2).

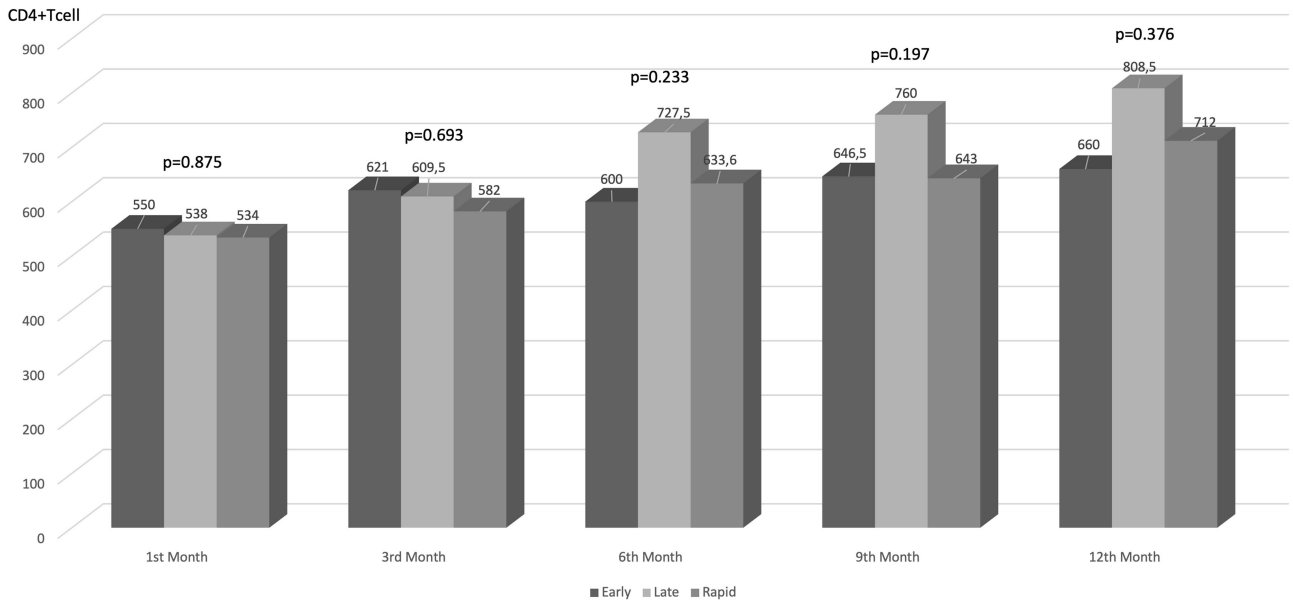

Figure 2 CD4+ T cells levels in patients.

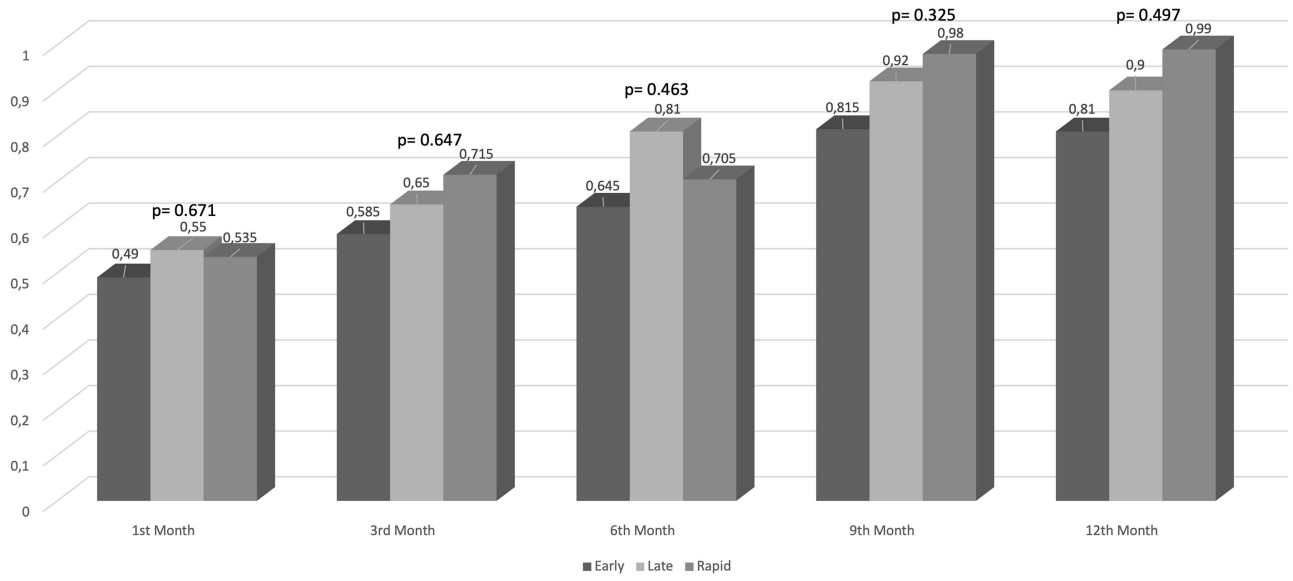

Figure 3 The ratio of CD4/CD8 ratio between the groups.

Table 2 Factors Associated with HIV Viral Load Suppression (< 200 Copies/mL); and CD4+ T Cell Count Increase (>150 Cells/mL) at 12th Month

	Virologic Response						Immunologic Response					
	Univariate			Multivariate			Univariate			Multivariate		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Gender												
Female	Ref						Ref					
Male	1.52	0.18–12.75	0.701				0.54	0.2–1.49	0.236	0.04	0.13–1.35	0.145
Age												
<25	Ref						Ref					
≥25	1.39	0.16–11.87	0.765				0.45	0.16–1.28	0.134	0.54	0.16–1.84	0.322
ART Start												
Rapid	Ref						Ref					
Early	0.67	0.07–6.27	0.723	0.77	0.07–8.46	0.831	0.83	0.15–4.62	0.833			
Late	0.28	0.64–1.23	0.091	0.55	0.11–2.88	0.48	1.67	0.65–4.30	0.289			
ART Type												
BIC/TAF/FTC	Ref						Ref					
TDF/FTC+DTG	2.08	0.23–18.8	0.516				0.829	0.27–2.57	0.746			
EVG/COB/TAF+FTC	1.47	0.13–17.21	0.761				0.453	0.11–1.85	0.271			
ABC/3TC/DTG	1	0.06–17.02	1				1.619	0.45–5.78	0.458			
Other	0	0-	0.999				0.63	0.11–3.78	0.613			
Initial **HIVRNA**												
<5Log10	Ref						Ref					
≥5Log10	5.75	0.69–48.07	0.106	4.13	0.47–36.08	0.199	0.64	0.28–1.47	0.295			
CD4+T cell												
≥350	Ref						Ref					
<350	9.14	1.81–46.08	0.007	6.03	1.07–33.93	0.041	0.22	0.06–0.8	0.021	0.15	0.03–0.68	0.047

Abbreviations: ABC/3TC/DTG, dolutegravir/abacavir/lamivudine; ART, Antiretroviral treatment; BIC/TAF/FTC, bictegravir/tenofovir alafenamide/emtricitabine; EVG/COB/TAF+FTC, elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine; HIV-1 RNA, human immunodeficiency virus ribonucleotide acid; TDF/FTC+DTG, tenofovir/emtricitabine) + dolutegravir.

Discussion

Current studies on the rapid start of ART in the real-world setting are limited. This study aimed to compare the treatment efficacy of RS, ES, LS of ART in the real world in naive PLWH at Months 1, 3, 6, and 12 in our country. We used the CD4+ T cell count, CD4/CD8 ratio normalization, and HIV RNA level to assess immunological and virological responses.

In our study, in newly diagnosed HIV-1 infected individuals between 2018 and 2020, the median time from HIV diagnosis to the start of ART was 7 (0–452) days (data not shown). There had been no data about the time of ART initiation in our country. This is intended to be the first of such data. Before 2018, the time to treatment initiation may have been longer than seven days as the clinics in our country implemented rapid start after 2018, and RS was applied in many outpatient clinics only after the emergence of the Covid-19 pandemic (after March 2020). Early treatment for PLWH began to be provided in most countries after 2015 when WHO implemented the "Treat All" policy.[26–29] This was

best demonstrated in a French cohort, where the median delay between HIV diagnosis and start of ART decreased from 9.07 months in 2007 to 0.77 months in 2017.[29]

In 2017, there was an increase in the rates of rapid treatment start, with the WHO's recommendation to start treatment on the day of diagnosis or within the first seven days.[16,30] As mentioned earlier, there is no standard definition of early ART initiation. The average time of ART initiation may vary depending on region, city, and country. For example, in studies conducted in London and Taiwan, rapid ART was two and seven days, respectively. In our study, about 62% of patients started ART within seven days of HIV diagnosis. This rate was relatively high compared to other studies.[9,13,17,18] This might be because hospital visits had to be limited during the Covid-19 pandemic, and the patients were treated early after diagnosis.

The first clinical trials of rapid ART were conducted in developing countries such as South Africa, yielding high virological responses. A first-visit ART initiation trial in South Africa resulted in a higher viral suppression rate at Month 10 in the rapid ART group compared to other participants (64% vs 51%).[10] On the other hand, in most studies, 29–50% of the patients did not achieve viral suppression 1012 months after rapid ART initiation.[10–14] As a result of these studies, rapid ART started to be investigated in developed countries.[31,32] In a San Francisco city clinic, serving patients with high rates of mental illness, substance abuse, and homelessness, 90% of patients achieved viral suppression in an average of 1.09 years, with rapid ART within the RAPID program.[18] In the same study, the rapid ART group had a higher rate of virological suppression at the final viral load measurement (94%) than the late ART group (81%). In another study from the US, the rapid ART approach was found to reduce time to first provider appointment, time to ART start, and time to viral suppression, but not the proportion of patients who achieved viral suppression.[33] In our study, we did not find a significant difference in virological suppression rates between the groups. However, we had high rates of virological suppression in all groups. Yet, the rate of viral suppression at Month 12 in the RS group (88.9%) was lower than in other groups (92.3% in the ES and 96.6% in the LS group). We plan to follow these patients further in the future. Virological suppression rates close to 90% in 12 months are quite high and sufficient for improvement. In our study, we found that the virological response was better in PWLH (CD4+ T < 350 cells/mL) presenting with late presentation. To further shorten the time to viral suppression and increase virological suppression rates to end the HIV epidemic, innovative approaches that reduce barriers to testing, care, and adherence are required.[34]

A multicenter study conducted in our country found that 79% of newly diagnosed cases were retained in care. Among these cases, viral suppression was achieved in 73% after six months of ART.[23] These ratios are higher than most European countries.[34–36] In our study, viral suppression rates were also found to be higher. Rapid ART initiation is linked to faster viral suppression in PLWH, resulting in a significantly reduced risk of transmission. Although in our study the rapid initiation of ART did not affect the viral suppression rates, it should be noted that faster viral suppression would mean fewer cases of transmission: so early "ART equals early viral suppression equals lower transmission."

The rapid increase in CD4+ T cell count shortens the duration of prophylaxis against opportunistic infections and reduces AIDS-associated morbidity and mortality.[19] However, late presenters treated with INSTIs may carry a greater risk of developing immune reconstitution inflammatory syndrome (IRIS) due to a rapid increase in CD4+ T cell count. It is known that the number of CD4+ T cells increases annually by 100–150 cells/mm^3 on average.[37] Therefore, in our univariate and multivariate analysis, we evaluated the immunological response as an increase in CD4+ T cell count of more than 150 cells/mL at 12 months. In our study, the median CD4+ T cell count was 427 cells/mm^3 and the increase observed was higher than 200 cells/mm^3 at Month 12. After INSTI use, the one-year increase in CD+4 T-cell should be modified by 200 cells/mm^3 or more per year. We found a similar result in our other study comparing INSTIs two years ago.[38] We found no difference in immunological response between the groups and that the rapid ART initiation did not affect the immunological response but we found that CD4+ T cell count increase (>150 cells/mL) at 12th month was better in PWLH (CD4+ T < 350 cells/mL) presenting with late presentation in total patients.

Despite ART, immune activation and inflammation persist in PWLH, leading to future comorbidities.[37] Starting treatment early leads to reduced inflammation,[39] and one of the best and established biomarkers of inflammation is the normalization of the CD4/CD8 ratio.[40] The CD4/CD8 ratio is indicative of immune dysfunction and a prognostic marker for non-AIDS mortality, and it also reflects the size of the viral reservoir in PLWH.[37] This rate is higher than 1 in immunocompetent individuals.[41] Although we could not find a significant difference between the groups in terms of

normalization of the CD4/CD8 ratio in our study, it was higher in the RS group in the last two months of the study. Several studies have shown that early initiation of ART is associated with a shorter time to normalization of the CD4/CD8 ratio.[42,43] In addition, there was no normalization in the CD4/CD8 ratio in our study groups after 12 months. Generally, the CD4/CD8 ratio normalization may not be achieved after three years, even in patients with CD4+ T cell >350 mm^3 at the start of antiretroviral therapy.[39,44,45]

The increase in CD4+ T cell counts in terms of immunological response is similar to the rise in CD4/CD8 ratios in chronic inflammation, showing us that starting ART early did not deteriorate either parameter. Rapid ART may be a method that can be used to increase the virological suppression in countries where the population of PLWH is high. It may be used to reduce the time to virological suppression in countries like Turkey with increased access to treatment and virological suppression.

Guidelines recommend ART regimens with a high barrier to resistance for rapid ART initiation, such as BIC/FTC/TAF, ritonavir-boosted DRV + (FTC or 3TC)/(TAF or TDF) or DTG + (FTC or 3TC)/(TAF or TDF).[19–21] Early virological suppression is achieved more rapidly with INSTIs than with protease inhibitors.[46,47] In our study, 81% of the treatment regimens were INSTI-based. In the San Francisco study, 90% of rapid ART regimens were INSTI-based, and 10% were DRV/r + FTC/TDF.[16] In our study, the most commonly used regimen in the RS and ES groups was BIC/FTC/TAF, with rates of 57.3% and 52.1%, respectively. DTG+TDF/FTC and BIC/FTC/TAF were the most commonly used regimens in the LS group (29.9% and 37.9% respectively). One of the reasons for selecting BIC/FTC/TAF for Rapid and Early ART groups in Turkey is believed to be that physicians preferred a regimen with low side effects due to hospital visit restrictions during the COVID-19 pandemic, as well as the ease of use of the single tablet.[47] Our number of patients with a Rapid ART before the COVID-19 pandemic was 13% after the pandemia, this rate increased to 45% (data is not shown). Real-world data of BIC/FTC/TAF in rapid start were also presented at the IDWeek 2020 by Zuppeli et al. It had been shown that patients had shorter time to virological suppression and higher virological suppression rates.[48]

A national cohort study conducted in a country with unlimited access to rapid ART, such as France, found that starting ART sooner did not benefit every patient. The viral and immunological evaluations were not performed in this study, suggesting that it is challenging to keep PLWH in care.[49] However, in many studies, it had been determined that the rate of retention in care was higher with rapid and early initiation of ART.[9,50]

There are certain limitations to this study. The rates of retention in care could not be evaluated. Our study was retrospective and coincided with the time of the COVID-19 pandemic during the planning and data collection phases. Most patients could not attend the follow-up visits, therefore, the data could not be included in the analysis as it would not be considered retention in follow-up. The patients included in this study were also followed up during that period. The main limitation of the study is that there is no information concerning the time since HIV infection. It is unclear how long the patients have been infected until they are diagnosed or they start the treatment. However, the multicenter design as well as the relatively high number of patients included are the strengths of this study.

Conclusion

To our knowledge, this is the first national-based study of rapid ART initiation in newly diagnosed PLWH. We were able to demonstrate that in ART-naive PLWH, it is feasible to start ART on the same day or within the first seven days of the initial clinical visit, which results in faster viral load suppression, and higher virological suppression rates. Our findings support the feasibility of the guidelines recommended rapid ART initiation.

Data Sharing Statement

The authors hereby confirm that the data supporting the results and findings of this study are available within the article.

Ethics Approval

Ethics committee approval was obtained at Health Sciences University Antalya Research and Training.

Hospital in Turkey in accordance with the 2008 Declaration of Helsinki (Registration No: 06.05.2021 6/11). The requirement for written informed consent was waived because of the retrospective design of this study. Demographic

information and laboratory analysis were collected from medical records. We confirmed that all the data was anonymized and maintained with confidentiality.

Consent for Publication

Individual consent was not mandatory as this was a record-based study. No individual data was captured.

Human and Animal Rights

No animals were used in this research. All human research procedures were in accordance with the articles set forth in the Declaration of Helsinki of 1975, as revised in 2013 (http://ethics.iit.edu/ecodes/node/3931).

Standard of Reporting

The study conforms to the STROBE guidelines.

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Disclosure

The authors declare no conflicts of interest, financial or otherwise.

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