INTEGRASE INHIBITORS USE AND CMV INFECTION PREDICT IMMUNE RECOVERY IN PEOPLE LIVING WITH HIV STARTING FIRST-LINE THERAPY

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ABSTRACT

Background: we explored predictors of CD4/CD8 ratio improvement and optimal immunological recovery (OIR) after initiation of antiretroviral therapy(ART) in naïve people living with HIV (PLWH).

Methods: Retrospective multicenter study including naïve PLWH starting ART with 2NRTIs + one InSTI or NNRTI or PI. PLWH were followed from the time of ART initiation (baseline) to the discontinuation of first-line regimen, virological failure, death or loss to follow-up. Estimated incidence and predictors of time to CD4/CD8 ratio normalization (defined as ≥1) and OIR (defined as CD4/CD8 ratio≥1 plus CD4≥500cells/µL plus CD4%≥30%) were explored by Kaplan Meier curves and Cox regression analysis.

Results: Overall, 1428 PLWH (77.8% males, median age 39 years, 55.1% with positive CMV antibodies, median HIV-RNA 4.80 log copies/mL, median CD4 323cells/μL, median CD4/CD8 ratio 0.32) were included, of which 21.5%(n=307), 44.5%(n=636) and 34%(n=485) treated with InSTI-, PI- and NNRTI-based regimens, respectively. The estimated proportion of CD4/CD8 normalization and OIR at 36 months was 38.6% and 32.9%, respectively. Multivariate analysis showed that InSTI-based regimens had a higher probability of CD4/CD8 ratio normalization and OIR both in the total population($p<0.001$ versus PI) and in advanced naïve PLWH ($p\le0.001$ versus PI and NNRTI). Moreover, subjects with positive CMV serology showed a lower probability of CD4/CD8 ratio normalization and OIR($p<0.001$).

Conclusions: InSTI-based regimens showed a better immune recovery, suggesting that the type of first-line ART can influence immune reconstitution. PLWH with positive CMV serology showed an increased risk of suboptimal immune recovery.

INTRODUCTION

Combined antiretroviral therapy (ART) has dramatically changed the prognosis of HIV infection, reducing AIDS-related morbidity and mortality[1]. ART regimens are able to indefinitely suppress plasma viral load in the majority of people living with HIV (PLWH), leading to immune reconstitution over time. Traditionally, immune function in PLWH is monitored by measuring CD4 cells count, since several studies have demonstrated that this parameter is the strongest predictor of disease progression and survival[2,3]. However, it has been demonstrated that PLWH are at increased risk of non AIDS-defining events also in the setting of adequate absolute CD4 cells count

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reconstitution[4]. Recent studies have shown that high levels of immune activation can still persist despite long term viral suppression and CD4 immune reconstitution; this is driven by the persistence of activated cytotoxic CD8 cells[5]. Most importantly, it has been demonstrated that immune activation in the setting of virological suppression can contribute to premature aging and to increased risk of cardiovascular events, renal diseases, neurocognitive disorders and non AIDS-related malignancies[6].

The CD4/CD8 ratio has been proposed as a simple and reliable marker to monitor T cell activation, innate immune activation and the presence of an immunosenescent T cell phenotype[7]. A low CD4/CD8 ratio has been associated with non-AIDS defining events, mortality and premature aging also in the subset of PLWH with virological control and CD4+ T cell count reconstitution[8–11]. As a consequence, there is growing interest in understanding factors associated to CD4/CD8 ratio improvement over time.

On the other side, also the CD4 percentage has been suggested as a marker of disease progression, independently of the absolute CD4 count[12]. Recently, absolute CD4 count, CD4 percentage and CD4/CD8 ratio have been concomitantly evaluated in a composite marker to define optimal immunological recovery (OIR) in naïve PLWH[13,14]. However, factors associated to adequate immune reconstitution, defined as CD4/CD8 normalization or OIR, are not completely understood. It seems particularly relevant to identify all the modifiable factors that could be involved in the immune reconstitution process in order to implement all the adequate intervention strategies.

On these bases, the aim of our study was to explore predictors of CD4/CD8 ratio normalization and OIR after initiation of first-line ART in naïve PLWH. In particular, our analysis was focused on the type of first-line regimen used, since in recent years a shift toward an increased use of integrase strand transfer inhibitors (InSTI) has been observed, but conflicting data are available about the potential immunological benefit of this drug class when compared to other regimens[15–19].

METHODS

Patients and follow-up

We performed a multicohort study retrospectively selecting treatment-naïve adult PLWH starting first-line ART from January 2009 to June 2019 at 6 clinical reference centers in Italy (Azienda Ospedaliero-Universitaria Senese, Siena; Catholic University, Rome; San Gallicano Hospital, Rome; San Gerardo Hospital, Monza; San Martino Hospital, Genoa; San Matteo Hospital, Pavia). All PLWH started treatment according to national or international guidelines and to clinical judgement of the caring physicians, during routine clinical practice. PLWH of all the involved centers signed an informed consent for use of their clinical and laboratory data in aggregated and anonymous form and are aware that the databases can be used to produce observational studies. The procedure of collecting data was notified to the Ethics Committees of the centers. Access to the database and data analyses are regulated by local institutional Ethics Committees and are conform to Italian and European privacy legislations.

Only PLWH treated with a combination of two nucleos(t)ide reverse transcriptase inhibitors (NRTI) plus one InSTI or one non-nucleoside reverse transcriptase inhibitor (NNRTI) or one protease inhibitor (PI) were included in the present analysis. Exclusion criteria were: age <18 years, regimens including >3 antiretroviral drugs, starting treatment during acute or early HIV infection (defined as having a western blot demonstrating HIV infection in Fiebig stages I–V)[14,20,21], concomitant AIDS-defining events (since PLWH with opportunistic infections can show delayed immunological recovery)[22–24]. We also excluded PLWH having a CD4/CD8 ratio ≥1 before starting the first-line regimen or those with missing absolute CD4 count, CD4 percentage and CD4/CD8 ratio at baseline and during follow-up.

PLWH were followed from the time of ART initiation (baseline) to the discontinuation of first-line regimen (defined as any modification, intensification or interruption of the regimen), virological

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failure (defined as HIV-RNA >50 copies/mL in two consecutive determinations after 6 months

from ART initiation or, after achievement of virological suppression, a rebound above 50

copies/mL in two consecutive determinations or >1,000 copies/mL in a single determination)[14,25],

occurrence of AIDS-defining events, diagnosis of malignancies, initiation of chemotherapies or

immunomodulators, death, loss to follow-up or up to 36 months of follow-up, whichever occurred

first.

Baseline characteristics and laboratory data were retrieved by electronic databases or chart review.

During follow-up, immunological parameters (i.e. absolute CD4 count, CD4 percentage and

CD4/CD8 ratio) were measured every 3-6 months by flow cytometry, according to clinical practice.

CMV IgG were measured through an enzyme-linked immunosorbent assay (ELISA).

Main endpoints

Two main endpoints were evaluated: (i) the time to CD4/CD8 ratio normalization, defined as a

CD4/CD8 ratio ≥1 confirmed in two consecutive determinations;[18] (ii) the time to OIR, defined as

a composite endpoint including the first occurrence of absolute CD4 count ≥500cells/μL plus

CD4/CD8 ratio ≥1 plus CD4 percentage ≥30% after ART initiation[14].

Statistical analysis

Descriptive statistics [number, proportion, median, interquartile range (IQR), 95% confidence

intervals (CI)] were used to describe the baseline characteristics of patients. Categorical variables

were compared between groups using the Chi-square test or Fisher's exact test, as appropriate.

Continuous variables were compared using the non-parametric Kruskal-Wallis and Mann-Whitney

U test. Incidence and predictors of time to CD4/CD8 ratio normalization and OIR were explored by

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Kaplan Meier curves and Cox regression analysis: all the investigated variables were explore in both univariate and multivariate models. A sensitivity analysis was also performed in the subgroup of advanced naïve PLWH (i.e. those with baseline CD4 <200 cells/µL). Only p values <0.05 were considered to be significant. All analyses were performed using the SPSS version 18.0 software package (SPSS Inc., Chicago, IL, USA).

RESULTS

Population's characteristics

A total of 1428 PLWH were included, whose main characteristics are reported in Table 1. Overall, 77.8% were males with a median age of 39 years; the main risk factor for HIV acquisition was represented by homosexual intercourse. Hepatitis C virus (HCV) coinfection was observed in 7.4% of subjects. More than half of PLWH had positive anti-Cytomegalovirus (CMV) IgG antibodies [overall n=787/1428, 55.1%; when considering only patients with an available CMV serology: n=787/972, 81%). At baseline median HIV-RNA was 4.80 log copies/mL. Median absolute CD4 count and CD4/CD8 ratio were 323 cells/µL and 0.32, respectively.

The prescribed first-line ART regimen was InSTI-, PI-, and NNRTI-based in 21.5% (n=307: 156 dolutegravir, 85 elvitegravir, 66 raltegravir), 44.5% (n=636: 178 darunavir, 192 atazanavir, 249 lopinavir, 17 other PIs) and 34.0% (n=485: 327 efavirenz, 148 rilpivirine, 9 nevirapine, 1 etravirine) of PLWH, respectively. PLWH in the three treatment arms significantly differed for several baseline characteristics (see table 1), as expected on the basis of the evolution of treatment guidelines over time and on prescription attitudes of caring physicians. Regarding baseline immunological status, PLWH treated with InSTI- or NNRTI-based regimens showed similar absolute CD4 count, CD4 percentage and CD4/CD8 ratio (p>0.100 for all comparisons), but these parameters were significantly lower in the PI-based group (p<0.001 for all comparisons). Of note,

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baseline immunological parameters (absolute CD4 count, CD4 percentage and CD4/CD8 ratio) did not significantly differ between the three treatment arms in the subgroup of advanced naïve PLWH (i.e. those with baseline CD4 ≤200 cells/µL)(data not shown).

Incidence and predictors of CD4/CD8 ratio normalization (CD4/CD8 ratio ≥1)

Over a median follow-up of 12.5 (IQR 5.9-27.0) months, 341 (23.9%) PLWH showed CD4/CD8 ratio normalization. Overall, incidence of CD4/CD8 normalization was 14.1 per 100 person-year of follow-up (PYFU). The estimated proportion of CD4/CD8 normalization at 12, 24 and 36 months was 11.9% (95%CI 9.9-13.9), 27.7% (95%CI 24.6-30.8) and 38.6% (95%CI 34.9-42.3), respectively (figure 1a).

Kaplan-Meier analysis showed that the probability of CD4/CD8 normalization was higher for InSTI-based regimens when compared to NNRTI-based and PI-based regimens (log rank test: p<0.001)(figure 1b). The estimated proportion of CD4/CD8 normalization at 36 months was 66.3% (95% CI 56.3-77.1), 39.6% (95% CI 33.7-45.5) and 27% (95% CI 21.7-32.3) for InSTI, NNRTI and PI. However, when we considered separately each drug within the InSTI class, no significant difference in CD4/CD8 normalization was observed between raltegravir, elvitegravir and dolutegravir (data not shown). Analyzing CMV serology, the probability of CD4/CD8 normalization was higher for PLWH showing absence of IgG antibodies (log rank test: p<0.001)(figure 1c). The estimated proportion of CD4/CD8 normalization at 36 months was 66.3% (95%CI 58.5-74.1) for those with negative CMV IgG versus 33.2% (95%CI 28.1-38.3) for positive CMV IgG. A sex stratified analysis is shown in supplementary figure 1.

Analyzing predictors of time to CD4/CD8 normalization by multivariate Cox regression analysis (table 2), PI-based regimens confirmed a significantly lower probability of reaching CD4/CD8 ratio ≥1 (adjusted hazard ratio, aHR 0.47 , 95%CI 0.34-0.65, p<0.001) when compared to InSTI, while

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for NNRTI a trend toward significance was observed (aHR 0.74, 95%CI 0.55-1.01, p=0.056). Also PLWH with positive CMV serology (aHR 0.50, 95%CI 0.38-0.66, p<0.001), with a longer time between HIV diagnosis and ART initiation (aHR 0.94 per one year increase, 95%CI 0.91-0.98, p=0.001), and showing blips (aHR 0.70, 95%CI 0.50-0.98, p=0.035) showed a lower probability of CD4/CD8 ratio normalization; at the opposite higher baseline HIV-RNA (aHR 1.35 per 1 log increase, 95%CI 1.11-1.63, p=0.002), CD4 percentage (aHR 1.09 per 1% increase, 95%CI 1.07-1.12, p<0.001) and CD4/CD8 ratio (aHR 1.14 per 0.10 increase, 9%%CI 1.07-1.22, p<0.001) were associated with a higher probability of CD4/CD8 ratio normalization.

Since the groups of PLWH treated with InSTI, NNRTI and PI significantly differed at baseline for viroimmunological characteristics, we performed a sensitivity analysis in the subgroup of PLWH with baseline CD4 ≤200 cells/mmc (n=384), to confirm the association between the type of first-line regimen and CD4/CD8 normalization in a more homogeneous population. In this subgroup, NNRTI-based (aHR 0.84, 95%CI 0.02-0.35, p=0.001) and PI-based (aHR 0.01, 95%CI 0.00-0.05, p<0.001) regimens confirmed the lower probability of reaching CD4/CD8≥1 when compared to InSTI (Supplementary Table 1). Moreover, to control also for the time to ART initiation which was different in the three treatment arms, we performed a further sensitivity analysis including only patients who started ART within 3 months from HIV diagnosis (n=268) and main results were confirmed (when compared to InSTI: NNRTI aHR 0.13, 95%CI 0.02-0.86, p=0.034; PI aHR 0.01, 95%CI 0.00-0.06, p<0.001).

Incidence and predictors of optimal immunological recovery

Over a median follow-up of 13.6 (IQR 6.1-31.0) months, 308 (21.6%) PLWH showed OIR. Overall, incidence of OIR was 12.0 per 100 PYFU. The estimated proportion of OIR at 12, 24 and

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36 months was 8.6% (95% CI 6.8-10.4), 19.7% (95% CI 17.0-22.4) and 32.9% (95% CI 29.2-36.6), respectively (figure 1d).

The probability of OIR was higher for InSTI-based regimens when compared to NNRTI-based and PI-based regimens (log rank test: p<0.001)(figure 1e). The estimated proportion of OIR at 36 months was 53.3% (95% CI 42.5-64.1), 33.7% (95% 27.8-39.6) and 24.3% (95% CI 19.2-29.4) with InSTI, NNRTI and PI. However, when we considered separately each drug within the InSTI class, no significant difference in OIR was observed between raltegravir, elvitegravir and dolutegravir (data not shown). Moreover, when considering CMV serology, the probability of OIR was higher for PLWH showing absence of IgG antibodies (log rank test: p<0.001)(figure 1f). The estimated proportion of OIR at 36 months was 54% (95%CI 45.6-62.4) for those with negative CMV IgG versus 29.4% (95%CI 24.5-34.3) for positive CMV IgG. A sex stratified analysis is shown in supplementary figure 2.

Analyzing predictors of time to OIR by multivariate Cox regression analysis (table 3), PI-based (aHR 0.53, 95%CI 0.37-0.76, p<0.001) and NNRTI-based (aHR 0.72, 95%CI 0.52-1.00, p=0.047) regimens confirmed a significantly lower probability of OIR when compared to InSTI. Also PLWH with positive CMV serology (aHR 0.62, 95%CI 0.47-0.83, p=0.001), a longer time between HIV diagnosis and ART initiation (aHR 0.94 per one year increase, 95%CI 0.91-0.98, p=0.003) and those showing blips (aHR 0.65, 95%CI 0.45-0.92, p=0.016) showed a lower probability of OIR; at the opposite higher baseline HIV-RNA (aHR 1.45 per 1 log increase, 95%CI 1.18-1.77, p<0.001), CD4 percentage (aHR 1.11 per 1% increase, 95%CI 1.08-1.13, p<0.001) and CD4/CD8 ratio (aHR 1.08 per 0.10 increase, 95%CI 1.01-1.15, p=0.034) were associated with a higher probability of OIR.

In a sensitivity analysis in the subgroup of PLWH with baseline CD4 ≤200 cells/µL (n=384), NNRTI-based (aHR 0.05, 95%CI 0.01-0.27, p<0.001) and PI-based (aHR 0.01, 95%CI 0.00-0.02, p<0.001) regimens confirmed the lower probability of OIR when compared to InSTI

(Supplementary Table 1). Main results were confirmed also when we analyzed only patients who started ART within 3 months from HIV diagnosis (n=268)(when compared to InSTI: NNRTI aHR 0.08, 95%CI 0.01-0.56, p=0.011; PI aHR 0.01, 95%CI 0.00-0.02, p<0.001).

DISCUSSION

Despite stable virological control and adequate increase in absolute CD4 count, a proportion of treated PLWH still presents an imbalance in immune function, which is associated to non-AIDS related morbidity[11]. The CD4/CD8 ratio and the OIR index (a composite marker combining absolute CD4 count, CD4 percentage and CD4/CD8 ratio) have been proposed as tools to evaluate immune recovery in the setting of virological suppression[7,14]. However, it is unclear whether different classes of antiretrovirals can be associated with better immunological recovery, and predictors of CD4/CD8 ratio normalization and OIR need to be fully elucidated.

In our study, we observed that InSTI use increased the probability of CD4/CD8 ratio normalization and optimal immunological recovery when compared to other drug classes. Most importantly, this finding was confirmed and reinforced in a homogeneous population of advanced naïve PLWH (i.e. those with CD4 <200 cells/µL), that currently still represents nearly 30% of new HIV diagnosis in European countries[26]. Current guidelines recommend the use of InSTI in first-line regimen for their efficacy and tolerability[27]. Our data seem to support the use of InSTI-based regimens as first-line ART also from an immunological point of view.

Some previous studies have investigated the potential influence of first-line regimens on CD4/CD8 recovery, with conflicting results. Some reports failed to demonstrate an association between InSTI and CD4/CD8 normalization. Milanes-Guisado et al. did not observe an association between immune restoration (measured as CD4 count, CD4 percentage or CD4/CD8 ratio increases) and the class of third antiretroviral drug[19]. Conversely, other reports suggest a better immunological

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outcome with InSTI. In the STARTMRK Trial, raltegravir showed a faster CD4/CD8 ratio normalization when compared to efavirenz[17]. De Salvador-Guillouet et al. showed a strong association between InSTI and CD4/CD8 ratio normalization after one year of follow-up[15], even if in this study the number of patients treated with this drug class was quite small and ART changes were allowed during follow-up. Herrera et al. showed that InSTI had a higher probability of CD4/CD8 ratio normalization at 48 weeks when compared to PI, but this rate was similar to that of NNRTI[18]; however, this study included also PLWH not reaching virological suppression and the follow-up was truncated to 48 weeks. In our study, we observed that the higher rate of CD4/CD8 ratio normalization with InSTI was maintained up to 36 months. Taken together, all these data seem to suggest a certain benefit of InSTI on CD4/CD8 ratio.

OIR is a parameter that has been previously evaluated in PLWH treated during or after acute[13,14] or chronic[28] HIV infection. OIR has the potential to integrate information about absolute CD4 count, CD4 percentage and CD4/CD8 ratio. However, few data are available about the impact of different types of first-line regimens on OIR. In our population, InSTI confirmed an association with OIR when compared to both NNRTI and PI. Such findings further highlight the potential immunological benefits of this drug class. A mechanistic hypothesis for this immunological benefit could be that the InSTI class may decrease inflammation and immune activation more than other antiretroviral classes[29,30], since InSTI are more lipid-friendly[31,32] and may concentrate at higher levels in enterocytes[33]; this last observation is quite important, since HIV infection results in massive depletion of immune cells within the gastrointestinal tract and the resultant microbial translocation may be an important driver of immune activation in HIV[34,35]. The ability of InSTI to rapidly suppress viral replication and the better tolerability of this drug class, which can in turn translate in an improved adherence, might also contribute to our findings.

In our population, we also observed that CMV+ serostatus was a predictor of poorer immune recovery, measured as both CD4/CD8 ratio normalization and OIR. Other previous studies also

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demonstrated that CMV-seropositivity can be related to suboptimal CD4/CD8 ratio[36,37], but its potential association with OIR were not previously investigated. It has been shown that asymptomatic CMV replication can negatively impact on CD4/CD8 ratio recovery, an effect mainly driven by an expansion of CD8 cells[38]. Altogether, these data raise the question whether treatment of asymptomatic CMV co-infection might improve immune recovery in naïve PLWH starting first-line ART[39]. Moreover, since CMV has also been associated to an increased risk of severe non-AIDS-defining events[40], anti-CMV therapeutic interventions could also provide a benefit in terms of morbidity and mortality. Such hypothesis should be further explored in randomized studies. Whether other factors may contribute to explain the association between CMV serology and immune recovery remain to be determined. It has been observed that socioeconomic disparities are associated to the seroprevalence of CMV infection[41]. Indeed, CMV seropositivity could also identify a disadvantaged population that is at increased risk of poor adherence. Unfortunately, socioeconomic status of PLWH included in the analysis was not collected and standardized adherence measurements were not available.

Among the other variables investigated, a shorter time between HIV diagnosis and ART initiation was associated with improved immune recovery defined both as CD4/CD8 ratio normalization and OIR. This finding highlights the need to further implement strategies aimed to improve early diagnosis and treatment of PLWH[42].

Some limitations should be recognized when interpreting the results of our study. Since this was a retrospective non randomized study, some unmeasured confounding factors might have been introduced. Moreover, characteristics of each treatment arm were not fully balanced at baseline. This can be attributable to different prescription attitudes of physicians during routine clinical practice and to variations in drug use over the years according to evolving treatment guidelines; a similar limitation had been previously observed in other studies exploring immune recovery after ART initiation in naïve PLWH[19]. However, to address this issue, we also performed a sensitivity

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analysis in a more homogeneous population of advanced naïve PLWH and results were unchanged. Since this was a retrospective study performed in the routine clinical practice, we could not measure adherence, a factor that could heavily impact on immune recovery. However, all the studied PLWH were followed until virological suppression was maintained and censored in case of virological rebound; as a consequence, low adherence probably had a limited influence on our findings. Another limitation can be that CMV-DNA was not measured, thus making us unable to explore the pathogenic role of asymptomatic active CMV replication on immune reconstitution[43]. Moreover, CMV serology was not determined in a proportion of PLWH; however, when we considered only PLWH with an available CMV serology, the proportion of subjects with a positive IgG result (81%) was similar to that observed in other studies[36,37,40]. Lastly, we did not perform an analysis assessing a potential correlation between each antiretroviral drug class and the incidence of non-AIDS defining events. Despite these limitations, our study has also some strengths such as the involvement of many reference clinics across Italy (which ensure generalizability of the results), the long term follow-up analysed and the inclusion of a large number of PLWH treated with newer InSTIs (which are generally poorly represented in other cohorts)[15–19].

In conclusion, we observed that PLWH treated with InSTI-based first-line ART showed a better immune recovery, when evaluated as CD4/CD8 ratio normalization or OIR. This finding suggests that the type of first-line ART can influence the extent of immune reconstitution and it further supports the use of InSTI as a preferred treatment option in ART naïve PLWH also from an immunological point of view. The potential immunological benefit of early ART is further confirmed by our results and it highlights the need to implement strategies aimed to improve early diagnosis and treatment of PLWH. The slower immune recovery observed in PLWH with positive CMV serology implies that CMV testing can be used as a marker to identify PLWH at higher risk of immunological failure. Whether anti-CMV treatment could be a therapeutic option for CMV-

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seropositive PLWH with inadequate immune recovery should be explored in adequately designed clinical trials.

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Figure 1. Kaplan-Meier curves for the estimation of time to CD4/CD8 ratio normalization (defined as CD4/CD8 ratio ≥1) and optimal immunological recovery (OIR, defined as CD4≥500 cells/mmc plus CD4%≥30% plus CD4/CD8 ratio ≥1).

Notes: Log rank test p<0.001 for figures 1b-c-e-f.

Table 1. Population characteristics at baseline, overall and according to the type of first-line regimen.

	Total population (n=1428)	According to first-line regimen			
		InSTI-based (n=307)	PI-based (n=636)	NNRTI-based (n=485)	p
Male gender	1111 (77.8)	253 (82.4)	461 (72.5)	397 (81.9)	**<0.001**
Age, years[*]	39 (31-46)	40 (32-48)	39 (32-46)	38 (31-46)	0.266
Non Italian born	277 (19.4)	56 (18.2)	147 (23.1)	74 (15.3)	**0.004**
Risk factor for HIV:					**<0.001**
Heterosexual	512 (35.9)	89 (29.0)	255 (40.1)	168 (34.6)	
Homosexual	665 (46.6)	144 (46.9)	254 (39.9)	267 (55.1)	
IDU	81 (5.7)	11 (3.6)	53 (8.3)	17 (3.5)	
Other/unknown	170 (11.9)	63 (20.5)	74 (11.6)	33 (6.8)	
HBsAg-positive	51 (3.6)	9 (2.9)	21 (3.3)	21 (4.3)	0.520
Anti-HCV positive	106 (7.4)	16 (5.2)	66 (10.4)	24 (4.9)	**0.001**
Months from HIV diagnosis[*],[**]	3.9 (0.9-32.3)	1 (0.5-3.3)	3.5 (0.8-40.1)	12.4 (2.1-41.1)	**<0.001**
IgG anti-CMV:					0.061
Negative	185 (13.0)	51 (16.6)	78 (12.3)	56 (11.5)	
Positive	787 (55.1)	164 (53.4)	337 (53.0)	286 (59.0)	
Unknown	456 (31.9)	92 (30.0)	221 (34.7)	143 (29.5)	
HIV-RNA at BL, log copies/mL[*]	4.80 (4.25-5.25)	4.85 (4.31-5.32)	4.90 (4.35-5.35)	4.64 (4.14-5.13)	**<0.001**
CD4 at BL, cells/µL[*]	323 (187-443)	339 (187-503)	273 (138-390)	364 (274-465)	**<0.001**
CD4 % at BL[*]	19 (13-25)	20 (13-27)	17 (10-24)	20 (16-26)	**<0.001**
CD4/CD8 ratio at BL[*]	0.32 (0.20-0.50)	0.36 (0.20-0.55)	0.28 (0.15-0.44)	0.37 (0.25-0.52)	**<0.001**
Type of first-line regimen:					
InSTI-based	307 (21.5)	-	-	-	
NNRTI-based	485 (34.0)	-	-	-	
PI-based	636 (44.5)	-	-	-	
Backbone:					**<0.001**
TDF or TAF + FTC	1199 (84.0)	240 (78.2)	505 (79.4)	454 (93.6)	
ABC + 3TC	123 (8.6)	56 (18.2)	44 (6.9)	23 (4.7)	
Other	106 (7.4)	11 (3.6)	87 (13.7)	8 (1.6)	
Blip during follow-up	236 (16.5)	21 (6.8)	153 (24.1)	62 (12.8)	**<0.001**

Notes: values are expressed as numer (percentage) or [*]median (interquartile range). [**] Fiebig Stage VI.

Abbreviations: 3TC, lamivudine; ABC, abacavir; BL, baseline; CMV, cytomegalovirus; FTC, emtricitabine; HBsAg, hepatitis B surface antigen; IDU, injecting drug use; InSTI, integrase strand transfer inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitors; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Table 2. Predictors of time to CD4/CD8 ratio normalization (Cox regression analysis)

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p	aHR (95% CI)	p
Male gender	0.87 (0.68-1.12)	0.280	0.89 (0.64-1.25)	0.515
Age (per 10 years increase)	0.94 (0.85-1.05)	0.271	1.07 (0.95-1.20)	0.266
Non italian born	0.88 (0.66-1.17)	0.375	0.99 (0.71-1.38)	0.933
Risk factor:				
Heterosexual	Ref		Ref	
Homosexual	1.01 (0.80-1.27)	0.929	0.79 (0.58-1.09)	0.153
IDU	0.65 (0.38-1.11)	0.114	1.34 (0.72-2.50)	0.355
Other/unknown	0.97 (0.64-1.46)	0.873	0.61 (0.37-1.02)	0.061
HBsAg-positive	0.91 (0.47-1.76)	0.772	1.25 (0.63-2.45)	0.525
Anti-HCV positive	0.47 (0.26-0.83)	**0.009**	0.68 (0.36-1.27)	0.224
Time from HIV diagnosis (per 1 year increase)	0.95 (0.92-0.98)	**<0.001**	0.94 (0.91-0.98)	**0.001**
IgG anti-CMV:				
Negative	Ref		Ref	
Positive	0.43 (0.34-0.55)	**<0.001**	0.50 (0.38-0.66)	**<0.001**
Unknown	0.33 (0.25-0.45)	**<0.001**	0.40 (0.29-0.56)	**<0.001**
HIV-RNA at BL (per 1 log copies/mL increase)	0.70 (0.60-0.82)	**<0.001**	1.35 (1.11-1.63)	**0.002**
CD4 at BL (per 100 cells/µL increase)	1.30 (1.25-1.37)	**<0.001**	0.98 (0.91-1.05)	0.528
CD4 % at BL (per 1% increase)	1.11 (1.10-1.12)	**<0.001**	1.09 (1.07-1.12)	**<0.001**
CD4/CD8 ratio at BL (per 0.10 increase)	1.41 (1.35-1.47)	**<0.001**	1.14 (1.07-1.22)	**<0.001**
Type of first-line regimen:				
InSTI-based	Ref		Ref	
NNRTI-based	0.58 (0.45-0.76)	**<0.001**	0.74 (0.55-1.01)	0.056
PI-based	0.31 (0.23-0.42)	**<0.001**	0.47 (0.34-0.65)	**<0.001**
Backbone:				
TDF or TAF + FTC	Ref		Ref	
ABC + 3TC	1.69 (1.19-2.39)	**0.003**	0.90 (0.59-1.35)	0.666
Other	0.66 (0.34-1.28)	0.214	0.78 (0.39-1.57)	0.485
Blip	0.39 (0.29-0.54)	**<0.001**	0.70 (0.50-0.98)	**0.035**

Notes: CD4/CD8 ratio normalization was defined as a CD4/CD8 ratio ≥1.

Abbreviations: 3TC, lamivudine; ABC, abacavir; aHR, adjusted hazard ratio; BL, baseline; CI, confidence intervals; CMV, cytomegalovirus; FTC, emtricitabine; HBsAg, hepatitis B surface antigen; HR, hazard ratio; IDU, injecting drug use; InSTI, integrase strand transfer inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitors; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Table 3. Predictors of time to optimal immunological recovery (Cox regression analysis)

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p	aHR (95% CI)	p
Male gender	0.95 (0.73-1.24)	0.693	0.87 (0.60-1.25)	0.439
Age (per 10 years increase)	0.94 (0.84-1.05)	0.249	1.07 (0.95-1.21)	0.274
Non italian born	0.79 (0.58-1.09)	0.146	0.90 (0.62-1.30)	0.577
Risk factor:				
Heterosexual	Ref		Ref	
Homosexual	1.06 (0.83-1.35)	0.629	0.94 (0.68-1.32)	0.731
IDU	0.66 (0.37-1.17)	0.154	1.76 (0.90-3.45)	0.101
Other/unknown	0.99 (0.63-1.53)	0.950	0.64 (0.36-1.13)	0.125
HBsAg-positive	1.12 (0.58-2.17)	0.741	1.33 (0.67-2.63)	0.420
Anti-HCV positive	0.47 (0.26-0.85)	**0.013**	0.59 (0.31-1.14)	0.116
Time from HIV diagnosis (per 1 year increase)	0.95 (0.92-0.98)	**0.001**	0.94 (0.91-0.98)	**0.003**
IgG anti-CMV:				
Negative	Ref		Ref	
Positive	0.50 (0.39-0.64)	**<0.001**	0.62 (0.47-0.83)	**0.001**
Unknown	0.31 (0.22-0.44)	**<0.001**	0.41 (0.28-0.60)	**<0.001**
HIV-RNA at BL (per 1 log copies/mL increase)	0.72 (0.62-0.86)	**<0.001**	1.45 (1.18-1.77)	**<0.001**
CD4 at BL (per 100 cells/µL increase)	1.33 (1.27-1.40)	**<0.001**	1.02 (0.95-1.10)	0.584
CD4 % at BL (per 1% increase)	1.12 (1.10-1.13)	**<0.001**	1.10 (1.08-1.13)	**<0.001**
CD4/CD8 ratio at BL (per 0.10 increase)	1.39 (1.32-1.45)	**<0.001**	1.08 (1.01-1.15)	**0.034**
Type of first-line regimen:				
InSTI-based	Ref		Ref	
NNRTI-based	0.57 (0.43-0.76)	**<0.001**	0.72 (0.52-1.00)	**0.047**
PI-based	0.33 (0.24-0.45)	**<0.001**	0.53 (0.37-0.76)	**<0.001**
Backbone:				
TDF or TAF + FTC	Ref		Ref	
ABC + 3TC	1.74 (1.20-2.52)	**0.004**	0.89 (0.56-1.39)	0.596
Other	0.71 (0.35-1.44)	0.339	0.85 (0.41-1.78)	0.665
Blip	0.36 (0.25-0.50)	**<0.001**	0.65 (0.45-0.92)	**0.016**

Notes: optimal immunological recovery was defined as an absolute CD4 count ≥500 cells/µL plus CD4 percentage ≥30% plus CD4/CD8 ratio ≥1.

Abbreviations: 3TC, lamivudine; ABC, abacavir; aHR, adjusted hazard ratio; BL, baseline; CI, confidence intervals; CMV, cytomegalovirus; FTC, emtricitabine; HBsAg, hepatitis B surface antigen; HR, hazard ratio; IDU, injecting drug use; InSTI, integrase strand transfer inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitors; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

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Notes: Log rank test p<0.001 for figures 1b-c-e-f.

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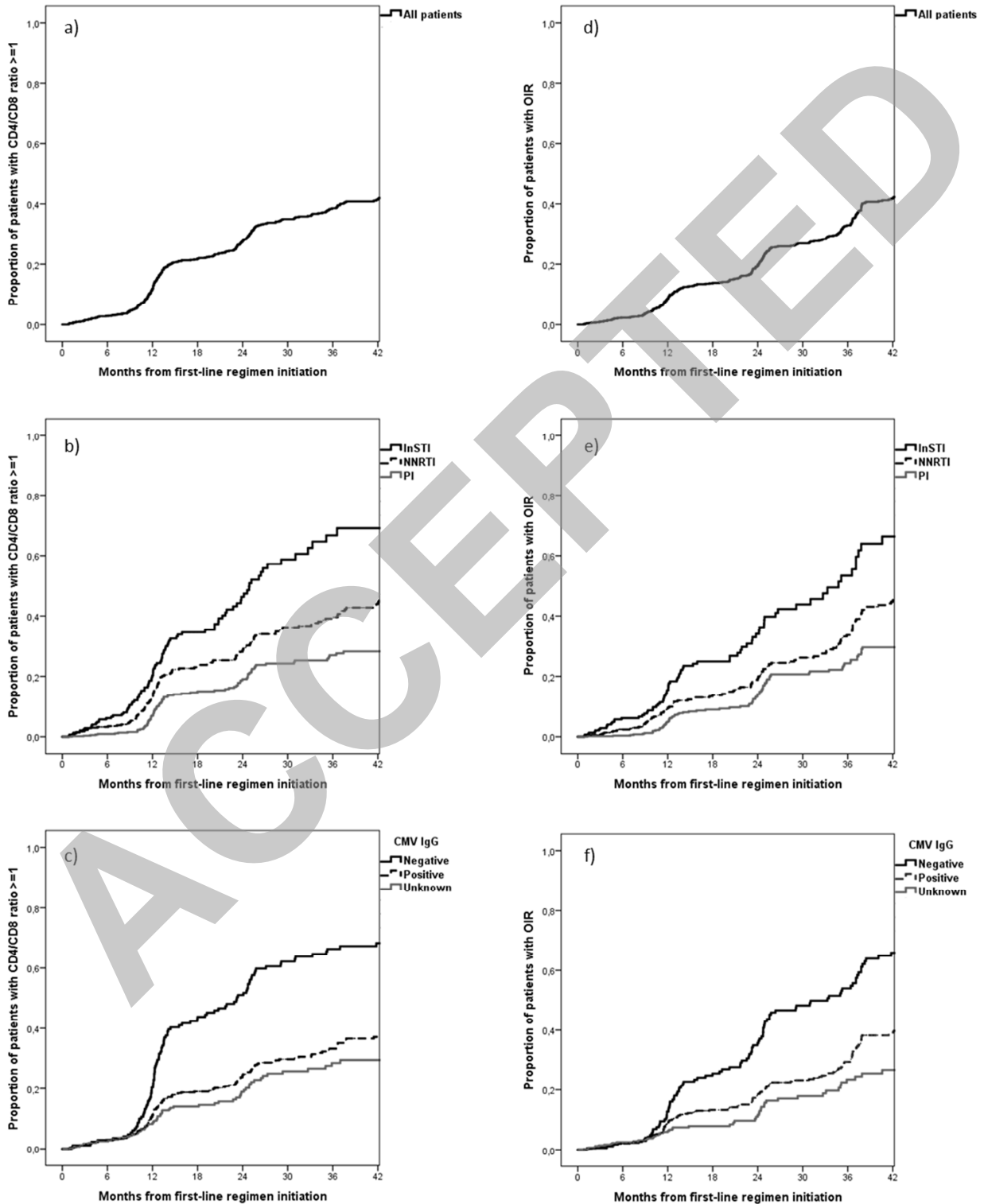
Abbreviations: OIR, optimal immunological recovery; InSTI, integrase strand transfer inhibitors; NNRTI, non nucleoside reverse transcriptase inhibitors; PI, protease inhibitors; CMV, Cytomegalovirus.