Virological and immunological impact of integrase inhibitor-based regimens initiated during primary HIV-1 infection

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Design: Current international guidelines recommend either boosted protease inhibitor (PI/r)-based or integrase inhibitors (INSTI)-based regimens during primary HIV infection (PHI), even though the latter have only demonstrated their superiority at the chronic stage. We compared the effectiveness of INSTI-based versus PI/r-based combined antiretroviral therapy (cART) initiated during PHI.

Methods: This study was conducted among patients who initiated cART between 2013 and 2017, using data from the ANRS-PRIMO cohort and the Dat'AIDS study. Cumulative proportions of patients reaching viral suppression (HIV-1 RNA <50 copies/ml) were calculated using Turnbull's estimator for interval-censored data. $CD4^+$ cells and $CD4^+/CD8^+$ ratio increases were estimated using mixed linear models. Results were adjusted for the data source.

Results: Among the 712 study patients, 299 received an INSTI-based cART. Patients' baseline characteristics were similar between groups. Viral suppression was reached more rapidly in INSTI-treated versus PI/r-treated patients ($P < 0.01$), with cumulative proportions of 32 versus 6% at 4 weeks, 72 versus 31% at 12 weeks, 91 versus 78% at 24 weeks and about 95% in both groups at 48 weeks. At 4 weeks, INSTI-treated patients had gained on average 40 $CD4^+$ cells/μl ($P = 0.05$) over PI/r-treated ones; mean $CD4^+$ counts were similar in the two groups at 48 weeks. The $CD4^+/CD8^+$ ratio followed the same pattern. Results were similar when restricted to a comparison between dolutegravir-based versus darunavir-based cART.

Conclusion: On the basis of this study and available literature, we recommend the use of INSTI-based cART for treatment initiation during PHI, as it leads to faster viral suppression and immune restoration.

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Introduction

Primary HIV infection (PHI) is the early and critical phase in which the virus invades various tissues and establishes viral reservoirs. This phenomenon is key regarding HIV pathogenicity: once in place, the reservoirs' low accessibility to currently available drugs drastically hinders any efforts to achieve viral eradication. Moreover, because of intense virion production, viral load during PHI is at its peak, thus making the host an efficient vector for viral transmission [1].

Because of its critical role in both short-term and long-term HIV pathogenicity, PHI is now considered a key therapeutic window in which combined antiretroviral therapy (cART) should be used to both reduce viral load and tackle viral reservoir establishment.

In recent years, guidelines have evolved towards an earlier cART during PHI: since 2013, it is admitted that treatment should be initiated as soon as treatment comprehension and adhesion is obtained, regardless of symptomatology and $CD4^+$ cell count [2].

In terms of treatment strategy, current international guidelines suggest a combination of two nucleoside analog reverse transcriptase inhibitors (NRTI) with either a boosted protease inhibitor (PI/r) [3,4], preferably darunavir because of high virological power [5] and fair genetic barrier [6], or alternatively an integrase strand transfer inhibitor (INSTI), such as dolutegravir.

INSTI has proven its superiority to PI/r during the chronic phase of the infection in treatment-naïve adults [7]. Yet, the effectiveness of INSTI-based cART has not been fully evaluated in PHI, when viral load is considerably higher [8]: only two small sample-size studies have been published to date [9,10]. In France, in analogy to cART guidelines regarding chronic HIV-1 infection, physicians have started prescribing an INSTI as the third drug (in replacement of a PI/r) for the treatment of PHI patients. Given these new practices, it now seems adequate to compare the effectiveness of these treatment strategies when initiated during PHI.

The objective of this study was to compare the virological and immunological responses among a large sample of 712 patients who initiated treatment during primary HIV-1 infection, between those treated with cART containing two NRTI with INSTI versus those treated with cART containing two NRTI with PI/r.

Methods

Data sources

The data set was extracted from two distinct sources:

The ANRS-PRIMO cohort

The ANRS-PRIMO prospective cohort [11] is a French multicenter cohort (95 centers), enrolling patients diagnosed with HIV-1 during the PHI phase. Once included, patients follow a preestablished follow-up protocol, with physical examination and lab-work performed on a strict schedule. The data were extracted in June 2017.

The ANRS-PRIMO cohort used the following inclusion criteria ($n_{\text{PRIMO}} = 2157$):

1. Aged at least 15 years at the time of enrollment;
2. Antiretroviral-naive (except for transient treatment taken in the context of PEP or PrEP);
3. Symptomatic or asymptomatic HIV-1 primary infection defined as:
   a. Incomplete HIV-1 western-blot profile;
   b. Detectable p24 antigen and/or plasma HIV-RNA with either:
      i. Negative or weakly positive ELISA within the previous 6 weeks;
      ii. Negative or undetermined HIV-1 western-blot within the previous 6 weeks;
   c. Positive ELISA test with a negative or weakly positive ELISA within the previous 3 months;
4. Affiliated to or benefiting from a French social security regimen.

The Dat'AIDS study

The Dat'AIDS study uses data extracted from the Nadis© [12] hospital database, an electronic health record (EHR) that stores clinical and biological data, which is used by several infectious diseases and internal medicine departments in France (18 centers). The data were extracted in January 2017. We removed patients for whom socio-demographic data were absent ($n = 1$) and patients who were already enrolled in the PRIMO cohort ($n = 224$). Linkage between databases was performed on demographic data (birth date and sex) and then manually checked based on biological data (date of sampling and results).

Within the Dat'AIDS database, in order to match PRIMO patients profile, we applied the following criteria ($n_{\text{Dat'AIDS}} = 1330$):

1. Aged at least 15 years at the time of enrollment;
2. Antiretroviral-naive;
3. Symptomatic or asymptomatic HIV-1 primary infection, as the main diagnosis.

Target population

The following inclusion criteria were then applied similarly on all patients, regardless of the data source (Supplementary Figure 1, http://links.lww.com/QAD/B589):

1. cART was initiated after 31 December 2012 ($n_{PRIMO} = 599$; $n_{Dat'AIDS} = 609$). We chose this threshold because the use of INSTI before 2013 was almost nonexistent. Additionally, since 2013, French guidelines stated that all HIV-infected patients should receive cART regardless of clinical and biological features.
2. cART was initiated within 3 days before and 30 days after biological HIV diagnosis ($n_{PRIMO} = 458$; $n_{Dat'AIDS} = 372$).
3. cART was either '2 NRTI + INSTI' or '2 NRTI + PI/r' ($n_{PRIMO} = 404$; $n_{Dat'AIDS} = 308$).

Of note, 4.6% of the patients enrolled in the PRIMO cohort during the study period reported a PrEP intake within 6 months prior to enrollment. This information was not available for patients from the Dat'AIDS database.

Analysis strategy

We first compared baseline patients' characteristics between the two data sources, using Mann–Whitney's *U* test for continuous variables, chi-squared test or Fisher's exact test for categorical variables and Cochran–Armitage test for trend for ordinal variables. We then compared patients characteristics between the two cART groups, '2 NRTI + INSTI' versus '2 NRTI + PI/r'; all comparisons between treatment groups were adjusted for the data source by using a logistic or linear regression model.

Virological response

We analyzed the virological response in a survival setting, where the success was defined as reaching plasma HIV-1 RNA concentration below 50 copies per milliliter. As plasma HIV-1 RNA concentration was measured discretely at each follow-up visit, the actual time of the event was unknown. Thus, we used the Turnbull method [13] to obtain a nonparametric maximum likelihood estimator (NPMLE) for the cumulative distribution function. We then plotted the estimated cumulative distribution curves for each treatment group and calculated the cumulative probability of success at different times since cART initiation (4, 12, 24 and 48 weeks) for each group. We used a generalized logrank test [14], which is an extension of the logrank test for interval-censored data, to compare the estimated cumulated proportion of virological response between treatment groups. We also applied a data source-adjusted log-logistic parametric model, which is particularly efficient for interval-censored data [15], in order to visually display smoothed cumulative distribution curves. We also performed similar comparisons after data source stratification. Finally, we compared the proportions of patients whose viral loads were measured at specific times, and the distributions of the number of viral load measurements since cART initiation, in order to ensure that treatment groups had similar follow-up patterns, thus limiting the risk of measurement bias.

Immunological response

We analyzed the immunological response using a longitudinal mixed model on $CD4^+$ measurements, taking into account intra-individual correlation. We truncated longitudinal data at 435 days in order to obtain similar follow-up distributions between treatment groups. We tested several clinically relevant break points and we retained the best model based on the Akaike Information Criterion (AIC). The models were adjusted for the data source. Additionally, we deliberately omitted the treatment group main effect in order to adjust for $CD4^+$ baseline values [16]. We then tested the regression coefficients with Student's *t*-tests and plotted each treatment group $CD4^+$ predicted trajectory (mean predicted values and prediction intervals) using a bootstrap procedure (1000 iterations). We calculated model-based prediction intervals at several times since cART initiation (4, 12, 24 and 48 weeks).

We applied the same strategy for the analysis of $CD4^+/CD8^+$ ratio increase.

Sensitivity analyses

We performed two sensitivity analyses:

1. A 'per-protocol'-like setting analysis, where patients stopping or switching cART regimen were censored at the time of first-line cART interruption. We did not consider a switch of one or more cART drug within the same class.
2. A drug-specific analysis, where we only considered patients treated with either Darunavir (for the PI/r-treated group) or Dolutegravir (for the INSTI-treated group).

Short-term tolerability assessment

In order to detect a possible difference in terms of early adverse effects between treatment groups, we compared the cumulative proportions of cART interruption or switch of any drug from the first line cART within the first 3 months of treatment by using Kaplan–Meier method and logrank test. Data were truncated after 3 months.

Additionally, we compared treatment groups in terms of weight gain at different times following cART initiation. We considered weights measured within a 60-day window centered on each specified time. When multiple measures were available within this time window, we chose the closest one to the specified time. We plotted the distributions of weight gain in each treatment group from cART initiation until 6, 12, and 24 months, and we tested for a difference of mean weight gain at each time using bilateral Welch's *t* tests. Finally, we tested for a difference of weight gain at each time between treatment groups by using a logistic regression model adjusted for the data source.

Results

Study patients

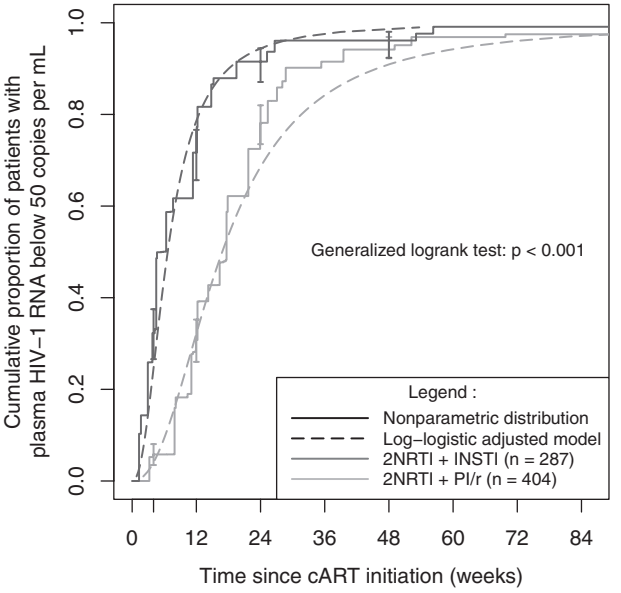
Seven hundred and twelve patients initiating cART during PHI were included in this study, 404 from the PRIMO cohort and 308 from the Dat'AIDS study (Supplementary Table 1, http://links.lww.com/QAD/B589). There were some marginally statistically significant differences between data sources: the PRIMO cohort enrolled a larger proportion of self-reported homosexual/bisexual men (80.1 versus 71.2%, $P = 0.03$) and comprised less sub-Saharan-born patients (4.5 versus 9.5%, $P = 0.01$) than the Dat'AIDS study; PRIMO patients were also heavier at baseline (70 versus 68 kg, $P = 0.02$), but this difference was not statistically significant after adjustment for sex and geographical origin ($P = 0.08$).

Overall, 413 patients received a PI/r-based regimen as a first line and 299 received an INSTI-based one (Table 1). PI/r-treated patients initiated cART earlier in terms of calendar time, thus their follow-up period was longer. INSTI-treated patients were more often drawn from the PRIMO cohort than PI/r-treated ones (63.9 versus 51.6%, $P < 0.01$). They were less often male patients than PI/r-receiving patients (88.3 versus 92.5%, data source-adjusted $P = 0.03$). Distribution of HIV-RNA, $CD4^+$ cell count, and $CD4^+/CD8^+$ ratio baseline values, measured within 7 days before and 3 days after cART initiation, did not differ between treatment groups.

Dolutegravir and darunavir were the most prescribed drugs among the INSTI-treated group (54.8%) and the PI/r-treated group (94.7%), respectively (Supplementary Table 2, http://links.lww.com/QAD/B589).

Virological response

Virological response (Fig. 1; Supplementary Table 3, http://links.lww.com/QAD/B589) was studied in 691 patients with available plasma HIV-RNA measurements from cART initiation (13 patients from PRIMO and 8 from Dat'AIDS were excluded from this analysis, constituting 9 PI/r-treated patients and 12 INSTI-treated ones).



Number of patients still at risk:

	cART initiation	4 weeks	12 weeks	24 weeks	48 weeks
INSTI	287	186.4	69.5	17.3	6.4
PI/r	404	375.7	263.4	79.3	20.3

Fig. 1. Comparison of virological response between integrase strand transfer inhibitor-based and protease inhibitor-based regimens initiated during primary HIV infection: cumulative distribution curves; the numbers of patients at risk are not integers because of the Turnbull method.

The cumulative proportion of patients with virological success was significantly higher for the INSTI-treated group (generalized logrank test: $P < 0.01$). At 4 weeks after cART initiation, the cumulative proportion of success for INSTI-treated patients was 32% (27–38%) versus 6% (3–8%) for PI/r-treated ones. This difference

Table 1. Comparison of baseline patient characteristics between combined antiretroviral therapy groups.

Variables at cART initiation	PI/r $n = 413$	INSTI $n = 299$	Data source-adjusted P value
Patients from PRIMO (versus Dat'AIDS)	213 (51.6%)	191 (63.9%)	<0.01
Male sex	382 (92.5%)	264 (88.3%)	0.03
Age (years)	34 [26; 45]	36 [27; 44]	0.63
Weight (kg)	69 [62; 77]	69 [61; 78]	0.90
Sub-Saharan-African-born	30 (8.0%)	13 (4.5%)	0.12
Self-reported homo/bisexual male	295 (76.8%)	205 (75.1%)	0.61
Follow-up duration (months)	23.9 [8.5; 35.9]	11.6 [3.8; 18.7]	<0.01
Delay from diagnosis to cART (days)	10 [6; 17]	10 [6; 16]	0.80
HIV-1 RNA (log10 copies/ml)	5.88 [5.1; 6.67]	5.68 [4.92; 6.58]	0.13
$CD4^+$ cell count (cells/μl)	458 [318; 618]	456 [326; 609]	0.60
$CD4^+/CD8^+$ ratio	0.52 [0.31; 0.79]	0.53 [0.33; 0.88]	0.10

Categorical variables are displayed as 'number (percentage)'. Continuous variables are displayed as 'median [Q1; Q3]'. We only considered biological values measured between 7 days before until 3 days after cART initiation. All P values were adjusted for the data source by using multivariate logistic or linear regression models, except for the data source comparison. cART, combined antiretroviral therapy.

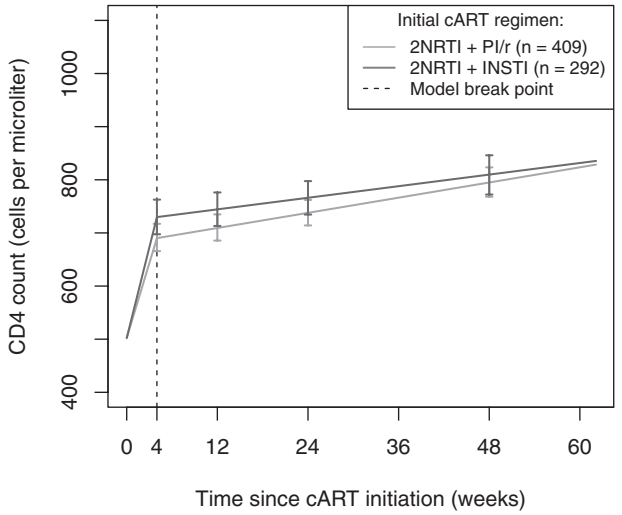


Fig. 2. Comparison of immunological response between integrase strand transfer inhibitor-based and protease inhibitor-based regimens initiated during primary HIV infection: $CD4^+$ count trajectories.

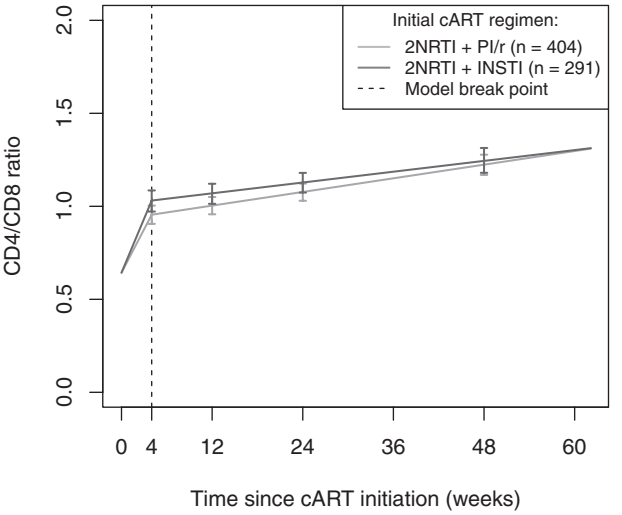


Fig. 3. Comparison of immunological response between integrase strand transfer inhibitor-based and protease inhibitor-based regimens initiated during primary HIV infection: mean $CD4^+/CD8^+$ ratio trajectories.

persisted at 12 weeks [72% (65–76%) versus 31% (26% – 36%)] and 24 weeks [92% (87–94%) versus 78% (73–82%)], and faded off at 48 weeks, when both groups reached high success proportions [96% (92–98%) versus 94% (91– 96%) respectively]. Similar results were obtained after data source stratification, or when only considering male patients, as well as in sensitivity analyses. At all times of interest, we observed similar proportions of patients whose viral loads were measured and similar distributions of the number of viral load measurements since cART initiation between treatment groups (Supplementary Figure 2, http://links.lww.com/QAD/B589).

Immunological response: $CD4^+$ cell count

$CD4^+$ immunological response (Fig. 2; Supplementary Table 4, http://links.lww.com/QAD/B589) was studied in 701 patients with available $CD4^+$ measurements after cART initiation (4 PI/r-treated and 7 INSTI-treated patients were excluded from this analysis).

The most fitted model was one with a single break point at 4 weeks after treatment initiation. In PI/r-treated patients, the model estimated a mean gain of 47 (95% prediction interval: 40–54) $CD4^+$ per week from cART initiation until the 28th day. INSTI-treated patients showed an additional gain of +10 (0–20) $CD4^+$ per week ($P = 0.05$). Predictions from the model, with both groups starting from the same baseline [501 (483–521) cells/μl), showed a greater mean increase of 40 $CD4^+$ for INSTI-treated patients at 4 weeks [729 (696–761) cells/μl versus 689 (663–715) cells/μl). Afterwards, PI/r-treated patients gain was 2 (2–3) $CD4^+$ per week, not different from the gain in INSTI-treated patients ($P = 0.17$). At 48 weeks, mean $CD4^+$ counts did not differ between groups [809 (773–843) cells/μl versus 794 (766–822) cells/μl], with an overall mean gain of around 300 cells/μl in both groups. Similar results were obtained when considering only male patients, as well as in sensitivity analyses.

Immunological response: $CD4^+/CD8^+$ ratio

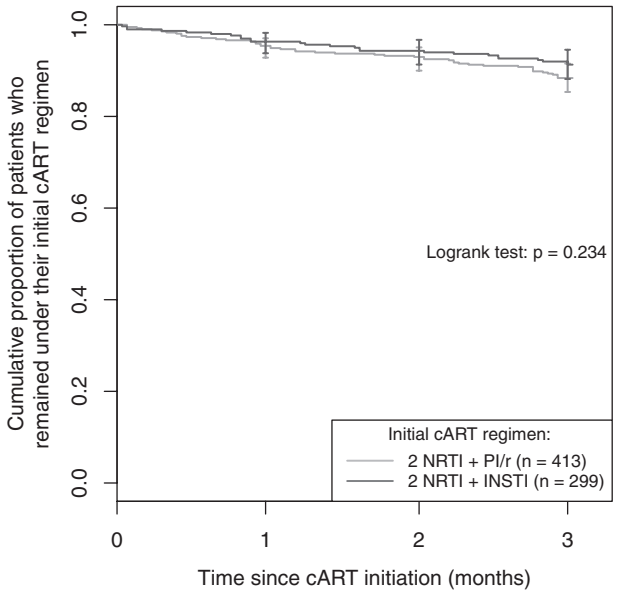
The $CD4^+/CD8^+$ ratio immunological response (Fig. 3; Supplementary Table 5, http://links.lww.com/QAD/B589) was studied in 695 patients with simultaneously available $CD4^+$ and $CD8^+$ measurements after cART initiation (9 PI/r-treated and 8 INSTI-treated patients were excluded from this analysis).

Similar to $CD4^+$ analysis, data were truncated at 435 days and a single 28th day break point mixed segmented model was used. The model estimated a mean gain of 0.08 [0.06–0.09] of $CD4^+/CD8^+$ ratio per week from cART initiation until the 28th day in PI/r-treated patients. INSTI-treated patients showed an additional gain of +0.02 (0–0.04) per week ($P = 0.03$). Predictions from the model, with both groups starting from the same baseline [0.64 (0.59–0.7) $CD4^+/CD8^+$ ratio), showed a greater mean increase of 0.08 for INSTI-treated patients at 4 weeks [1.03 (0.97–1.09) versus 0.95 (0.91–1.01)]. Afterwards, gain in PI/r-treated patients was less than 0.01 per week, not different from the one in INSTI-treated patients ($P = 0.12$). At 48 weeks, there was no difference between groups [1.24 (1.18–1.31) versus 1.22 (1.17–1.28)], with an overall mean gain of around 0.6 $CD4^+/CD8^+$ ratio points in both groups. Similar results were obtained when considering only male patients, as well as in sensitivity analyses.

Short-term tolerability assessment

Early treatment switches or interruptions

Kaplan–Meier curves (Fig. 4; Supplementary Table 6, http://links.lww.com/QAD/B589) showed similar



Number of patients still at risk:

	cART initiation	1 month	2 months	3 months
INSTI	299	288	282	275
PI/r	413	394	384	365

Fig. 4. Comparison of frequency of combined antiretroviral therapy switch or interruption between integrase strand transfer inhibitor-based and protease inhibitor-based regimens initiated during primary HIV infection, within the first 3 months from initiation.

trends in early treatment switch or interruption between groups (logrank test $P = 0.23$): at 1 month, 95% (93–97%) of PI/r-treated patients were still under their initial cART drug regimen versus 96% (94–98%) for INSTI-treated ones. At 3 months, these proportions were 88% (85–92%) versus 91% (88–95%), respectively. Similar results were obtained after adjusting for the data source or when considering only male patients.

Weight gain since treatment initiation

Weight gain did not differ between groups: at 6 months, PI/r-treated patients had gained on average 1.8 (standard deviation = 4.3) versus 1.6 (3.2) kg for INSTI-treated ones ($P = 0.57$ and data source-adjusted $P = 0.62$); at 12 months, PI/r-treated patients had gained on average 2.8 (5.1) versus 1.8 (3.6) kg for INSTI-treated ones ($P = 0.08$ and data source-adjusted $P = 0.11$); at 24 months, PI/r-treated patients had gained on average 2.2 (5.7) kg versus 3.0 (5.4) kg for INSTI-treated ones ($P = 0.49$ and data source-adjusted $P = 0.61$).

Discussion

This is the largest study to date comparing virological and immunological responses between INSTI-based and PI/r-based drug regimens initiated during PHI, gathering 712 patients from two different multicenter data sources.

First, we highlight the benefits of the INSTI class regarding the virological response when initiated during PHI: the cumulative proportion of success for INSTI-treated patients versus PI/r-treated ones was 32 versus 6% after 4 weeks following cART initiation, 72 versus 31% after 12 weeks, 92 versus 78% after 24 weeks, and 96 versus 94% after 48 weeks. Results for PI/r-treated patients are in line with data from the literature [9,17]. The faster virological response in INSTI is consistent with what has been shown both in a large clinical trial performed on patients treated during the chronic phase of HIV [7] and an observational study in treatment-naïve patients [18], who had lower viral load at baseline than in our study. It is also in line with previous findings regarding raltegravir-intensified ART among severely immunocompromised sub-Saharan African patients [19]. This faster viral suppression is of clinical interest as it could reduce HIV-induced inflammation and prevent neurological damage [20,21]. From a public health perspective, PHI patients are a major potential source of onward HIV transmission [22,23] because of high genital and plasma viral load [24]. As early initiation of cART leads to a decrease in HIV-1 transmission [25], we hypothesize that early viral suppression through the high virological power of INSTI-based regimen makes it a candidate of choice for reducing transmission clusters. This is of particular importance in highly sexually active populations of MSM.

Regarding the immunological impact, INSTI-treated patients gained 40 $CD4^+$ cells more than PI/r-treated ones during the first 4 weeks following treatment initiation ($P = 0.05$). This higher early-acquired $CD4^+$ count in INSTI-treated patients, albeit the difference was of modest magnitude, was compensated during the following weeks for PI/r-treated patients: both groups reached similar $CD4^+$ counts at 48 weeks, with a mean gain of around 300 $CD4^+$ from baseline. Of note, this gain of approximately 300 $CD4^+$ cells over year was superior by almost 50% to what is observed in chronically infected patients [7]. A higher $CD4^+$ gain for patients treated in PHI versus patients treated during the chronic phase has already been shown [26]. The $CD4^+/CD8^+$ ratio followed a similar trend: INSTI-treated patients showed an additional gain of +0.08 ($P < 0.05$) during the first 4 weeks following treatment initiation. Thereafter, similar $CD4^+/CD8^+$ ratios were reached at 48 weeks, about 0.6 ratio points above baseline level. These results are consistent with previous findings regarding the benefits of cART initiation during acute/early infection regarding $CD4^+$ restoration [27], $CD4^+/CD8^+$ ratio normalization [28], and overall T-cell immune functions [29].

This study has some limitations. First, no treatment compliance data were available. However, the dolutegravir versus darunavir comparison consisted of comparing

treatment groups with similar intake modalities (oral administration, only once a day), thus limiting the risk of a potential compliance bias. Second, previous antiretroviral drug intake in the context of PEP or PrEP might have affected the patients' virological response. However, only 4.6% of the PRIMO patients reported to have been exposed to PrEP within 6 months prior to enrollment. To our knowledge, none of them was infected while taking PrEP. Regarding the Dat'AIDS study, which contained a lower proportion of self-reported homosexual/bisexual men, it is reasonable to believe that the percent of PrEP-exposed patients was even lower. Moreover, considering the short half-life of drugs that are standardly used in PEP and PrEP strategies, such preenrollment antiretroviral exposure is unlikely to have affected the viral suppression rate. Third, short-term tolerability could only be assessed by the frequency of treatment switch/interruption and by weight gain, both of which were similar between groups. Regarding the latter, our results do not confirm some recent findings [30], but long-term tolerability remains to be assessed. Finally, this was an observational study, and thus patients were not randomly assigned to a treatment group. Even though most baseline characteristics had similar distributions between treatment groups, this does not fully prevent from a potential indication bias as there could be unmeasured confounding factors. Of note, adjustment for the data source, sex stratification, 'per-protocol' analysis and drug-specific analysis led to similar results.

Conclusion

On the basis of this study and available literature, we recommend the use of INSTI-containing cART for patients being treated during PHI, as it leads to earlier virological response and faster immune restoration. Considering early cART initiation has been shown to offer long-term reduction in HIV reservoir size [26], we hypothesize that the earlier virological response obtained with INSTI-based regimen used during PHI could translate into reduced size of viral reservoirs. This specific question is to be addressed in the ongoing ANRS OPTIPRIM 2 clinical trial.

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Contributions from authors: R.V., A.C., and L.M. designed the study. L.T. extracted the data. R.V. and L.M. performed the data analysis. R.V. produced the figures and tables. R.V., A.C., and L.M. wrote the first version of the manuscript. I.P.M., J.R., C.G., R.S., P.D., L.C., C.D., D.R., L.S., C.A., and C.L.C. contributed to data collection and writing of the manuscript.

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Conflicts of interest

There are no conflicts of interest.

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