C_{trough} decreased 22%, 11% and 38%, respectively.[5] This decrease in dolutegravir parameters in healthy volunteers was not considered to be clinically relevant by the authors. Our study confirmed this hypothesis and demonstrated adequate plasma concentrations following the once-daily dosing of 800/100 mg darunavir/ritonavir plus 50 mg dolutegravir. No significant change in liver, renal or haematological function was reported.

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Transparency declarations

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High decay of blood HIV reservoir when tenofovir/emtricitabine/elvitegravir/cobicistat is initiated during the acute primary HIV infection

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Sir,

Early treatment during primary HIV infection (PHI) brings benefits by reducing the circulating viral load and the size of the reservoirs.[1] The French guidelines[2] propose to treat PHI with a triple antiretroviral combination including two NRTIs plus a third agent: an integrase strand transfer inhibitor (INSTI) or a PI. Among INSTIs, dolutegravir was chosen because of its bioavailability, virological power, genetic barrier and limited drug interactions although there is no clinical trial evaluating it in this context.

The use of the combined form of abacavir/lamivudine/dolutegravir to treat PHI is limited due to the need for human leucocyte antigen (HLA) typing to exclude the abacavir sensitivity conferred by HLA B*57:01. Data on the use of tenofovir/emtricitabine/elvitegravir/cobicistat in this indication are also limited. This elvitegravir combination presents the advantage of a single tablet without risk of hypersensitivity and the cobicistat pharmacokinetic boost allows rapid acquisition of elvitegravir plasma levels compatible with optimal virological efficacy.

Table 1. Viro-immunological characteristics of PHI patients treated with tenofovir/emtricitabine/elvitegravir/cobicistat

Patient	Age (years)	Sex	Delay of treatment (days)	Origin	Fiebig stage	Length of treatment (months)	HIV RNA copies/mL	HIV DNA copies/10^6 PBMCs	CD4 cells/mm^3
1	47	male	4	France	2	D0	1543000	270	500
						M1	46	59	1144
						M2	<40	37	1129
						M4	<40	<8	1012
						M6	<40	27	NA
						M12	<20	17	1317
						M18	<20	<8	1183
2	39	male	NA	France	2	D0	10000000	NA	177
						M2	74	264	395
						M4	<20	107	NA
						M8	24	90	NA
						M12	36	155	380
						M18	<20	8	561
3	43	male	28	France	4	D0	86053	NA	532
						M1	<40	129	662
						M4	<20	109	1484
						M8	<20	<70	NA
						M12	69	182	991
						M18	<20	63	1104
4	34	male	4	France	2	D0	10000000	NA	278
						M1	51	9	NA
						M3	43	43	NA
						M7	<20	191	762
						M12	<20	210	683
						M18	<20	<8	635
5	27	male	NA	France	2	D0	8469000	9386	297
						M1	221	373	658
						M3	0	82	851
						M7	0	286	799
						M12	29	34	937
						M18	34	137	619
6	52	male	5	France	3	D0	9740000	6947	413
						M1	<20	<8	586
						M3	<20	74	618
						M6	<20	NA	517
						M12	<20	<8	526

D0, day 0, M, month; NA, not available.

We report a case series of patients with PHI treated with tenofovir/emtricitabine/elvitegravir/cobicistat; we monitored blood total HIV DNA load, a biomarker estimating the viral reservoir.[3]

Six patients were included from April 2014 to August 2015. The plasma HIV RNA load was initially measured by a real-time HIV-1 RT-PCR method (mp2000 Abbott®) with a detection limit of 40 HIV RNA copies/mL and then by a different method (Cobas 6800 Roche®) with a detection limit of 20 HIV RNA copies/mL. The level of total HIV DNA was quantified in whole blood cells by ultrasensitive real-time PCR targeting the long terminal repeat region using the ANRS consensus technique (Biocentric®, France).[4] Results are expressed as number of HIV-1 DNA copies/10^6 PBMCs, with a detection threshold of 8 copies/10^6 PBMCs. Follow-up was performed up to 18 months.

The six patients were MSM, with a median age of 41 years (range = 27–52). Four of them were Fiebig stage 2[5] and the two other patients were Fiebig stage 3 and 4, respectively. At initiation of ART, the median HIV RNA was 6.95 $\log_{10}$ (IQR = 6.18 $\log_{10}$–7 $\log_{10}$) with a median CD4 count of 355 cells/mm^3 (IQR = 278–500). The median level of HIV DNA was 3.84 $\log_{10}$ copies/10^6 PBMCs (IQR = 2.73–3.97). The ART was started a median of 4.5 days (IQR = 4–16.5) after the diagnosis of the PHI. The status of optimal viro-immunological responder (OVIR) was defined as HIV RNA <50 copies/mL and HIV DNA <2.3 $\log_{10}$ copies/10^6 PBMCs, as well as a normalization of immune reconstitution markers: absolute CD4+ T lymphocyte count >500 cells/mm^3, percentage of CD4 T cells >30% and CD4+/CD8+ ratio >1.[6] Five patients obtained OVIR status after a median of 84 days (IQR = 28–336) of treatment. All patients had undetectable HIV RNA at a median of 75 days (IQR = 30–120). The median gain of CD4 at the 12th month was 432 cells/mm^3 (IQR = 203–640) and the median decrease in HIV

RNA at the 1st month was 5.03 $\log_{10}$ (IQR = 4.58 $\log_{10}$–5.3 $\log_{10}$). Two patients reached undetectable blood HIV DNA before the 6th month, but had subsequently low levels of HIV DNA (1.43 and 1.23 $\log_{10}$ copies/10^6 PBMCs for one patient and 1.86 $\log_{10}$ copies/10^6 PBMCs for the other patient). The clinical and viro-immunological characteristics of all six patients are summarized in Table 1.

The impact of early ART in PHI is now well validated given the clinical, virological, immunological and epidemiological benefits.[7,8] Only one study reported the use of tenofovir/emtricitabine/elvitegravir/cobicistat in PHI, with a gain of 350 CD4 cells at week 48 and a rapid decrease in viral load at week 4.[9] Our study confirms these results by showing an early and sustained virological response and provides additional data on the decrease in HIV DNA in PHI treated with tenofovir/emtricitabine/elvitegravir/cobicistat.

The OVIR status was obtained in five of six patients less than 120 days after ART initiation. This may reflect the correct diffusion in sanctuaries, although there are no data on the diffusion of INSTIs in the CNS and the digestive compartment.

The natural polymorphism of the integrase gene varies and minor mutations may affect the efficacy of INSTIs.[10] Thus, a prevalence around 1.5% of polymorphic INSTI mutations was described in the French PHI cohort (FPC), with a predominance of the E157Q mutation. In addition, transmitted viruses may carry NRTI mutations (prevalence of 5.2% in the FPC), affecting the tenofovir/emtricitabine backbone and then weakening elvitegravir, a molecule presenting a lower genetic barrier to resistance than dolutegravir.[11]

Tenofovir/emtricitabine/elvitegravir/cobicistat use requires vigilance when prescribed during PHI and there is a need to check the results of drug resistance testing as soon as possible after ART initiation to exclude the presence of any transmitted or polymorphic drug resistance mutation.[12]

Tenofovir/emtricitabine/elvitegravir/cobicistat is a potent ART, which can reduce the HIV reservoir when initiated swiftly following the PHI. Further data are needed to confirm full diffusion of the drugs in the reservoirs and to compare with other antiretroviral combinations. This combination could represent a therapeutic option in the management of PHI.

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