Short communication

Response to HAART in French patients with resistant HIV-1 treated at primary infection: ANRS Resistance Network

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Objective: The aim of the study was to analyse the response to highly active antiretroviral therapy (HAART) initiated at the time of primary HIV infection (PHI) in patients infected with a virus resistant to ≥1 drug of their treatment compared with patients infected with a wild-type virus.

Methods: We analysed data from 350 patients who were enrolled from 1996–2004 in the French ANRS PRIMO Cohort or in the ANRS Resistance Group and treated with HAART during PHI. During the study period, HAART was initiated before the result of the genotypic resistance test was available. We compared patients infected with a virus resistant to ≥1 drug of their regimen (GR group, *n*=46) with patients harbouring a wild-type virus (WT group, *n*=304). Virological and immunological response to treatment according to drug-resistance profile was analysed 3 months and 6 months after HAART initiation.

Results: In GR and WT groups, HIV RNA level was <400 copies/ml in 68% and 83% (*P*=0.02) and <50 copies/ml in 23% and 40% (*P*=0.08) 3 months after HAART initiation. In multivariable logistic regression taking into account gender, age, boosted PI regimen, plasma HIV RNA and CD4$^+$ T-cell count at HAART initiation, patients with virus resistant to ≥1 drug of their regimen were significantly less likely to achieve undetectable viral load at month 3 (odds ratio 0.32, 95% confidence interval 0.15–0.72) than the others. This difference was sustained up to month 6.

Conclusion: In this large cohort of HAART-treated PHI-patients, the presence of drug resistance mutations led to suboptimal response to early therapy.

Introduction

Transmission of drug-resistant HIV-1 (dr-HIV) occurs with a frequency of 5–29% of all primary infections in Europe and in North America [1–9]. In France, the overall incidence of transmitted dr-HIV has been stable since 1996 and has reached 12% [10–12]. Detectable resistance can persist in plasma and in blood cells over 5 years after primary HIV infection (PHI) without drug-selective pressure [13–18]. The

clinical implications are of serious concern because multidrug resistance (MDR) can result in treatment failure and clinical progression of PHI patients with MDR virus [19,20]. Few studies have evaluated the association between baseline susceptibility to anti-HIV drugs and virological response to treatment when patients are treated with HAART at the time of PHI. The objective of this study was to compare the virological and immunological response to HAART in patients harbouring virus resistant to ≥1 drug of their regimen with patients infected with a wild-type virus, all patients being treated at the time of PHI.

Patients and methods

Study population

Our study population comprised patients presenting with PHI, enrolled either in the multicentre prospective French Primo Cohort (ANRS CO 06) [21–23] or in the Primo Study of the ANRS AC11 Resistance Group [12,13] between 1996 and 2004.

The decision of initiating HAART relied on the primary care physician in each clinical setting. HAART was defined as two nucleoside reverse transcriptase inhibitors (NRTIs) combined with protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs).

For all patients, plasma samples were collected at inclusion and stored for further genotypic resistance testing for an epidemiological purpose. Therefore, when initiated during PHI, HAART began before the results of the genotypic resistance test were available.

Clinical and biological examinations were planned at enrolment and month (M)3 in both studies, and at M6 and then every 6 months in the PRIMO cohort.

Genotypic resistance analysis

Genotypic resistance studies were performed from baseline plasma frozen samples by sequencing reverse transcriptase (RT) and protease genes as described previously [11]. Drug resistance was defined according to the 2006 French ANRS algorithm (www.hivfrenchresistance.org).

HIV RNA measurements

Plasma HIV-1 RNA was measured using RT-PCR (Cobas, Amplicor®, Roche Diagnostics, Meylan, France; threshold 400 or 50 copies/ml) or bDNA (Quantiplex®, Bayer Diagnostics, Eragny, France; threshold 500 or 50 copies/ml).

Statistical analysis

Patients were categorized according to whether they harboured a wild-type virus (WT patients) or had a virus with genotypic resistance to ≥1 drug of the regimen they initially received (GR patients). Follow up of the patients was censored when they interrupted HAART or, among the GR patients, when they switched to a more active combination therapy according to their virus drug resistance profile; this censoring explains why some viral loads were not taken into account in the analysis of the virological response.

Virological and immunological response to HAART according to the drug resistance profile were investigated at M3 and M6 after HAART initiation. We first compared the percentage of patients with a viral load <400 copies/ml at M3 ±1 month and M6 ±1 month between the two groups. We further compared HIV RNA reduction, defined as the difference between HIV RNA at enrolment and M3; parametric interval-censored survival analysis was used to take into account the censoring of HIV RNA measurements due to the limit of quantification [24,25] and to avoid an HIV RNA reduction greater than HIV RNA at baseline [26]. When no measurement of viral load was available at M3 ±1 month, the viral load level was assumed to be included between the value of the last recorded measurement and 1 copy/ml [26]. The cutoff date for the analysis was April 2005.

Results

From November 1996 to November 2004, 350 patients initiated HAART at the time of primary HIV infection: 304 were infected with a wild-type virus and 46 were infected with a resistant virus. The median month of enrolment was August 2000. HAART was initiated within a median time of 39 days after infection (interquartile range [IQR] 32–52 days); treatment contained 3 drugs in 93.7% of cases and ≥4 drugs in 6.3%. For the GR patients, the number of active drugs was 0 in 2 patients, 1 in 12, 2 in 30 and 3 in 2 patients (Table 1). Three months after HAART initiation, the HIV RNA level was <400 copies/ml in 83% of WT versus 68% of GR patients (P=0.02; Table 2). When the analysis was restricted to the patients in whom viral loads were measured by an assay with a 50 copies/ml detection level, a viral response <50 copies/ml was observed in 40% of WT and 23% of GR patients (P=0.08). Conversely, no significant difference was found in the median $CD4^+$ T-cell counts recorded at M3 between the WT and GR patients (626 versus 661×10^6 cells/l, respectively; P=0.94). In a multivariate logistic regression including gender, age, baseline viral load and $CD4^+$ T-cell counts, time since infection and boosted PI regimen, patients harbouring a virus with a genotypic resistance to ≥1 drug of their regimen were less likely to obtain a virological response

Table 1. Description of the resistance mutational patterns for the 46 patients infected with a drug-resistant virus and who initiated HAART at the time of primary infection

ID	Treatment at enrolment	Inactive drugs	Active drugs, *n*	RT mutations	Protease mutations
1	d4T–DDI–IDV–RTV	d4T	3	215E	No mutation
2	ZDV–3TC–IDV–LPV/r	IDV	3	–	10I, 35D, 71T, 77I, 90M
3	ZDV–3TC–LPV/r–NFV	ZDV, NFV	2	41L, 215Y	10I, 36I, 90M
4	ZDV–3TC–RTV	ZDV	2	67N, 70R, 210W, 215Y	77I
5	ZDV–3TC–IDV	ZDV	2	41L, 98S, 210W, 215Y	63A, 77I
6	ZDV–3TC–RTV	ZDV	2	215Y	63P
7	d4T–DDI–NVP–SAQ/r	d4T, DDI	2	41L, 184V, 215F	63P
8	ZDV–3TC–NFV	ZDV	2	215C	No mutation
9	ZDV–3TC–EFV	ZDV	2	98S, 215D	77I
10	ZDV–3TC–EFV	ZDV	2	215A	20M, 35D, 36T, 63S
11	ZDV–3TC–RTV	ZDV	2	67N, 210W, 215S	No mutation
12	d4T–DDI–NFV	d4T	2	41L, 188C, 210W, 215S	No mutation
13	ZDV–3TC–IDV/r	ZDV	2	41L, 116Y, 215C	No mutation
14	ZDV–3TC–RTV	ZDV	2	70R, 215E	No mutation
15	ZDV–3TC–DDI–LPV/r	ZDV, DDI	2	67N, 69D, 210W, 215S	10V
16	ZDV–3TC–NFV	ZDV	2	67N, 103R, 215C, 219Q	No mutation
17	ZDV–3TC–SQV	ZDV	2	215S	No mutation
18	ZDV–3TC–NFV	ZDV	2	41L, 215C	10V, 36I
19	ZDV–3TC–NFV	ZDV	2	215E	10V
20	ZDV–3TC–LPV/r	ZDV	2	215D	41K, 53L, 63P, 77I
21	ZDV–3TC–NFV	ZDV	2	41L, 215D	No mutation
22	ZDV–3TC–IDV/r	ZDV	2	67N, 70R, 215I, 219E	20I, 36I, 41K
23	d4T–ABA–IDV	d4T	2	67N, 103R, 215C, 219Q	No mutation
24	d4T–DDI–NFV	d4T	2	67N, 69D, 70R, 210W	82A
25	ZDV–3TC–LPV/r	3TC	2	179I, 184V	36I
26	ZDV–3TC–RTV	3TC	2	184I	63I
27	ZDV–3TC–RTV	3TC	2	184V	63P, 71V
28	ZDV–3TC–EFV	3TC	2	69N, 70R, 184V	No mutation
29	ZDV–3TC–EFV	EFV	2	188L	20I, 36I, 41K, 63P
30	ZDV–3TC–EFV	EFV	2	188L	20I, 36I, 63P
31	ZDV–3TC–IDV	IDV	2	–	46L/M, 54L, 71T
32	d4T–DDI–NFV	NFV	2	–	36I, 71V, 90M
33	ZDV–3TC–EFV	ZDV, 3TC	1	41L, 44D, 67N, 69D, 108I, 118I, 184V, 210W, 215Y, 219R	10I, 33F, 36L, 46L, 54V, 71V, 82T, 84V, 90M
34	ZDV–3TC–NVP	ZDV, NVP	1	103N, 210W, 215Y	10I, 24I, 36I, 46L, 54I/V, 71V, 82T, 84V
35	d4T–3TC–NFV	d4T, NFV	1	41L, 69D, 181C, 215Y	10I, 48V, 82A, 90M
36	ZDV–3TC–NFV–NVP	ZDV, 3TC, NFV	1	41L, 184V, 215Y	10I, 63P, 77I, 84V
37	ZDV–3TC–RTV	ZDV, 3TC	1	41L,184I, 210W, 215Y	10I, 63P
38	ZDV–3TC–IDV	ZDV, 3TC	1	184V, 210W, 215Y	No mutation
39	ZDV–3TC–EFV	ZDV, EFV	1	67N, 69D, 70R, 181C, 215F, 219Q	10I, 20R, 36I, 54V, 71V, 82A, 90M
40	ZDV–3TC–EFV	ZDV, EFV	1	41L, 44Q, 188L, 215D	36I, 90M
41	ZDV–3TC–NFV	ZDV, 3TC	1	67N, 69D, 70R, 75I, 103N, 184V, 215F	63P
42	ZDV–3TC–EFV	ZDV, 3TC	1	67N, 69N, 184V, 215F, 219E	84V
43	ZDV–3TC–IDV	3TC, IDV	1	62V, 69N, 70R,184V	46I
44	ZDV–3TC–IDV/r	3TC, IDV/r	1	74V, 108I, 184V	10I, 20R, 36I, 46I, 54V, 63T, 82A
45	ZDV–3TC–NFV	ZDV, 3TC, NFV	0	67N, 69N, 70R, 103N, 108I, 116Y, 151M, 184V, 210W, 215V, 219Q	10F, 36I, 46I, 63P, 82A
46	ZDV–3TC–IDV	ZDV, 3TC, IDV	0	41L, 67N, 69N, 70R, 74I, 184V, 215F, 219Q	10I, 36I, 46I, 54V, 63H, 82A

Active and inactive drugs were defined according to the 2006 French ANRS algorithm (www.hivfrenchresistance.org). 3TC, lamivudine; ABA, abacavir; d4T, stavudine; DDI, didanosine; EFV, efavirenz; IDV, indinavir; NFV, nelfinavir; NVP, nevirapine; r, ritonavir-boosted; RTV, ritonavir; SAQ, saquinavir; ZDV, zidovudine.

Table 2. Baseline characteristics, virological and immunological response 3 and 6 months after HAART initiation during primary HIV infection

	Patients with a WT virus (*n*=304)	Patients with a resistant virus (*n*=46)	*P*-value
Characteristics at HAART initiation			
Women, % (*n*)	17 (51)	26 (12)	0.13
Median age, years (IQR)	33 (28–42)	35 (25–42)	0.79
PI-containing HAART, % (*n*)	89 (272)	78 (36)	0.03
Boosted PI regimen, % (*n*)	36 (108)	22 (10)	0.07
Median plasma HIV RNA, $\log_{10}$ copies/ml (IQR)	5.3 (4.8–5.9)	5.0 (4.3–5.7)	0.10
Median CD4$^+$ T-cell count, x10^6 cells/l (IQR)	475 (353–632)	485 (359–736)	0.54
Median time since infection, days (IQR)	39 (32–53)	38 (32–51)	0.79
Virological and immunological response at M3 (±1 month)*			
HIV RNA <400 copies/ml, % (*n*)	83 (233)	68 (27)	0.02
HIV RNA <50 copies/ml, % (*n*)	40 (111)	23 (7)	0.08
Median CD4$^+$ T-cell count, x10^6 cells/l (IQR)	626 (488–832)	661 (532–787)	0.94
Virological and immunological response at M6 (±1 month)†			
HIV RNA <400 copies/ml, % (*n*)	96 (248)	78 (18)	<0.01
HIV RNA <50 copies/ml, % (*n*)	78 (201)	57 (13)	0.02
Median CD4$^+$ T-cell count, x10^6 cells/l (IQR)	667 (516–837)	736 (519–860)	0.55

*Available in 281 wild-type (WT) patients and 43 genotypically resistant (GR) patients †Available only in the PRIMO patients (259 WT patients and 23 GR patients). HAART, highly active antiretroviral therapy; IQR, interquartile range; PI, protease inhibitor; WT, wild type.

Table 3. Characteristics at PHI diagnosis associated with achieving virological response (<400 copies/ml) 3 months after HAART initiation during PHI: univariate and multivariate logistic regression

Characteristics at PHI diagnosis	Crude OR (95% CI)	*P*-value	Adjusted* OR (95% CI)	*P*-value
Resistant virus (versus WT virus)	0.43 (0.21–0.89)	0.02	0.32 (0.15–0.72)	<0.01
Women (versus men)	2.18 (0.89–5.35)	0.09	1.81 (0.71–4.63)	0.22
Age (for a 10-year increase)	1.23 (0.93–1.62)	0.15	1.33 (0.98–1.79)	0.06
Plasma HIV RNA (for a 1 $\log_{10}$ copies/ml increase)	0.54† (0.38–0.77)	<0.01	0.52 (0.35–0.76)	<0.01
CD4$^+$ T-cell count (for a 100×10^6 cells/l increase)	1.09† (0.96–1.24)	0.17	1.03 (0.90–1.18)	0.64
Boosted PI regimen	1.27 (0.70–2.32)	0.45	1.08 (0.93–1.25)	0.33

*Adjusted for the listed variables and time since infection. †Adjusted for time since infection. CI, confidence interval; HAART, highly active antiretroviral therapy; OR, odds ratio; PHI, primary HIV infection; PI, protease inhibitor; WT, wild type.

<400 copies/ml 3 months after HAART initiation than the other patients (adjusted odds ratio [OR] 0.32; 95% confidence interval [CI] 0.15–0.72; Table 3).

Six months after HAART initiation, a better virological response was still observed in WT patients than in GR patients: 96% of WT patients had a viral load <400 copies/ml, versus 78% of GR patients (P<0.01; Table 2). Plasma viral load was <50 copies/ml in 78% of the WT patients versus 57% in GR patients (P=0.02). No significant difference was found in median CD4$^+$ T-cell count.

The crude reduction in viral load between HAART initiation and M3 was -3.47 $\log_{10}$ copies/ml among the WT patients, compared with -2.90 $\log_{10}$ copies/ml among the GR patients (P<0.01). After adjustment for gender, age, HIV RNA and CD4$^+$ T-cell count at enrolment, time since infection and boosted PI regimen, the difference in reduction of viral load levels at M3 (Δ= -0.45) and M6 (Δ= -0.51) between the WT and GR patients remained significant (P<0.01). A greater reduction in viral load was also observed 3 months after HAART initiation among the WT patients than among the 32 GR patients treated with ≥2 active drugs (Δ= -0.33; P=0.10); the adjusted difference in reduction of viral load was significant between the two groups of patients (Δ -0.38; P= 0.02).

Discussion

In our large cohort of patients followed and treated since primary HIV-1 infection, we observed that transmitted drug-resistant virus can lead to suboptimal virological response at M3 and M6, when first-line HAART

regimen contained ≥1 inactive drug. Few studies have been conducted in patients infected with resistant virus and treated with HAART at the time of primary infection [1,10,27–30]. A link has been established between infection with a resistant strain and a delay in obtaining a virological response after treatment in patients harbouring resistant virus compared with patients infected with wild-type strains [1,10]. Grant *et al.* [27] and Little *et al.* [1] found that time to viral suppression was greater among subjects with genotypical or phenotypical resistance to their regimen. This difference was a median time of 7–8 weeks longer in both of these studies. In contrast, Fox *et al.* [29] in London showed that only patients infected with multidrug resistant virus had a significantly lower virological response to first-line ART. We also observed an effect of the number of active drugs in GR patients contrary to what has been described in the CASCADE Virology collaboration [30].

After 6 months on HAART, we noted a similar increase in $CD4^+$ T-cell count in the two groups of patients suggesting that $CD4^+$ T-cell count in HAART-treated patients was preserved, at least in the short term, even in the presence of resistant virus. A previous study has suggested that transmitted resistant virus might have no effect on clinical outcome [19], whereas others have reported rapid $CD4^+$ T-cell count decreases [13,20,30,31].

Sexual transmission of resistant viral variants occurs and such variants can persist over many months or even years in the absence of therapy [15,17]. In a recent urban North American study, early infection accounts for approximately half of onward transmissions [32]. In view of the recognition of primary infection as a major driver of transmission, the reduction of transmission risk, by reducing viral load, should also be considered as a measurable benefit of early interventions [33]. Persisting viral replication despite HAART or a delayed virological response such as we observed might increase secondary sexual transmission of drug-resistant variants.

Our results, associated with the frequency of transmitted drug resistance of 12% in France, strengthen the recent guidelines that recommend performing genotypic resistance tests prospectively in all patients at the time of diagnosis of HIV [34]. Results should be available soon after HIV diagnosis. When HAART is initiated, virological efficacy needs to be closely monitored in patients to allow a rapid modification of first-line regimen in case of detection of resistant virus.

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These results were presented in part at the XIVth International Drug Resistance Workshop, 7–11 June 2005, Quebec City, Canada (oral presentation).

Additional file

An additional file listing 'Collaborators Participating in the ANRS Primo Cohort Study' can be accessed via the Volume 12 Issue 8 contents page for *Antiviral Therapy*, which can be found at www.intmedpress.com (by clicking on 'Antiviral Therapy' then 'Journal PDFs').

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