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Antiretroviral therapy for HIV controllers: Reasons for initiation and outcomes in the French ANRS-CO21 CODEX cohort

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Author information

Associated Data

Supplementary Materials

Abstract

Research in context

Evidence before this study

HIV controllers (HIC) represent a rare subset of persons living with HIV able to spontaneously control the viral replication and maintain very low viral loads with occasional viral blips (b-HIC) or undetectable viral loads (u-HIC). The rationale for antiretroviral therapy (ART) in this population remains debated, and while previous studies reported a decrease of immune activation markers upon treatment, the benefits of a systematic therapy remain unclear. This study reports the frequency of ART initiation by the clinician-in-charge, reasons to treat, treatment outcome on immunovirological parameters, and rate of side-effects and treatment discontinuation in the French cohort of HIC.

Added value of this study

During a median follow-up of 14.8 years, only 30% of the 301 HIC prospectively followed required ART initiation. The main reasons were a decrease in CD4 T cells counts (40%), loss-of-virological control (14%) and non-AIDS defining events (13%). Treatment reduced immune activation surrogates in b-HIC but not u-HIC. Fourteen percent of the patients discontinued ART and 10 maintained viral control after treatment cessation.

Implications of all the available evidence

HIC is a stable status that does not systematically require ART initiation and can be recovered after treatment cessation. Overall, ART initiation in HIC should be evaluated based on individual risk/benefit analyses and can possibly be discontinued for selected participants.

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1. Introduction

HIV controllers (HIC) are HIV-infected individuals who can achieve spontaneous viral control without requiring combined antiretroviral therapy (ART), representing approximately 0.5% of all HIV-infected people. Since their identification [1,2], HIC have been thoroughly studied to decipher the mechanisms of viral control. These studies revealed a specific immunological phenotype, associating the ability of HIV-specific CD8 T cells to suppress HIV replication combined with metabolic plasticity [3,4], enrichment of protective HLA alleles, preserved functional HIV-specific CD4 T cells [5], slower CD4 decrease over time [6], and a less pronounced immune exhaustion phenotype [7] relative to non-controller treated individuals.

HIC can be subdivided into two categories: participants with strictly undetectable viral loads (u-HIC: no detectable viral loads from 12 months after seroconversion to the last follow-up) and those experiencing viral blips (b-HIC: viral loads in the 50–2000 copies/mL range) [8,9]. The relevance of this distinction is supported by a distinct phenotype, featuring higher rates of viral and immunological progression amongst b-HIC and a higher risk of non-AIDS-defining events (nADEs) [6,[9], [10], [11]].

Recommendations for ART initiation extend to all individuals from the diagnosis of HIV infection, regardless of the CD4 count, but remain elusive for the HIC population. The benefits of ART remain unclear for these individuals, aside from specific clinical situations, such as viral progression [12]. Indeed, the main purpose and proven effect of ART is to reduce viral replication, monitored by measuring viral loads. In the setting of controllers, ART management should depend on the individual treatment goal [13].

Chronic inflammation drives HIV-associated comorbidities in non-controllers, such as cardiovascular disease and neurocognitive impairment, and decreases upon ART [14]. Thus, some have suggested that ART could be similarly beneficial for HIC. Chronic inflammation in HIC has been investigated in several studies, with contrasting findings. Several reported above-normal immune activation in HIC [15], [16], [17], but the link with increased cardiovascular disease was not clear [18,19]. Moreover, large prospective cohort studies did not consistently find a high rate of nADEs in HIC [10,20], or the results were unclear [21,22], suggesting a low comorbidity burden.

Recent retrospective and prospective studies reported the effects of ART in HIC. ART appears to decrease the immune-activation profile in certain controllers and has been associated with a diminution in immune exhaustion markers [23,24]. However, the effects on CD4 T-cell counts appear to be only modest or inexistant [23,25,26]. Another unsolved question is the potential benefit of ART in HIC and especially u-HIC to achieve HIV cure.

We report the indications, outcomes, and long-term follow-up of 90 HIC treated by ART upon the clinician's decision and prospectively followed in the CODEX cohort.

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2. Methods

2.1. Participant recruitment

We retrospectively analyzed the data from 302 HIC included in the previously described CODEX cohort [27]. Briefly, this cohort prospectively enrolls participants defined as follows: participants infected with HIV-1 for at least five years and whose five last consecutive plasma viral loads were < 400 copies/mL without antiretroviral therapy. All included participants provided written consent and the study protocol was approved by the Comité de Protection des personnes Ile-de-France VII.

2.2. Data collection

All participants included in the CODEX cohort are prospectively followed and have at least one medical visit per year during which data are collected [8,27]. The CD4 and CD8 T-cell counts, plasma HIV-l RNA viral load (VL), as measured by routine and ultrasensitive assays [11], total HIV-1 DNA [11], AIDS-defining-events (ADEs), nADEs, and immune-activation parameters (frequency of $HLADR^{+}CD38^{+}$ *T* cells) were analyzed.

2.3. Definitions

Confirmed immunological progression was defined as a $CD4^{+}$ *T*-cell count <350/mm^3 or a decline of more than 200/mm^3 from an immediately preceding $CD4^{+}$ count of ≥600/mm^3 on two consecutive measurements. Confirmed viral progression was defined as two consecutive HIV-1 RNA VL measurements >2000 copies/mL. If both criteria were met, participants were considered to experience combined progression. Such cases were referred to as suspected immunological and/or virological progression if the above criteria were met for only one blood sample [27].

Undetectable controllers (u-HIC) were defined as participants with strictly undetectable routine HIV-1 RNA VL (irrespective of the detection threshold) from the first recorded VL up to the last visit or ART initiation [8]. Blipper controllers (b-HIC) were defined as HIC participants with possible detectable HIV-1 RNA VL but never reaching two consecutive VL over 2000 copies/mL, otherwise classifying them as viral loss of control.

2.4. Treatment initiation

Treatment initiation was decided by the physician in charge of the patient. For each patient, the clinician had to declare the reason for ART initiation and the ART regimen prescribed. During follow-up, all data on adverse events (AEs), treatment discontinuation, and drug-regimen changes were collected. Women receiving ART during pregnancy were not identified as ART-treated if they stopped ART definitively post-partum.

2.5. Statistical analysis

Quantitative and qualitative data are reported as medians [interquartile range, IQR] and numbers (%), respectively. Wilcoxon–Mann–Whitney tests were used for intergroup comparisons of quantitative data and Chi-square or Fisher's exact tests for intergroup comparisons of qualitative data, as appropriate. Statistical significance was set to $p < 0.05$. All statistical analysis were performed using *R*-Studio software v1.3.1056 and PRISM v8.0 (GraphPad software, La Jolla, CA, USA).

2.6. Role of the funding source

The funder played no role in the design, conduct, or reporting of this study. LP, FB, CL, EG, VAF, ASC, OL and NN had access to the dataset; LP, FB, VAF, ASC, OL and NN decided to submit the manuscript for publication.

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3. Results

3.1. Clinical and demographic data of the 302 participants included in the CODEX cohort

In total, 302 HIC were included in the cohort from July 6, 2007 to January 3, 2018 (**Supplemental Fig. 1**). The median [IQR] time between HIV diagnosis and treatment initiation or last follow-up was 14.8 years [10.3–20.2]. The median follow-up after enrollment in the cohort was 5.4 years [2.9–10.1]. At last evaluation and/or ART initiation, 73 (24%) participants were classified as u-HIC and 228 (76%) as b-HIC. Among them (Suppl Table 1), u-HIC were more frequently women (1.8 women per man vs 1 women per man among b-HIC, $p = 0.019$), had a higher nadir of CD4 T-cell counts ($p = 0.01$), and more frequently carried the HLA B57/58 haplotype (51% of u-HIC vs 35% of b-HIC, $p = 0.010$), as already reported [8].

Among the 301 participants with available data, 90 (30%) were treated by ART. The median date of treatment initiation was April 22, 2015 and all participants were treated between April 22, 2007 and May 10, 2019. Among the 73 u-HIC, seven received ART (9%) versus 83 of 228 b-HIC (36%, $p < 0.001$) (**Supplemental Table 1**). There were no differences in terms of geographic origin or teaching center/semi-urban clinic care between treated and untreated patients (data not shown).

3.2. Characteristics of the 90 treated HIC compared to 211 untreated HIV controllers

The median age at treatment initiation was 48.0 years [41.8–55.7] and the sex-ratio among treated participants was 1. Treated participants had a longer time from diagnosis than untreated participants (17.5 years, vs 13.9 years, $p < 0.001$), with a lower CD4 T-cell count nadir (383.68 versus 554.3, $p < 0.001$). b-HIC participants had a median plasmatic viral load of 398 copies/mL [92–1342] at treatment initiation. The frequency of b-HIC was significantly higher in the treated than untreated HIC population (92% versus 69%, $p < 0.001$). The opposite was true for u-HIC (8% among treated versus 31% in untreated HIC, $p < 0.001$). The maximal and median HIV median plasma viral loads and percentage of detectable viral loads were higher and the median CD4 T cells count was lower in treated patient's group, which was expected as patients were mainly treated for immunological or viral progression (as discussed below). Treated participants more frequently carried HLA*B27 and less frequently HLA-B57/58 ($p = 0.02$ and $p = 0.01$ respectively) (Table 1). In order to further investigate the virological loss-of-control in HLA*B27 patients, and considering previous reports of viral escape in HLA*B27 patients due to mutations in the B27-restricted Gag antigen, we performed ELISPOT assays to assess the specific T cell responses to Gag 263–272. Among 19 treated $B27^+$ HIC, 15 (79%) had already detectable responses to Gag 263–272 at enrollment versus 14/19 (74%) untreated $B27^+$ HIC. Among the four $B27^+$ HIC treated for viral progression with available longitudinal data, two had undetectable

responses to mutated peptides at enrollment but developed detectable CD8 responses at the time of viral progression (*data not shown*).

Table 1

Characteristics of the 90 HIC treated compared to 211 untreated HIC.

Variable	Treated HIV controllers (*n* = 90)**	Untreated HIV controllers (*n* = 211)***	*P*
Age (years)	48.0 [41.8–55.7]	50.1 [43.5–56.4]	0.20
Sex-ratio (female/male)	1.00	1.20	0.55
Time from diagnosis* (years, median [IQR])	17.5 [13.6–23.7]	13.9 [10.06–20.01]	**<0.001**
HIV controller subtype			
b-HIC	*N* = 83 (92%)	*N* = 145 (69%)	<0.001
u-HIC	*N* = 7 (8%)	*N* = 66 (31%)	
Maximal HIV-1 plasma viral load (median [IQR]) §	1268 [342–5791]	200 [40–664]	**<0.001**
% with detectable HIV-1 plasma viral loads	41.1%	24.2%	**<0.001**
Mean HIV-1 plasma viral loads (median [IQR]) §	354 [158–855]	165 [106–331]	**<0.001**

Variable	Treated HIV controllers (*n* = 90)**	Untreated HIV controllers (*n* = 211)***	*P*
CD4 T-cell count nadir (median [IQR]) §	360 [278–461]	550 [414–685]	**<0.001**
HLA*B27^{+}	*N* = 19 (21%)	*N* = 23 (11%)	**0.02**
HLA*B57/58^{+}	*N* = 26 (29%)	*N* = 94 (44%)	**0.01**
Protective HLA	Data available for 89/90	Data available for 203/211	
0	*N* = 50 (55%)	*N* = 101 (48%)	0.24
1	*N* = 36 (40%)	*N* = 105 (50%)	
2	*N* = 4 (4%)	*N* = 6 (2%)	

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Legend: uHIC: undetectable HIV controller, bHIC: blipper HIV controller. SD: standard deviation *Duration of follow-up from first positive serology **Last available values before ART initiation ***Last available values § Data calculated from the obtention of viral control as defined in the Methods section.

3.3. Reasons to introduce ART

Among the 90 treated participants, 36 (40%) were treated for confirmed immunological progression, 13 (14%) for confirmed loss of virological control, 11 (12%) for suspected virological loss of control, and six (7%) for suspected immunological progression. The remaining 24 (27%) received ART for non-immunological or virological reasons. Among them, 12 (13%) were treated because of one or more nADEs, four (4%) because of an actual or planned pregnancy, four (4%) upon the doctor's decision (without any other explanation), three (3%) upon the patient's decision (motivated for all three by couple serodifference), and one (1%) for renal transplantation [28]. Ten participants had several reasons for introducing ART: immunological progression and non-AIDS-defining cancers (*n* = 3), immunological progression and other nADEs (*n* = 2: one had recurrent bronchitis, the other recurrent shingles), immunological progression and suspected viral progression (*n* = 3), immunological progression and an ADE (*n* = 1, cutaneous Kaposi sarcoma), and pregnancy and a nADE (*n* = 1, hepatitis B) (Fig. 1).

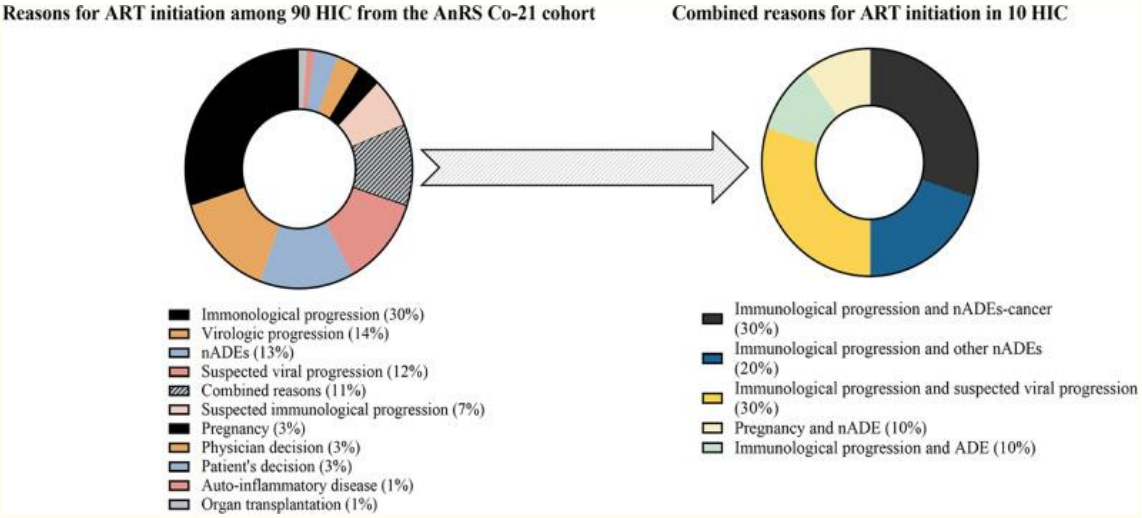

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Fig. 1

Reasons for ART initiation among 90 HIV controllers. ADE: AIDS-defining-event, nADE (s): non-AIDS-defining-event (s).

Among u-HIC, the main reason for ART initiation was immunological progression for four participants (57%). One u-HIC was treated for suspected immunological progression and two for other causes: one fulminant hepatitis B and the other upon the physician's decision.

Among b-HIC, the main reasons to initiate ART were immunological progression for 32 (39%) participants and loss of virological control for 13 (16%). Eleven (13%) b-HIC were treated for suspected loss of virological control and five (6%) for suspected immunological progression (**Supplemental Fig. 2**). The remaining 22 (27%) were treated for non-immunological or virological reasons (**Supplemental Table 2.)**

3.4. AIDS- and non-AIDS-defining events

Among the 90 participants treated by ART, two experienced one ADE (2%), and 17 (18%) one or more nADEs (responsible for ART initiation in 12) (Table 2).

Table 2

nAdes and Ades presented by the 90 HIV controller participants.

Ades and nAdes, no. (%)	u-HIC (*n* = 7)	b-HIC (*n* = 83)
nAdes leading to ART initiation, no. (%)	**2 (14%)**	**16 (19%)**
Hepatitis B	1 (14%)	4 (5%)*§

Ades and nAdes, no. (%)	u-HIC (*n* = 7)	b-HIC (*n* = 83)
Hepatitis C	0	2 (2%)
Neurosyphillis	0	1 (1%)
Recurrent bacterial infections	1 (14%)	1 (1%)
Shingles	0	2 (1%)
Cardiovascular comorbidities	0	2 (2%)
Cognitive impairment	0	1 (1%)
Non-AIDS-defining cancers	0	3** (4%)
ADEs leading to ART initiation, no. (%)	**0**	**1 (1%)**
Kaposi sarcoma	0	1 (1%)
Ades and nAdes occurring after ART initiation, no. (%)	**0**	**2 (2%)**
Non-Hodgkinian lymphoma	0	1 (1%)

Ades and nAdes, no. (%)	u-HIC (*n* = 7)	b-HIC (*n* = 83)
Non-AIDS-defining cancer	0	1 (1%) §

*One b-HIC patient was treated for pregnancy and had concomitant chronic hepatitis B **Three participants treated by ART for immunological progression presented with bronchial adenocarcinoma, HPV-positive squamous-cell carcinoma of the tonsil and pancreatic adenocarcinoma. § One patient was treated for chronic hepatitis B and developed a lung cancer 4 years later.

Two b-HIC participants developed AIDS after ART initiation, one because of non-Hodgkin diffuse B-cell lymphoma concomitant with loss of virological control, leading to ART (VL and CD4 at ART initiation: 2229 copies/mL and 191 cells/mm^3) and one because of cutaneous Kaposi sarcoma and immunological progression (VL and CD4 at ART initiation: 210 copies/mL and 431 cells/mm^3).

Seventeen participants experienced 18 nADEs, leading to ART initiation for 12 (71%). Among them, nine presented with infections (hepatitis B in 4, hepatitis C in 2, syphilis in 1, recurrent otitis and pharyngitis in 1, shingles in 1), two with cardiovascular comorbidities, and one with neurocognitive impairment.

Five participants treated for immunological progression (*n* = 3), loss of virological control (*n* = 1), or hepatitis B (*n* = 1) developed nADEs, either before ART or in the first three months following ART initiation: one patient had recurrent bacterial bronchitis (9 episodes), another thoracic shingles, and three developed non-AIDS-defining cancers: bronchial adenocarcinoma (4 years after ART initiation for hepatitis B), HPV-induced squamous-cell tonsil carcinoma (concomitant with immunological progression), and metastatic pancreatic adenocarcinoma quickly following immunological progression. One patient treated for hepatitis B developed metastatic lung cancer four years later while receiving ART.

The most frequent nADEs were other infections (*n* = 12, 67%). Many of these participants had viral co-infections (hepatitis B for 5, hepatitis C for 2).

3.5. Antiretroviral therapy: treatment regimens and tolerance

The most commonly prescribed ART regimens were 2 NRTI (Nucleoside analog reverse-transcriptase inhibitors) + 1 NNRTI (Non-nucleoside reverse-transcriptase inhibitors) for 41 (46%) participants, 2 NRTI and 1 PI (protease inhibitor) for 33 (37%), and 2 NRTI + 1 INSTI (Integrase strand-transfer inhibitors) for 10 (11%). Among the six remaining participants, five received bitherapy (4 b-HIC and 1 u-HIC: 2 received 2 NRTI, 2 received 1 NRTI + 1 INSTI) and one received INSTI as monotherapy (1 b-HIC treated with dolutegravir). Sixteen (18%) participants experienced 17 AEs, mainly digestive and neurological, leading to treatment withdrawal for 5 (31%) (Table 3). No AE was grade 3 or higher. There were no significant differences between uHIC and bHIC concerning the nature of the AE. Median follow-up after treatment initiation was 2.9 years [1.3–5.1].

Table 3

Follow-up of the 90 HIV controller participants treated by ART.

Variable	All participants (*n* = 90)	u-HIC (*n* = 7)	b-HIC (*n* = 83)
Main reason for ART initiation			
Loss of virological control	*N* = 13 (14%)	*N* = 0	*N* = 13 (16%)
Immunological progression	*N* = 36 (40%)	*N* = 4 (57%)	*N* = 32 (39%)
Suspected loss of virological control	*N* = 11 (12%)	*N* = 0	*N* = 11 (13%)
Suspected immunological progression	*N* = 6 (7%)	*N* = 1 (14%)	*N* = 5 (6%)
Other reasons	*N* = 24 (27%)	*N* = 2 (29%)<	*N* = 22 (27%)*
VL before ART (median [IQR])	268 [50–1258]	LOD	398 [92–1342]
CD4 T cell counts before ART (median [IQR])	479 [365–669]	390 [352.8–461.8]	486 [369.5–672]
ART regimen			
2 NRTI + 1 NNRTI	*N* = 41 (46%)	*N* = 1 (14%)	*N* = 40 (48%)
2 NRTI + 1 II	*N* = 32 (36%)	*N* = 5 (71%)	*N* = 27 (33%)
2 NRTI + 1 PI	*N* = 10 (11%)	*N* = 0	*N* = 10 (12%)
Other regimens	*N* = 7 (8%)	*N* = 1 (14%)	*N* = 6 (7%)
Adverse events	*N* = 17 (19%)	*N* = 1 (14%)	*N* = 16 (16%)
Grade 1	*N* = 12 (14%)	*N* = 0	*N* = 12 (14%)
Grade 2	*N* = 5 (6%)	*N* = 1	*N* = 4 (5%)
Composition	*N* = 6 (7%)	*N* = 0	*N* = 6 (7%)
Neurologicals§	*N* = 6 (7%)	*N* = 1	*N* = 5 (6%)
Digestives§	*N* = 1 (1%)	*N* = 0	*N* = 1 (1%)
Psychiatric	*N* = 1 (1%)	*N* = 0	*N* = 1 (1%)
Muscular	*N* = 3 (2%)	*N* = 0	*N* = 3 (2%)
Others			

Variable	All participants (*n* = 90)	u-HIC (*n* = 7)	b-HIC (*n* = 83)
Reason for ART	*N* = 13 (13%)	*N* = 2 (29%)	*N* = 11 (12%)
discontinuation:	*N* = 6 (46%)	*N* = 1 (14%)	*N* = 5 (5%)
Patient decision	*N* = 5 (38%)	*N* = 1 (14%)	*N* = 4 (5%)
Adverse event§§	*N* = 2	*N* = 0	*N* = 2
Unknown§§§			
Duration of treatment before	56.50 [35.75–	26 [17–35]	67 [42.75–
discontinuation (days)	260.50]		297.75]
HIV controller status after treatment	*N* = 13	*N* = 2	*N* = 11
discontinuation	*N* = 3 (23%)	*N* = 2 (100%)	*N* = 1 (9%)
u-HIC	*N* = 6 (46%)	*N* = 0	*N* = 6 (54%)
b-HIC	*N* = 0	*N* = 0	*N* = 0
Loss of virological control	*N* = 0	*N* = 0	*N* = 0
Immunological progression	*N* = 4	*N* = 0	*N* = 4
Non evaluable§§§§			
Resumed ART after discontinuation	*N* = 11 (12%)	*N* = 2 (29%)	*N* = 9 (11%)
Time before resuming ART after	245 [160–360]	150 [134–167]	275 [162–642]
discontinuation (months)			

Data are presented as medians [IQR] or numbers (%). HIC: HIV controllers, uHIC: undetectable HIV controller, bHIC: blipper HIV controller, ART: combined antiretroviral therapy, NRTI: nucleotide reverse transcriptase inhibitors, NNRTI: non-nucleotide reverse transcriptase inhibitors, II: integrase inhibitors, PI: protease inhibitors, VL: plasma HIV-1 viral load. §One patient presented two adverse events §§Three participants discontinued ART after digestive adverse events, one after a psychiatric adverse event, and one after a neurological adverse event §§§One patient was treated for renal transplant and treatment was discontinued afterwards. §§§§Four participants had less than 3 viral-load measurements between

treatment discontinuation and resumption. *$p < 0.001$ for the difference between u-HIC and b-HIC. LOD: limit of detection threshold. Viral loads value before ART were all undetectable in the u-HIC subset of patients (detection limit set at <10 copies/mL for one patient, <20 copiess for 2 patients and <40 copies for 4 patients).

3.6. Effect of ART on CD4, CD8 T-cell counts and activation markers

Data on CD4 and CD8 T-cell activation were available at last visit before ART introduction and six months post-ART for 40 participants, along with CD4, CD8, and CD4:CD8 ratio counts (Fig. 2).

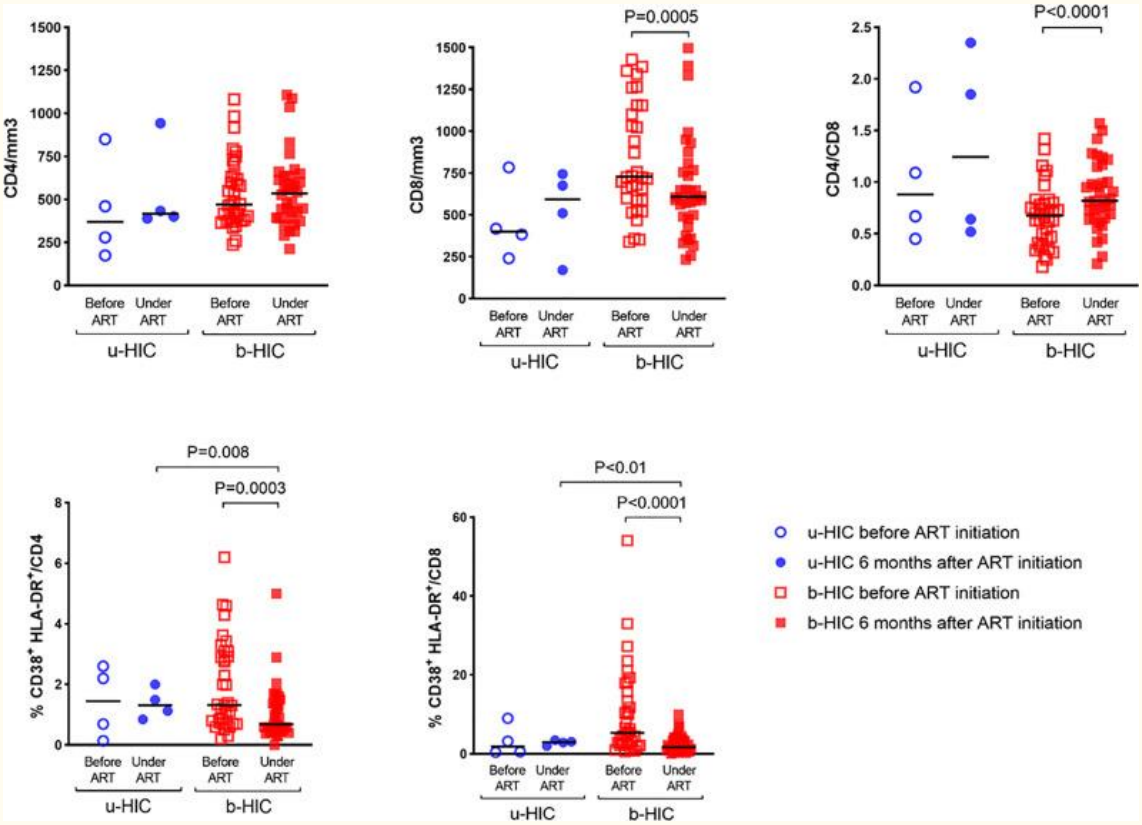

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Fig. 2

Immunological effect of cART in 5 uHIC and 35 bHIC. (a) CD4 T-cell count before and after ART. (b) CD8 T-cell count before and after ART. (c) CD4/CD8 ratio before and after ART. (d) Proportion of peripheral $HLADR^+CD38^+$ activated CD4 T cells before and after ART. (e) proportion of peripheral $HLADR^+CD38^+$ activated CD8 T cells before and after ART.

In 4/7 u-HIC with exhaustive data available, treatment did not increase or reduce CD4 or CD8 T-cell counts, the CD4/CD8 ratio (**Fig. 2a-c**), or the proportion of peripheral activated CD4 or CD8 lymphocytes (**Fig. 2d and e**). Median [IQR] cell counts were 370 [252–557] CD4/mm^3, 401 [347–510] CD8/mm^3, and 0.88 [0.61–1.30] CD4/CD8 before ART and 417 [397–561] CD4/mm^3, 593 [426–692] CD8/mm^3, and 1.25 [0.61–1.98] CD4/CD8 six months after ART initiation, respectively.

In 36/83 b-HIC with exhaustive data available, treatment resulted in a significant decrease in total CD8 T-cell counts (from a median [IQR] of 730 [597–1182] to 609 [487–828] CD8/mm^3, median of −150 CD8/mm^3, $p = 0.0005$) and an increase in the

CD4/CD8 ratio (median of +0.19, $p < 0.0001$) but not total CD4 T-cell counts (471 [386–633] to 535 [393–636] CD4/mm^3, median of +32 CD4/mm^3, $p = 0.16$), and a decrease in the proportion of activated CD4 and CD8 T cells (decrease of 0.65%, $p = 0.003$, and 4.18%, $p < 0.0001$, respectively).

3.7. Effect of ART on ultrasensitive HIV RNA

usRNA was measured before and after ART initiation for 41 participants. Before ART, 38 participants had detectable usRNA and upon ART, it remained detectable for only nine (after exclusion of the two participants who permanently discontinued ART). Among them, only four had concomitant detectable VL. Overall, the median difference in u.s.HIV RNA was −0.18 log copies/mL after 6 months of ART. Seven were u-HIC, and only 1/7 had detectable HIV RNA upon treatment (measured at 0.67 log copies/mL).

3.8. Post-treatment HIV viral control

Thirteen participants discontinued ART after a median of 64 days [44–275]. The reasons for ART discontinuation were an AE for five, patient decision for four, and unknown for two (Table 3 **and Supplemental Table 3**). Eleven resumed ART after a median of 245 days [160–555.5]. The median follow-up from ART cessation until ART resumption or last medical visit was 305 days [235–728].

Among them, two participants were u-HIC: no data were available between treatment cessation and resumption for one. The other patient was treated for suspected viral progression eight days before cessation and then remained treatment-free for 183 days and experienced five consecutive undetectable VLs before ART resumption.

Among the 11 b-HIC who discontinued ART, nine reverted to their b-HIC phenotype, whereas two progressed, including one patient with a renal transplantation (Supplemental Table 3).

Overall, the CD4 T-cell count decreased after treatment cessation for two participants. Among the four patients treated for immunological progression, CD4 T-cell counts decreased for only one.

Among the two participants that did not resume ART, one (patient #2′, **Supplemental Table 3**) was treated because of loss of virological control, discontinued ART after 1089 days, was lost to follow-up, and presented two years later with persistent loss of virological control. He showed viral loads from 2140 to 14,848 copies/mL until the last follow-up five years after treatment cessation. The other patient (bHIC) was treated because of associated chronic hepatitis C, stopped ART after 366 days, and showed viral loads from 0 to 2000 copies/mL at the last evaluation (three years after treatment cessation).

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4. Discussion

Recommendations concerning ART introduction in HIC are debated. We therefore aimed to describe the frequency and reasons for ART initiation in 90 patients from a prospective cohort of 301 HIC.

In our study, 90 (30% of the CODEX cohort) received ART over a median follow-up of 14.8 years since HIV diagnosis. Most participants (84/90, 93%) received ART regimens consistent with international recommendations [29]. Sixteen (18%) experienced AEs. Overall, 13 participants discontinued ART (14%), including five for adverse side effects (6% of the entire treated population), and 11 later resumed. These results are coherent with a recent meta-analysis of 77,999 participants, among whom 29.4% discontinued first-line ART, 8.9% because of AEs, suggesting relatively good observance and tolerance of ART in HIC [30].

As expected, treated participants had a lower CD4 *T*-cell nadir, were more frequently b-HIC than u-HIC, and had a lower frequency of protective HLA B57/58 carriage [31]. The over-representation of HLA B27 among treated participants could be associated with viral escape from the HLA B27-restricted anti-Gag cytotoxic CD8 *T*-cell response [32], as observed for two patients in our study. Treated participants had a longer time from HIV diagnosis than untreated participants, suggesting a possible loss of virological control over time in HIC. The main reasons for ART initiation were immunological progression (40% of treated participants, representing 12% of the overall cohort over a median follow-up of 14.8 years), rather than virological progression (14% of treated participants). Seventeen (19%) participants received ART for suspected immunological or virological loss of control without fulfilling proposed criteria for progression. However, others have reported that an elevated frequency of viral blips and/or a low CD4 *T*-cell nadir may predict both virological and immunological progression [27,33,34], possibly reflecting low-level viral replication in tissues.

In our study, b-HIC were more likely to receive ART than u-HIC, possibly reflecting the higher frequency of viral blips in this population, and overall a less stable controller status in b-HIC than in u-HIC. Indeed, b-HIC definition includes controller patients with heterogeneous phenotype, whereas u-HIC share several common features of strong viral control, such as low level of HIV blood reservoir, combined protective HLA alleles and reduced immune activation [8]. One unsolved question is the effect of ART is these patients with spontaneously undetectable viral loads. Our group has previously reported that u-HIC had very low-to-undetectable reservoirs [8,35] and that HIV DNA could even spontaneously decrease over time [11]. Anti-HIV antibodies might be undetectable [8] (reflecting the very low level of antigenic stimulation in a similar manner to patients with sterilizing cure such as the Berlin patient [36]). We could analyze ultrasensitive HIV RNA levels and showed a reduction of 0.18 log copies/mL overall. Unfortunately, we could not analyze the effect of ART on total HIV DNA or anti-HIV antibodies in HIC before and after ART introduction.

Seventeen participants experienced nADEs during follow-up, responsible for ART initiation for 12 (13%). Nine of these nADEs were infections, including 4 HBV and 2 HCV coinfections. Six (7%) controllers, all b-HIC, developed cancer during follow-up, leading to ART initiation, preceeded or concomitant with virological/immunological progression. As anti-tumoral immunity could disrupt the immunological homeostasis required to control HIV infection, these data highlight the need to closely monitor HIC with immunological progression to diagnose potential cancer earlier. It is possible that earlier ART introduction reduces the occurrence of nADEs in HIC, as undetectable HIC do not experience higher rates of nADEs than ART-controlled participants [10], but similar data on b-HIC vary in different studies [21,22,37]. The role of hepatitis B or C in the occurrence of nADEs is possible in cohorts with a high incidence of co-infections

[10,20,21], which is not the case in the French population [8]. These results pinpoint the need for prevention and regular screening for nADEs and co-infections in HIC, but data supporting the effect of ART on preventing nADEs or treatment in HIC is lacking.

Four b-HIC participants were treated during pregnancy. Three continued treatment after delivery and one stopped ART and then resumed 305 days later. Further studies are required to evaluate the impact of pregnancy on HIC. In contrast, 46 HIC women received ART only during their pregnancy and their HIC phenotype did not change afterwards (data not shown).

Three b-HIC patients decided to initiate ART because of unprotected sexual intercourses with seronegative persons. The question of HIV transmission by HIC remains unresolved, but it is usually considered that patients with undetectable viral loads are not likely to transmit the infection, as in patients with undetectable viral loads upon ART [38]. While HIV RNA has been detected in the semen of HIC patients, concomitantly to viral blips [39], no case of HIV transmission from HIC patients has been reported, neither in our prospective cohort of 301 HIC followed for a median of 14.8 years, nor in the literature.

In our study, ART was associated with fewer activated circulating CD4 and CD8 lymphocytes, decreased CD8 T-cell counts, and a higher CD4/CD8 ratio but no change in CD4 T-cell counts in participants with detectable viral load before treatment. These data suggest that ART reduces HIV-associated chronic inflammation. However, these effects were relatively small and consistent with the results of Okulicz et al., who found a moderate increase of 200 CD4 T cells/mm^3 in HIC after 24 months of treatment [25] Moreover, Li et al. did not report an increase in CD4 T-cell counts in a recent prospective study; either at 24 or 48 weeks of ART [23]. In contrast, these immunological parameters did not change in the subset of uHIC, questioning the impact of ART in these participants. However, these results should be confirmed in further studies with a longer follow-up.

Our study was conducted in « real-life » settings, as the indications of ART introduction were based on the physician's decision and not a controlled trial. The treatment was well tolerated in HIC and only 18% of participants experienced minor AEs, responsible for ART discontinuation for 6% of all treated participants. These data are important, as French guidelines recommend a patient-centered approach for ART initiation in controllers [29]. In a recent prospective study, HIC reported a slight but significant increase in their quality of life after 24–48 weeks of ART [23]. However, another study reported higher scores in physical and social quality of life for HIC than non-controller treated participants, but lower scores in mental quality of life, interpretated as being associated with the uncertainty of the disease evolution [40]. Further studies are required to investigate the effect of ART on HIC quality of life.

Thirteen participants discontinued ART and 11 resumed it after a mean of 405 days. Most remained HIC after treatment cessation, in agreement with Jilg et al. [41]. Moreover, the CD4 counts of 3/4 participants treated for immunological progression either increased or stabilized. Although these results must be interpreted with caution due to the small sample size and sparce immunovirological data, they suggest that temporary ART could be a therapeutic option and should be further evaluated in prospective studies, including surveillance of the emergence of viral resistance in the HIC population.

The main limitations of our study included this retrospective analysis of prospectively collected data, the absence of quality-of-life assessment throughout treatment, and the relatively short follow-up after treatment. However, we analyzed the largest number of controller participants to date in a "real-life" setting, including a description of ART-related AEs and treatment discontinuation and the analysis of ART-dependent effects on immunological parameters.

In this analysis of a prospective cohort, 30% of HIC followed for a median of 15 years received ART. The main reasons for ART initiation were immunological progression, loss of virological control, and sometimes nADEs. Antiretroviral therapy led to a modest improvement in the CD4/CD8 ratio and reduction of immune activation in the subset of bHIC. Despite limited data, HIC who discontinued ART appeared to resume spontaneous viral control. Overall, ART initiation in HIC should be evaluated based on individual risk/benefit analyses and can possibly be discontinued for selected participants.

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5. Contributors

L. Plaçais: study design, literature search, figures, data collection, data analysis, data interpretation, writing. F.Boufassa: figures, data collection, data analysis, data interpretation

C. Lécuroux: data collection, data analysis, data interpretation. E. Gardiennet: data collection. V. Avettand-Fenoël: data collection, data analysis, data interpretation. A. Saez-Cirion: data collection, data analysis, data interpretation. O. Lambotte: data collection, study design, data analysis, data interpretation, writing supervision. N. Noël: data collection, study design, figures, data analysis, data interpretation, writing supervision. L.Plaçais, N.Noël, F.Boufassa had access to the underlying data.

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Declaration of Competing Interest

Dr Noel reports research funds from ANRS and being employee at Universite Paris Saclay and APHP, speaker fees from BMS and MSD outside the submitted work. Dr Lambotte reports research funds from ANRS and being employee at Universite Paris Saclay and APHP, speaker fees from MSD and Gilead, and grant from Gilead outside the submitted work. Dr Saez-Cirion reports research found from ANRS, being employee at Institute Pasteur and speakers fees from MSD, ViiV healthcare, Janssen and Gilead. Dr Gardiennet reports payment from ANRS to institution. Dr Avettand-Fenoel reports payments to institution from ANRS and ViiV healthcare, honoraria from Gilead and ViiV healthcare, support for travel from ViiV healthcare and Roche outside the submitted work. All the other authors have no conflicts to report.

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Data sharing statement

Deidentified data might be available from the corresponding author upon reasonable request.

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Footnotes

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2021.100963.

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Appendix. Supplementary materials

Click here to view.(62K, docx)Image, application 1

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