# Does HIV Infection Alter Parkinson Disease?

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**Objective:** To describe the clinical features, treatment(s), and outcomes of 15 HIV-infected patients with idiopathic Parkinson disease (PD) and sustained virus suppression and immunologic reconstitution, from a reference cohort of 9847 persons living with HIV (PLH).

**Methods:** This retrospective, single-center matched case–control 1:2 study included PLH-PD patients evaluated over a 12-year period (2002–2013) with mean follow-up of 6.5 years. PD clinical features and dopamine replacement therapy (DRT) were compared, and biologically relevant HIV data were assessed.

**Results:** PD prevalence in PLH was similar to that of the general population. At onset, clinical presentations and therapeutic management were similar for both groups. Rapidly effective DRT was well tolerated without combined antiretroviral therapy interactions or virus escape. At the end of the follow-up, compared with HIV-negative PD, PLH had a significantly lower median Unified Parkinson's Disease Rating Scale motor score (4 vs 14; $P <$ 0.001), median Hoehn and Yahr stage (1 vs 2; $P = 0.0005$), and median Handipark scale score (2 vs 3; $P = 0.0036$) under the same daily DRT. One PLH underwent highly successful deep brain stimulation of the subthalamic nucleus.

**Conclusions:** HIV-associated PD is similar to idiopathic PD with some features suggesting an HIV-induced functional adaptation of dopaminergic neurons that might counterbalance the PD-induced neuronal loss. Concurrent HIV infection does not compromise the outcome of idiopathic PD.

**Key Words:** Parkinson disease, central nervous system, HIV, AIDS, viral infections, basal ganglia

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## INTRODUCTION

In countries where combined antiretroviral therapy (cART) is widely available, the HIV epidemic is entering a chronic phase in which the majority of persons living with HIV (PLH) have a life expectancy approaching general population norms.[1] As a consequence, more PLH are aged 50 years or older, estimated to represent, by 2015, the majority of all PLH in Western countries. Prone to developing age-related diseases, male PLH, compared with HIV-negative men, have a higher burden of neurologic diseases that may also develop at younger ages.[2]

The central nervous system (CNS) is highly vulnerable to HIV infection, particularly the dopamine (DA)-rich brain regions. Basal ganglia play a pivotal role because they are a virus-replication hot spot, and the substantia nigra suffered up to 25% neuronal loss in AIDS.[3] Parkinsonism in patients with AIDS was frequent before the cART era. Although ART successfully reduces the plasma HIV viral load (plVL), it is not effective at attenuating HIV-induced neuroinflammation that can lead to deregulation of the dopaminergic system.[4]

Since the identification of increased alpha-synuclein deposition in the substantia nigra of aging PLH,[5] the hypothesis that expression and progression of neurodegenerative diseases, for example, Parkinson disease (PD), might be facilitated by HIV was advanced.[4] Pathogenetic mechanisms of PD and HIV-associated neurologic complications partially overlap and include chronic neuroinflammation, oxidative stress, lymphocytic infiltration, and impaired mitochondrial function.[3,6] Hence, some authors considered a predisposition, even a pathogenetic link, between HIV and long-term cART, with PD development.[4,7] However, that notion originated from a few isolated cases or small series (Table 1).[7–12]

We undertook this retrospective, single-center case–control study to determine whether idiopathic PD characteristics are indeed different in PLH. We distinguished PD, the idiopathic form of the disease, from Parkinsonism, the broader descriptive term referring to heterogeneous diagnoses. Moreover, the Parkinsonism seen in patients with AIDS is often atypical in presentation, with symmetrical signs of bradykinesia and rigidity, frequent lack of rest tremor, and early presentation of postural instability and gait difficulty.[13,14] Because of different samples and Parkinsonism case definitions in HIV infection, we chose to limit our study to idiopathic PD according to the United Kingdom

Parkinson's Disease Society (UKPDS) Brain Bank criteria[15] with asymmetry at onset and response to L-dopa.

# METHODS

## Ethics Approval

This study was approved by the Institutional Review Board of Fondation Ophtalmologique Adolphe de Rothschild. Informed consent was waived because of anonymous data collection.

## Study Population

Between 2002 and 2013, we identified 15 PLH-PD patients followed in 3 university hospital infectious diseases units caring for 9847 PLH in the Paris area. This reference cohort is composed of 71% men [mean age of 47 (25% >50) years; 92% taking cART for a median of 10 years; plVL undetectable in >85%; and median CD4 cell count 550/μL]. Inclusion criteria for PLH-PD were (1) PD diagnosed according to the UKPDS Brain Bank criteria[15] by 2 neurologists, one of whom is a movement-disorder specialist (J.-P.B. or M.Z.); (2) DaTSCAN showing typical asymmetric hypofixation in the striatum and putamen at PD onset; (3)

**TABLE 1.** HIV-Associated Idiopathic Parkinson Disease in the Literature

| Ref | Age (yrs) at Onset/Sex | Time Since the First HIV+ | CD4 Nadir/Current, /μL | plVL Onset/Current, Copies/mL |
|---|---|---|---|---|
| 7 | 55/M | 10 yrs | 180/380 | NR/undetectable |
| 7 | 44/M | 4 yrs | 510/728 | NR/undetectable |
| 7 | 53/M | 13 yrs | 88/450 | NR/undetectable |
| 8 | 60/M | 1 yr | 38/NR | 450,000/NR |
| 8 | 73/F | 3 mo | 251/404 | 33,000/undetectable |
| 9 | 66/M | 10 yrs | NR | NR |
| 10 | 40/M | 20 yrs | NR/650 | NR/undetectable |
| 11 | 44/M | PD 4 yrs before HIV+ | NR/436 | NR/1053 |
| 12 | 48/M | Same time | NR | NR |

| Ref | Symptoms at Onset | Clinical Features | DRT/LED, mg/d | Evolution | PD Duration, yrs |
|---|---|---|---|---|---|
| 7 | Unilateral rest tremor | Hypomimia, left-sided rest tremor, rigidity and bradykinesia, loss of left arm swing | Null/400 | NR | 2 |
| 7 | Unilateral rest tremor | Right hand rest tremor, mild symmetric limb rigidity, bradykinesia, bilaterally reduced arm swing, foot dystonia | Null/600 | NR | 3 |
| 7 | Unilateral rest tremor | Hypomimia, right-sided rest tremor, rigidity, bradykinesia, bilaterally reduced arm swing | Good/300 | NR | 3 |
| 8 | Unilateral rest tremor | Right-sided bradykinesia and rigidity | Good/375 | Improvement | 6 |
| 8 | Unilateral rest tremor | Hypomimia, right-sided bradykinesia | Good/NR | Improvement | 4 |
| 9 | Unilateral rest tremor | Right-sided tremor, bradykinesia, and rigidity | Good/700–750 | Improvement but fluctuations within a 2-yr period. Indinavir-induced dyskinesia | 5 |
| 10 | NR | Rigidity and bradykinesia | Good/NR | Improvement but severe fluctuations after 7 yrs necessitating DBS | 8.5 |
| 11 | Tremor | Tremor | Good/1250 | Improvement but severe fluctuations after 3 yrs necessitating DBS | 15 |
| 12 | Unilateral rigidity | NR | NR | NR | NR |

F, female; M, male; NR, not reported; Ref, reference.

normal 1.5 Tesla brain magnetic resonance imaging (MRI) and spectroscopy at PD onset; (4) absence of cognitive impairment at onset with a total Montreal cognitive assessment score >26/30; and (5) follow-up available for >2 years. Exclusion criteria were (1) head injury with loss of consciousness >5 minutes; (2) cerebral opportunistic infection or lymphoma; (3) neurologic disease other than PD; (4) psychiatric disorders other than depression or anxiety; and (5) neuroleptic treatment or amphetamine use. Two male HIV-negative controls, randomly selected from the James Parkinson Unit database at Fondation Rothschild, were matched to each case for age and PD duration, because they are among the strongest contributors to PD progression in the general population.[16] Inclusion criteria for controls were (1) PD diagnosed according to the UKPDS Brain Bank criteria; (2) absence of cognitive impairment at PD onset with a total short portable mental status questionnaire <2; and (3) absence of HIV infection. Their exclusion criteria were the same as for PLH-PD. Case and control diagnoses were monitored during follow-up to ensure high diagnostic accuracy and exclude those with atypical Parkinsonism.

## Data Analysis

Clinical PD characteristics were first symptoms at onset, the modified Hoehn and Yahr (H-Y) stage,[17] Unified Parkinson's Disease Rating Scale (UPDRS) motor score,[17] fluctuations, falls, freezing, dyskinesia, and Montreal cognitive assessment–assessed mental status for PLH-PD,[18] and the short portable mental status questionnaire for controls.[19] To evaluate activities of daily living and handicap severity, we routinely use the Handipark scale, specifically developed for PD and validated, correlated with the Schwab and England, UPDRS, and H-Y scales with an independent score from the moment the patient is examined.[20] Clinical PD severity was assessed in an operationally defined "on state" based on expert judgment at the time of the consultation, which is regularly used in many studies.[21–24] Thus, patients and controls were not necessarily at the peak of optimal response (true "on state"). Because the same definition was used for both groups, our results are valid and comparable. Also, DA replacement therapy (DRT) information was collected as follows: daily levodopa-equivalent dose (LED) based on standard methods for calculation,[25] repeated-dose regimen, and duration of levodopa use. Impulse control disorders (ICDs) were systematically sought during each consultation.

## Statistical Analyses

Data are expressed as medians (range), unless stated otherwise. The differences between the distributions of categorical data were compared using Fisher exact test, with $P < 0.05$ defining significance, whereas continuous variables were compared with the Wilcoxon rank-sum test. JMP.10 software (2012 SAS Institute, Cary, NC) was used.

## RESULTS

The clinical and laboratory findings for PLH-PD patients are presented in Table 2. All were taking cART,

and 11 of 15 had CD4 cell counts >500/µL at PD onset. All had sustained virus suppression and immune reconstitution during follow-up exceeding 5 years. The median time since HIV diagnosis was 22.7 (3.4–29.4) years. PLH-PD patient 8 and 4 controls had family histories of PD.

The PD characteristics of cases and controls are detailed in Table 3. At PD onset, their neurological examinations, median UPDRS motor scores, and therapeutic management with the same diagnosis-to-starting first-line therapy (a DA agonist for most) or levodopa interval were comparable. At the end of the follow-up, the median daily LED and repeated-dose regimen per day, cognition, and rates of fluctuations, drug-induced dyskinesias, freezing or falls were also similar.

In contrast some PLH-PD patients' features differed from controls. At the last consultation, with the same daily LED and regimen for both groups, PLH had significantly lower median UPDRS motor score, the lower median modified H-Y stage, and lower median Handipark scale score (Table 3). More PLH reported hallucinations consisting essentially of feeling of presence (70%). ICDs were also more frequent in PLH, involving excessive buying and generosity (n = 8), internet addiction (n = 3), pathologic internet gambling poker (n = 1), or hypersexuality (n = 2).

Four PLH-PD patients exhibited a very unusual feature consisting of a stereotyped subacute severe motor degradation over a few weeks that was totally reversed by levodopa dose intensification. The patients' responses to usual medications became less consistent, with longer OFF periods. PLH complained of unrestricted ambulation declining to <500 m, freezing, wearing off, falls, and camptocormia with abdominal pain. These patients experienced frank worsening of their bradykinesia and axial rigidity that principally resulted in abnormal posture, with an UPDRS motor score increment within a few weeks of ≥20 points, reaching a maximum total score of 60/108 points for patient 6, whereas his score before worsening had been 12/108 points. In parallel, the H-Y stage progressed from 1 or 1.5 to 3 or 4, without any associated confusional state. No precipitating factors, that is, reduction or discontinuation of dopaminergic medication, introduction of drugs known to worsen Parkinsonism (neuroleptics, antidepressants, and antiemetics), infections, gastrointestinal tract diseases, or bone fractures were found, despite extensive workups. All patients rapidly recovered from their previous-worsening neurological status after increasing the daily levodopa dose, ranging from 100 to 300 mg/d. DA agonists were ineffective. Within a mean of 4 months, the UPDRS motor scores and H-Y stage were totally restored, and patients regained their previous level of function that lasted for >2 years, without any other therapeutic adjustment.

After 12 years of good symptomatic control, PLH-PD patient 15 underwent deep brain stimulation of the subthalamic nucleus (DBS-STN) because of severe fluctuations with peak-dose dyskinesias and >6 hours-a-day OFF periods, despite a total daily LED of 1500 mg. Before DBS-STN, his ON state UPDRS motor score was 12/108 and worsened to 54/108 in the OFF state. No short-term or long-term adverse event was recorded after the same DBS-STN procedure as that for the general population: his UPDRS motor score fell to

**TABLE 2.** Epidemiologic, Clinical and Biologic Data for 15 HIV-Infected Patients With PD

| Patients | Age, yrs/Sex | Transm/CDC Stage | Age, yrs Onset | CD4 (Nadir/Onset/Current), /µL | plVL Onset/Current, Copies/mL | PD Onset Symptoms |
|---|---|---|---|---|---|---|
| 1 | 66/M | MSM/A | 56 | 288/372/466 | 0/0 | Unilateral tremor |
| 2 | 71/M | MSM/A | 67 | 526/526/611 | 6914/0 | Unilateral tremor |
| 3 | 52/M | MSM/A | 47 | NR/805/900 | 0/11 | Rigidity, bradykinesia |
| 4 | 53/M | HS/C | 49 | NR/1200/1086 | 0/0 | Rigidity, bradykinesia |
| 5 | 60/M | HS/B | 55 | 246/366/245 | 0/846 | Rigidity, bradykinesia |
| 6 | 69/M | MSM/A | 66 | 564/1850/2120 | 0/0 | Rigidity, bradykinesia |
| 7 | 47/M | MSM/A | 42 | 372/536/689 | 184,200/0 | Micrographia, difficulties shaving |
| 8 | 62/M | MSM/A | 51 | 137/168/848 | NR/0 | Unilateral tremor |
| 9 | 75/M | MSM/A | 70 | 376/1204/1153 | 0/0 | Rigidity, tremor |
| 10 | 55/M | MSM/C | 50 | NR/820/1100 | 0/0 | Micrographia, difficulties biking |
| 11 | 45/M | UK/A | 40 | NR/648/542 | 0/0 | Unilateral tremor |
| 12 | 54/M | MSM/A | 44 | 235/NR/538 | NR/28 | Rigidity, bradykinesia |
| 13 | 68/M | MSM/A | 59 | 220/500/427 | 0/0 | Unilateral tremor |
| 14 | 57/M | MSM/C | 52 | 5/517/602 | 0/0 | Unilateral tremor |
| 15 | 73/M | MSM/A | 58 | 253/568/687 | 338,977/0 | Unilateral tremor |

| Patients | PD Duration, yrs | Current LED, mg/d | UPDRS Motor Onset/Current | H-Y Stage Onset/Current | Handipark Current Score | Current MoCA (Rough/z-score) |
|---|---|---|---|---|---|---|
| 1 | 10.42 | 1900 | 7/9 | 0/1 | 2 | 30/2.02 |
| 2 | 3.42 | 300 | 6/2 | 0/1 | 2 | 29/1.56 |
| 3 | 4.42 | 375 | 28/8 | 1/1 | 2 | 30/2.32 |
| 4 | 4.42 | 1033 | 35/6 | 1/3 | 6 | 28/1.66 |
| 5 | 5.42 | 1160 | 37/12 | NA/1.5 | 3 | 25/1.5 |
| 6 | 5.42 | 900 | 15/1 | 1/1.5 | 2 | 30/1.84 |
| 7 | 5.42 | 450 | 21/15 | 1/1 | 3 | 29/1.71 |
| 8 | 11.43 | 166 | 5/2 | 0/1 | 2 | 30/1.87 |
| 9 | 5.42 | 300 | 11/2 | NA/1 | 2 | 28/1.27 |
| 10 | 4.42 | 830 | 14/1 | 1/1 | 3 | 30/1.6 |
| 11 | 5.42 | 275 | 6/1 | 0/1 | 2 | 27/1.2 |
| 12 | 9.42 | 450 | 17/4 | NA/2 | 3 | 30/4.67 |
| 13 | 8.42 | 600 | 26/3 | NA/1 | 2 | 30/1.87 |
| 14 | 4.42 | 405 | 28/8 | NA/1 | 2 | 30/1.67 |
| 15 | 14.42 | 1166 | 12/6 (DBS) | 1/2.5 | 3 | 29/4.08 |

All had typical DaTSCANs. All values were performed "on drug."

CDC, Centers for Disease Control and Prevention; HS, heterosexual contacts only; M, male; MoCA, Montreal cognitive assessment; MSM, men having sex with men; NR, not reported; Transm, HIV transmission route; UK, unknown.

6/108 and, at his last consultation, 2.5 years later, daily LED was 575 mg/d, UPDRS motor was 12/108 with no fluctuations.

## DISCUSSION

Evidence from clinical, imaging, biochemical, murine models, and pathological studies underscored a major contribution of bilateral basal ganglia dysfunction in HIV-associated neurologic complications, particularly the pathogenesis of HIV dementia, a subcortical dementia with the core symptoms resembling PD.[3] Positron emission tomography studies demonstrated a bilateral decreased of dopaminergic transporters within the caudate and putamen in HIV-infected patients with dementia compared with seronegative controls.[26]

However, the dopaminergic transporter–reduction patterns in PLH were not typical of those seen in PD but showed parallel findings of greater reduction in the putamen than the caudate.[26]

Before the widespread use of cART, Parkinsonism was relatively frequent in AIDS, being predominantly iatrogenic, or associated with opportunistic infections or HIV infection itself. During the pre-cART era (1986–1999), Parkinsonism affected up to 5%–10% of all PLH.[3,14] In the post-cART era with better control of HIV infection, that frequency fell to 0.2%, whereas the mean age of these patients rose from 37.2 to 62.5 years.[8] Differences between health care systems are important concerns when evaluating the true prevalence of cART era CNS complications. Indeed, 49% of all PLH in the United States do not remain under care and only 19% are estimated to achieve circulating HIV suppression.[27] In

**TABLE 3.** Parkinson Disease Characteristics in Persons Living With HIV and Controls

| Characteristic | PLH-PD (n = 15) | PD Controls (n = 30) | P |
|---|---|---|---|
| Actual age, yrs | 60.3 (45 to 75) | 60.3 (45 to 75) | 0.5 |
| Age at PD onset, yrs | 52.4 (40 to 70) | 53.8 (39 to 71) | 0.6 |
| PD duration, yrs | 5.4 (3 to 14) | 5.9 (1 to 12) | 0.62 |
| H-Y stage at the end of follow-up | 1 (1 to 3) | 2.2 (1 to 4) | 0.0005 |
| Years from onset to first-line therapy | 0 (0 to 1) | 0 (0 to 5) | 0.14 |
| Years from onset to levodopa initiation | 1 (0 to 4) | 1 (0 to 5) | 0.13 |
| Duration of levodopa use, yrs | 4.8 (1 to 14) | 4.3 (0 to 9) | 0.28 |
| Daily LED at the end of follow-up, mg | 450 (166 to 1166) | 512 (0 to 1300) | 0.54 |
| Daily repeated-dose regimen | 3 (1 to 10) | 4 (1 to 7) | 0.13 |
| UPDRS motor score | | | |
|   Onset | 15 (5 to 37) | 10 (5 to 33) | 0.31 |
|   End of follow-up | 4 (1 to 15) | 14 (6 to 38) | <0.0001 |
|   Delta | −13 (−29 to 2) | 3 (−14 to 24) | <0.0001 |
| Handipark score at end of follow-up | 2 (1 to 6) | 3 (1 to 8) | 0.0036 |
| Initial symptoms, n (%) | | | |
|   Tremor | 8 (53) | 14 (48) | 1 |
|   Rigidity | 8 (53) | 3 (10) | 0.0033 |
|   Bradykinesia | 7 (46) | 11 (38) | 0.74 |
| Complications at the last visit, n (%) | | | |
|   Motor | | | |
|     Fluctuations | 3 (20) | 13 (43) | 0.19 |
|     Falls | 2 (13) | 4 (13) | 1 |
|     Freezing | 3 (37) | 2 (8) | 0.078 |
|   Nonmotor | | | |
|     ICDs | 9 (60) | 8 (26) | 0.049 |
|     Hallucinations | 5 (33) | 2 (7) | 0.032 |
|     Global cognitive impairment | 0 | 4 (14) | 0.28 |

All values were performed "on drug." Values are median (range), unless stated otherwise.

contrast, in France, and other countries where cART is provided free, 87% of PLH are currently under care with only 9.7% of patients experiencing virological failure.[28] In the cART era, parkinsonian symptoms were noted in up to 80% of PLH over 50 years of age from the Hawaii Aging with HIV Cohort, leading to the conclusion of increased extrapyramidal motor signs with aging.[29] Among PLH older than 50 years and those younger than 40 years, respectively, 47% and 55% had detectable plVL and 20.7% and 11.1% had HIV-associated dementia. Because their HIV-control indices were not optimum, those patients seemed to more closely resemble those before the cART era. That study also found an excessively high percentage of healthy controls having parkinsonian symptoms also, that is, 52.9% of matched HIV-negative subjects had ≥1 extrapyramidal sign and 15.7% exhibited ≥3 signs on the UPDRS motor test. Moreover, no brain imaging was available to exclude a causal lesion. Cohorts that include untreated or not virologically suppressed subjects overestimate the true prevalence of neurological complications in the cART era and are a great cause of alarm for patients and physicians, as recently highlighted for HIV-associated neurocognitive disorders.[30] Hence, in studies with asymptomatic and aviraemic HIV-seropositive individuals on cART, the prevalence of HIV-associated neurocognitive disorders is similar to the prevalence expected in HIV-negative populations.[30]

Tisch and Brew[7] described 3 PLH-PD patients, aged 44–53 years, from an Australian cohort of 2500 PLH. Their patients had atypical features distinguishing them from idiopathic PD: 2 of 3 had a poor or null response to levodopa, despite having reached therapeutic doses (400 mg/d for 1 and 600 mg/d for the other), and 2 of 3 had early bilateral signs after symptoms onset, whereas they usually appear after a mean of 4 years in idiopathic PD.[31]

The diagnosis of idiopathic PD is still mainly clinical. All our patients complied with the UKPDS Brain Bank criteria,[15] which are the benchmark of iPD diagnosis and routinely used by all studies as the gold standard to make the diagnosis process as objective and accurate as possible.[32] Moreover, these rigorous diagnostic criteria applied during a specialist's assessment, as in our study, achieved 95% diagnostic accuracy.[32] As recommended, we regularly reapplied these criteria to all our patients, HIV+ or not, and, notably, at the end of the median 6.5-year follow-up to minimize clinical misdiagnosis and exclude atypical features. Hence, retrospective application of the UKPDS Brain Bank criteria improved the diagnostic accuracy to 90%.[32,33] Brain magnetic resonance imaging of PLH excluded AIDS-associated Parkinsonism with opportunistic infection, tumor, or CNS Whipple disease.[14] DaTSCAN is not mandatory for the diagnosis of idiopathic PD. We added it to the

UKPDS Brain Bank criteria to confirm the presence of a frank asymmetric hypofixation in the striatum and putamen in all PD-PLH and to assure that a degenerative process was indeed responsible for the parkinsonian symptoms.[33] DaTSCAN sensitivity and specificity for the diagnosis of early iPD patients were 79% and 97%, respectively.[34] Finally, the excellent and sustained clinical benefit of DRT during a mean follow-up of >6 years provided the best confirmation of the diagnosis of idiopathic PD for our patients. Indeed, for subjects responsive to DRT, diagnostic accuracy of PD for disease lasting >5 years reached 88%.[35] Studied subjects were part of a PLH cohort taking effective cART with most having sustained virus suppression and >500 CD4 lymphocytes per microliter. In resource-rich health care settings, these are the most relevant subjects to study the consequences of prolonged HIV infection and cART on cerebral function.

Forty percent of our HIV-infected PD patients were 50 years or younger at onset, as described in case reports.[7,10–12] If the bulk of the population with the classic iPD form is 40–75 years of age,[36] exhibiting a bimodal distribution of iPD-onset age with peaks at 40–44 years and 75–79 years,[37] this relatively young age of onset might also be linked to the specificity of the free health care system in France. All PLH have quarterly consultations and a systematic thorough annual check-up with their infectious diseases specialists. Moreover, our cohort patients have easy access to neurological consultations. The results of several studies demonstrated that a range of prediagnostic features are present several years before iPD diagnosis, with a mean time between first symptoms noted by patients and diagnosis reaching 10.2 years.[38] These favorable conditions might have referred patients as soon as their initial symptoms were present.

During a 12-year period, we diagnosed only 15 PD among a cohort of 9847 PLH, which is much less than expected based on the study by Tisch and Brew[7] who predicted a 4–8 times higher PD incidence in PLH. Indeed, according to their calculation, we should have diagnosed at least 44–176 PLH with PD during our study period. In our cohort, the PD incidence and prevalence rates were 12.7 person years and 152 per 100,000, respectively. In Western general populations, the annual PD incidence rates range from 9 to 22 per 100,000 inhabitants[39] and prevalence of 100–200 per 100,000 persons.[40] Our results do not support a higher PD frequency in PLH with good HIV-control indices.

Overall, PD clinical characteristics and therapy did not differ between PLH and controls. With the same treatment guidelines proposed for idiopathic PD, PLH had rapid and good responses to DRT that was well tolerated in combination with cART. We did not observe drug intolerance or cART interactions, as rarely described,[11] notably with protease inhibitors.[9] The results of animal studies suggested that levodopa could increase the risk of HIV replication and affect immune cells resulting in accelerated disease progression.[41] HIV-control indices remained stable during follow-up. The long-term therapeutic responses were also particularly good, and PLH benefited from the same so-called "honeymoon" period described for idiopathic PD. Our patients 1 and 8 had unilateral tremors as their presenting symptom, responded very well to DRT, and were staged H-Y 1 after 10 years of follow-up. The results of several studies on the general population demonstrated that tremor-dominant iPD has a slower disease progression rate, with 70% of patients remaining at H-Y stage 1 or 2 for years.[42] As early as 1967, when no DRT was available, Hoehn and Yahr[43] reported in their seminal article that about one third of their iPD patients, regardless of phenotypes, had remained in stage 1 or 2 for until 10 years. Our patient 15 and 2 other published cases[10,11] suggest that DBS-STN, when pertinent, should be proposed with the same inclusion and exclusion criteria as for the general population.

The past decade has seen growing recognition of iPD phenotypic heterogeneity in the patterns of initial symptoms and progression rates. All these differences do not invalidate the iPD diagnoses, as demonstrated by autopsy studies.[44] As reported for the general population, our case–control study based on the same diagnosis criteria for both groups demonstrated some phenotypic differences between HIV+ and HIV-negative patients. Notably, some characteristics were specific to PD in PLH, raising the possibility of HIV-induced DA-transmission changes by comparison with idiopathic PD. With the same total mean daily LED and dose regimen at the last consultation, PLH-PD patients performed significantly better than controls, with lower Handipark scale and UPDRS motor scores, and an H-Y stage. In keeping with the natural history of treated idiopathic PD, controls had a mean H-Y stage of 2 after 4.3 years on levodopa and 42% of them had reached H-Y stage 2.5 at the last visit.[31] With the same PD duration, 80% of PLH had an H-Y stage <2. In our experience (unpublished data), the mean Handipark scale score after 4 years on levodopa was 4.4, whereas this score was <2 for 60% of our PLH-PD patients. Nonmotor complications (eg, ICD and feeling of presence) were also more frequent in PLH than controls, whereas DRT doses and regimens were similar. Notably, DA agonists were not overprescribed in PD-PLH compared with controls (100% vs 94%, respectively). In particular, none of these PD-PLH reported recreational or polydrug use.

Dysfunction of dopaminergic neurotransmission, with hypersensitivity of the nigrostriatal pathways in the CNS of PLH, has been demonstrated.[41] The results of numerous studies support the hypothesis that HIV induces neuroinflammation in the structure and function of the CNS reward pathways.[45] A number of transgenic rodent models have been validated for investigating neurologically related issues, notably HIV-related pathology and immune dysfunction.[45] A gp120-transgenic mouse model showed increased sensitivity to the rewarding effects of methamphetamine.[45] PLH are also more likely to abuse substances than the general population, notably men having sex with men.[46] It could be the consequence of a premorbid risk-taking personality but HIV could also be involved in sensitizing individuals to the pleasurable effects of these substances.[45] A functional adaptation in presynaptic and postsynaptic dopaminergic neurons leading to up-regulation of DA receptors could be a plausible explanation of the PD discrepancies associated with HIV infection and cART.[47] Those authors described abnormal dopaminergic markers with sharply increased DA-transporter concentrations, decreased DA synthesis, fewer

DA D$_2$ autoreceptors at the presynaptic level, and more DA D$_3$ receptors at the postsynaptic level, whereas DA D$_1$ receptors remained unchanged.[47] Postmortem studies from individuals with HIV encephalitis suggested increased dopaminergic tone in the striatum.[47] These shifts are opposite to what is observed in idiopathic PD, in which striatum dopaminergic tone and receptor occupancy are low.[6] This HIV-induced functional adaptation of dopaminergic neurons might counterbalance the degenerative neuronal loss and explain the discrepancies observed in PLH-PD patients.

For treated PD patients, the average annual progression of motor symptoms is modest but continuous[48] with worsening resulting from irreversible progression of neuronal loss. Other than intervening events, particularly infectious and gastrointestinal illnesses, discontinuation of dopaminergic medications, and administration of antidopaminergic drugs, severe acute worsening of UPDRS motor scores is highly improbable in idiopathic PD.[31,33] We observed such rapid deterioration in 4 of 15 PLH-PD patients in the absence of precipitating events, leading to considerable rises of their UPDRS motor scores, accompanied by unresponsiveness to the same drug regimen that had adequately corrected symptoms so far. These patients did not differ from the others, with comparable parkinsonian phenotype or longer PD duration. Moreover, they had the same age at PD onset, responses to DRT, mean daily LED, the UPDRS motor scores, and H-Y stage, when deterioration occurred and at the last consultation. They did not develop PD-related or HIV-associated cognitive impairment. Their HIV infection was immunovirologically controlled without any viral escape. Hence, their cART has not been modified. Posture was most affected because of the appearance or worsening of axial hypertonicity. It is generally accepted that axial tone and posture abnormalities are more common in advanced PD, are not levodopa-responsive phenomena,[49] and even worsen under levodopa.[50] The UPDRS motor score and H-Y stage returned to their previous levels, a mean of 4 months after the intensification of the total levodopa dose. This impressive, acute functional deterioration was like a "bolt from the blue," and was rapidly and long-lastingly levodopa-responsive. To our knowledge, it is unique to HIV-associated PD and very unusual in idiopathic PD.

The principal strength of this study is its recruitment of participants from a large cohort of immunovirologically controlled PLH and the long-term follow-up of PD since onset, enabling description of the natural history of treated PD in PLH. Previous reports were hampered by small patient numbers or isolated case reports, short follow-up, and absence of matched controls. Our study's limitations include unavailable neurologic examination results for the entire PLH cohort, but they were available for those referred by their infectious diseases specialists. However, in France, all PLH have a systematic annual check-up with thorough physical examination, and access and referral to weekly neurologic consultation in each of the 3 Infectious Diseases Units participating in this study is assured by 2 neurologists (A.M. and A.G.). The risk that a PLH-PD patient could have been missed is highly improbable over the 12-year study period.[35] Some sex discrepancies were reported, with a higher PD burden in men[51]; because all our PLH-PD patients are men, we cannot extrapolate our results to HIV-infected women. Our control and PLH-PD patients may not necessarily be representative of an underlying population of newly diagnosed PD patients, because they were derived from clinics specializing in PD and neurologic disorders linked to HIV infection. The better response to DRT of HIV-infected PD patients could be biased by the retrospective character of this study. These limitations are tempered by the fact that the same selection criteria were applied for both cases and controls.

A higher incidence of medical comorbidities will probably emerge with the aging of PLH. Although more new PD cases are likely to be diagnosed in PLH, we consider this association to be merely a simultaneous occurrence with no etiopathogenetic link, like the majority of authors who reported PD in association with HIV.[10] The same therapeutic regimen should be proposed to PLH-PD patients but some peculiarities associated with HIV infection suggest better and sustained responses to DRT. Our results need to be confirmed with prospective and multicenter studies.

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