Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

demiol Glob Health 2017;7:185–9, http://dx.doi.org/10.1016/j.jegh.2017.06.001.
[8] Aggarwal K, Agarwal A, Jaiswal N, Dahiya N, Ahuja A, Mahajan S, et al. Ocular surface manifestations of coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. PLoS ONE 2020;15, http://dx.doi.org/10.1371/journal.pone.0241661.
[9] Halabi KC, Saiman L, Zachariah P. The epidemiology of respiratory syncytial virus in New York city during the COVID-19 pandemic compared with previous years. J Pediatr 2021, http://dx.doi.org/10.1016/j.jpeds.2021.10.057.
[10] Foley DA, Phuong LK, Peplinski J, Lim SM, Lee WH, Farhat A, et al. Examining the interseasonal resurgence of respiratory syncytial virus in Western Australia. Arch Dis Child 2021, http://dx.doi.org/10.1136/archdischild-2021-322507.

M. Ricco [a,*]
M. Valente [b]
F. Marchesi [b]
[a] *AUSL–IRCCS di Reggio Emilia, Servizio di Prevenzione e Sicurezza negli ambienti di Lavoro (SPSAL), Via Amendola n.2, Reggio Emilia (RE), Italy*
[b] *Department of Medicine and Surgery, University of Parma, Via Gramsci n.14, 43123 Parma (PR), Italy*

* Corresponding author at: Local Health Unit of Reggio Emilia, Via Amendola n.2, 42122 Reggio Emilia (RE), Italy.
E-mail address: matteo.ricco@ausl.re.it (M. Ricco)

Received 17 January 2022

Accepted 26 January 2022
Available online 2 February 2022

https://doi.org/10.1016/j.idnow.2022.01.006

Exhaustive assessment of Reunion Island inpatients with COVID-19 during the first wave

On Reunion Island, a French overseas department of 860,000 inhabitants located in the Southwestern part of the Indian Ocean (SWIO), the first confirmed case of coronavirus disease 19 (COVID-19) was imported by March 11, 2020. Considering the intense air traffic, we hypothesized that importations would be a major source of COVID-19 cases on Reunion Island. It was even more likely given that high-level standard of care, regional organization and policies confer a central role to Reunion Island for receiving air-flight medical evacuations from the SWIO region (Mauritius, Madagascar, Mayotte, and The Comoros).

So far, limited information is available to describe the characteristics of inpatients from insular tropical settings. The Reunionese population is still relatively young but yet strongly affected by obesity (11%), diabetes (9.8%), and dengue, raising fear of increasing severe COVID-19 infections [1–3].

The purpose of this study was to describe the clinical severity of all COVID-19 inpatients presenting at the referral hospital of SWIO.

The COVID-EPI retrospective cohort study was conducted within Félix Guyon University Hospital, the only referral facility allowed to treat patients with COVID-19 on Reunion Island. Between March 11 and May 10, 2020, we enrolled all consecutive COVID-19 inpatients either diagnosed by a positive SARS-CoV-2 reverse-transcription polymerase chain reaction (RT-PCR) from a nasopharyngeal swab specimen or positive antibodies. We divided our study period into two periods: Stage-1 period (introduction of an emergent pathogen into the territory) for admissions between March 11 and March 24, 2020, and Stage-2 period (start of its autochthonous spread) between March 25 and May 10, 2020 (end of lockdown). Hospitalization policy changed to comply with national and local guidelines according to the stage of the outbreak.

Consent to participate was obtained orally for each patient before enrolment in the cohort after written information had been handed out.

Epidemiological, clinical, sociodemographic characteristics and outcomes were collected from electronic medical records. Length of stay was provided by the Medical Informatics Department, blood group by the French blood establishment, and health insurance status by the administrative department of the hospital.

Clinical outcomes included the length of hospital stay, intensive care unit (ICU) admission, vital status at discharge [4], type of discharge for patients discharged alive, readmission, and vital status on day 28 post admission.

Continuous variables were described using median and interquartile range (IQR) values and categorical variables as percentages. Comparison between Stage-1 and Stage-2 periods were performed using Student's *t* test or Mann-Whitney test or Chi2 or Fisher's exact test, as appropriate. Two-sided tests and a significance threshold set at $p \leq 0.05$ were used. All statistical analyses were performed using the SAS® software (v9.4, SAS Institute, Cary, NC, USA, 2013).

Out of 436 COVID-19 cases diagnosed on the island, 171 (39%) required hospitalization. Among these, 168 were enrolled in the COVID-EPI cohort.

The median age of inpatients was 50 years (IQR: 35-63, range 3-86 years). Half were females, of whom five were pregnant. Eighty-two inpatients (50%) had one or more comorbidities (including age and obesity), 70 (43%) excluding age. The most common comorbidities were hypertension, obesity, and diabetes mellitus (Table 1).

Stage-2 inpatients were more likely autochthonous than Stage-1 inpatients. However, there were no significant differences between imported and autochthonous cases regarding age, comorbidities, severity of illness, and time from symptom onset to RT-PCR and from symptom onset to admission. Importantly, most imported cases (82%) were permanent residents of the island. Among 159 symptomatic people, the five most common symptoms at onset of illness were fever, dry cough, asthenia, myalgia, and headache.

Median time between fever onset and apyrexia was 9 days (IQR: 6-13 days).

Forty (23%) inpatients had a severe to critical COVID-19 presentation. There was a trend towards more severe forms of COVID-19 in Stage-2 compared with Stage-1 ($P = 0.059$). None of the patients have been included in an interventional research study protocol (Table 2).

The median length of stay was seven days (IQR: 3-13 days). Seventeen (10%) patients required admission to the ICU. One patient died in the ICU, 12 days after admission (death attributable to COVID-19). He was an 82-year-old man with hypertension and chronic kidney failure, who had been medically evacuated from Mayotte Island. Evacuated patients from Mayotte or Comoros Islands ($n = 9$) more frequently presented with comorbidities (89% vs. 47%; $P = 0.034$) and were more likely to be admitted to the ICU (33% vs. 9%; $P = 0.050$).

Our data highlight the low severity of the illness on our territory during the first wave of the COVID-19 epidemic (low infection fatality rate: 0.6%). Several factors may influence SARS-CoV-2 severity here. First, COVID-19 severity can be modulated by age [5]. Compared to some other European hospital-based studies, our population was about 10 to 20 years younger [6–8]. People under 20 years of age represent 31% of the Reunionese population [9]. Second, the health service has never been overburdened. Postponement of non-urgent care was implemented in the hospital as soon as March 11, 2020 (6 days prior to the national lockdown), thus increasing hospital bed capacity. Treatment has evolved during this period according to new scientific knowledge. In addition, early

Table 1
Epidemiological and clinical characteristics of 168 inpatients with coronavirus disease 2019 on Reunion Island (March 11–May 10, 2020).

	Total (n = 168)	Stage 1 (n = 68) March 11- March 24	Stage 2 (n = 100) March 25–May 10	P-value
Sociodemographic characteristics				
Age, years[c]				0.466
< 18 y	4 (2)	2 (3)	2 (2)	
18–44 y	62 (37)	27 (40)	35 (35)	
45–54 y	27 (16)	13 (19)	14 (14)	
55–64 y	38 (23)	14 (21)	24 (24)	
65–74 y	21 (12)	9 (13)	12 (12)	
Aged ≥ 75 y	16 (10)	3 (4)	13 (13)	
Male gender	86 (51)	31 (46)	55 (55)	0.231
Health insurance (n = 167)[b]	161 (96)	67 (100)	94 (94)	0.082
Supplemental health insurance (n = 162)				0.150
Yes	115 (71)	52 (78)	63 (66)	
Social benefits for vulnerable population	28 (17)	7 (10)	21 (22)	
No	19 (12)	8 (12)	11 (12)	
Place of birth (n = 118)[c]				0.088
Reunion Island	68 (58)	26 (54)	42 (60)	
Mainland France	25 (21)	15 (31)	10 (14)	
Other Indian Ocean Island	18 (15)	4 (9)	14 (20)	
Other	7 (6)	3 (6)	4 (6)	
Place of residence (n = 167)[c]				0.065
Reunion Island	143 (86)	61 (91)	82 (82)	
Mainland France	17 (10)	6 (9)	11 (11)	
Other (Mayotte and Comoros Islands)	7 (4)	0 (0)	7 (7)	
Epidemiological data				
Imported cases (n = 167)	132 (79)	61 (90)	71 (72)	0.005
Of which medical evacuation (Yes)	9 (7)	0 (0)	9 (13)	0.004
Healthcare workers (n = 154)[b]	10 (6)	7 (12)	3 (3)	0.048
Contact with positive COVID-19 case (n = 158)	69 (44)	26 (39)	43 (47)	0.290
Of which household transmission	42 (61)	13 (50)	29 (67)	0.150
Comorbidities				
Hypertension	41 (24)	14 (21)	27 (27)	0.342
Obesity (Body mass index ≥30 kg/m^2)[b]	23 (14)	3 (4)	20 (20)	0.005
Diabetes mellitus	23 (14)	6 (9)	17 (17)	0.130
Cardiovascular disease (n = 167)[b]	17 (10)	2 (3)	15 (15)	0.017
Cerebrovascular disease[b]	8 (5)	2 (3)	6 (6)	0.476
Chronic respiratory disease (n = 167)	22 (13)	11 (16)	11 (11)	0.310
Immunosuppression (n = 167)[b]	4 (2)	0 (0)	4 (4)	0.147
Malignancy[b]	7 (4)	0 (0)	7 (7)	0.042
Dementia and psychiatric disorders[b]	7 (4)	0 (0)	7 (7)	0.042
Number of comorbidities (n = 164)				< 0.001
None	82 (50)	46 (70)	36 (37)	
≥ 1 comorbidity	82 (50)	20 (30)	62 (63)	
Smoking (n = 162)				0.045
Never	118 (73)	50 (75)	68 (71)	
Past	29 (18)	15 (22)	14 (15)	
Active	15 (9)	2 (3)	13 (14)	
Blood group (n = 76)				1
Blood group O	25 (33)	9 (33)	16 (33)	
Blood group A	37 (49)	13 (48)	24 (49)	
Other blood groups (B, AB)	14 (18)	5 (19)	9 (18)	
Clinical presentation				0.022
Symptomatic	140 (84)	61 (90)	79 (79)	
Pauci-symptomatic	19 (11)	7 (10)	12 (12)	
Fully asymptomatic	9 (5)	0 (0)	9 (9)	
Symptoms at disease onset (n = 159)				
Fever	104 (65)	49 (72)	55 (60)	0.128
Dry cough	91 (54)	37 (54)	54 (59)	0.534
Asthenia	52 (33)	18 (26)	34 (37)	0.148
Myalgia	52 (33)	23 (34)	29 (32)	0.795
Headache	49 (31)	18 (26)	31 (34)	0.305
Dyspnea	43 (26)	11 (16)	32 (35)	0.008
Ageusia	38 (23)	11 (16)	27 (30)	0.048
Diarrhea	34 (21)	8 (12)	26 (29)	0.011
Symptom main locations (n = 159)[c]				0.003
Upper respiratory tract	70 (42)	41 (60)	29 (32)	
Lower respiratory tract	59 (35)	18 (27)	41 (45)	
Abdominal	11 (7)	2 (3)	9 (10)	
Other	28 (16)	7 (10)	12 (13)	
Coinfection with dengue fever[b]	3 (2)	0 (0)	3 (3)	0.273
Time, median (IQR [a]), days				
between symptom onset and RT-PCR	4 (2-7)	3 (2-5)	5 (2-9)	0.013
between symptom onset and admission	5 (3-9)	4 (3-6)	7 (4-10)	0.001
Additional tests				
Chest X-ray (yes) (n = 167)	65 (39)	44 (65)	21 (21)	< 0.001

Table 1 (*Continued*)

	Total (*n* = 168)	Stage 1 (*n* = 68) March 11- March 24	Stage 2 (*n* = 100) March 25–May 10	*P*-value
Abnormal (*n* = 59)[b]	31 (53)	20 (45)	11 (73)	0.078
1st chest CT scan (yes)	68 (40)	15 (22)	53 (53)	< 0.001
Abnormal[b]	59 (87)	13 (87)	46 (87)	1
Bilateral distribution of patchy shadows or ground glass opacity (*n* = 67)[b]	53 (79)	12 (80)	41 (79)	1
Injected chest CT scan (yes) (*n* = 166)	46 (28)	13 (19)	33 (34)	0.039
At least one ECG (*n* = 166)	107 (64)	36 (55)	71 (71)	0.030
At least one abnormal (*n* = 106)	36 (34)	7 (19)	29 (41)	0.023
QTc on 1st ECG, median (IQR[a]), ms	392 (367-420)	380 (360-417)	392 (374-420)	0.313

Data is shown as n (column percentages) or median. All *p*-values refer to comparisons between the two periods using the Mann-Whitney U test for quantitative variables and the Chi^2 test for categorical variables. RT-PCR, reverse-transcription polymerase chain reaction; CT scan, computed tomography; ECG, electrocardiogram.

[a] Interquartile range.

[b] Fisher's exact test.

[c] Fisher-Freeman-Halton test.

Table 2
Severity of illness, complications, therapeutic and clinical outcomes of 168 inpatients with coronavirus disease 2019 on Reunion Island (March 11–May 10, 2020).

	Total (*n* = 168)	Stage 1 (*n* = 68) March 11- March 24	Stage 2 (*n* = 100) March 25–May 10	*P*-value
Severity of illness (*n* = 159)[b]				0.059
Mild	107 (64)	49 (72)	49 (54)	
Moderate	21 (13)	6 (9)	15 (16)	
Severe	36 (21)	13 (19)	23 (25)	
Critical	4 (2)	0 (0)	4 (4)	
Complications				
Anemia	18 (11)	2 (3)	16 (16)	0.009
Bacterial pneumonia (*n* = 167)	15 (9)	5 (7)	10 (10)	0.542
Digestive complications[a]	11 (7)	3 (4)	8 (8)	0.528
Acute renal failure or extra-renal purification[a]	10 (6)	1 (2)	9 (9)	0.050
ARDS[a]	6 (4)	1 (2)	5 (5)	0.403
Pleural effusion[a]	6 (4)	1 (2)	5 (5)	0.403
Altered mental status[a]	6 (4)	2 (3)	4 (4)	1
Cardiac rhythm disorders[a]	4 (2)	1 (2)	3 (3)	0.648
Pulmonary embolism[a]	3 (2)	1 (2)	2 (2)	1
Thrombosis[a]	3 (2)	0 (0)	3 (3)	0.273
Cardiac ischemia[a]	3 (2)	0 (0)	3 (3)	0.273
Bacteremia[a]	3 (2)	0 (0)	3 (3)	0.273
Endocarditis[a]	2 (1)	1 (1)	1 (1)	1
At least one complication (*n* = 167)	50 (30)	14 (21)	36 (36)	0.029
Therapeutic outcomes				
Pharmaceutical treatment				
Anticoagulant[a]	42 (25)	4 (6)	38 (38)	<0.001
Antibiotics	40 (24)	10 (15)	30 (30)	0.022
Antivirals	33 (20)	12 (18)	21 (21)	0.591
Steroids[a]	16 (10)	3 (4)	13 (13)	0.106
Highest level of respiratory support (*n* = 165)[b]				0.507
None	125 (76)	55 (81)	70 (72)	
Oxygen inhalation (nasal cannula/face mask)	32 (19)	12 (18)	20 (21)	
High flow oxygen	2 (1)	0 (0)	2 (2)	
NIV	3 (2)	1 (2)	2 (2)	
IMV	3 (2)	0 (0)	3 (3)	
Clinical outcomes				
ICU admission[a]	17 (10)	4 (6)	13 (13)	0.193
Vital status at discharge (at study end point)[b]				1
Discharged alive	166 (99)	68 (100)	98 (98)	
Deceased	1 (1)	0 (0)	1 (1)	
Currently hospitalized	1 (1)	0 (0)	1 (1)	
Type of discharge for patients discharged alive (*n* = 166)[a]				0.145
Home	162 (98)	68 (100)	94 (96)	
Facilities (rehabilitation)	4 (2)	0 (0)	4 (4)	
GOS at discharge (*n* = 167)[b]				0.875
1. Death	1 (1)	0 (0)	1 (1)	
2. Persistent vegetative state	0 (0)	0 (0)	0 (0)	
3. Severe disability	1 (1)	0 (0)	1 (1)	
4. Moderate disability	4 (2)	1 (1)	3 (3)	
5. Low disability	161 (96)	67 (99)	94 (95)	
Readmitted	13 (8)	7 (10)	6 (6)	0.307

Table 2 (*Continued*)

	Total (n = 168)	Stage 1 (n = 68) March 11- March 24	Stage 2 (n = 100) March 25–May 10	P-value
Vital status at 28 days after admission (n = 167)[a]				1
Alive	166 (99)	68 (100)	98 (99)	
Died	1 (1)	0 (0)	1 (1)	

Data is shown as n (column percentages). All P-values refer to comparisons between the two periods using the Mann-Whitney U test for quantitative variables and the Chi[2] test for categorical variables. ARDS, Acute Respiratory Distress Syndrome; NIV, Non-invasive ventilation; IMV, Invasive mechanical ventilation; ICU, Intensive Care Unit; GOS, Glasgow Outcome Scale.

[a] Fisher's exact test.

[b] Fisher-Freeman-Halton test.

diagnosis at the time of travel return and systematic monitoring during Stage-1 may have contributed to prevent progression to severe disease.

We observed changes in the clinical presentation of COVID-19 over the study period and a non-significant trend towards more severe forms of the disease in the Stage-2 period that could be explained by an increase in the virulence as the transmission rate grew [10]. However, this hypothesis must be counterbalanced by the fact that hospitalization policy has also evolved over time, voluntarily selecting comorbid and severe patients who consulted later in hospital during the Stage-2 period.

This hospital-based study is one of the first to report exhaustive high-quality data about SARS-CoV-2 infection, from an insular tropical setting of the Indian Ocean. The study is still ongoing, which will allow us to follow the evolution of patients' characteristics, especially for the South African variant

Ethical approval

An oral non-opposition to participate was obtained for each patient before inclusion in the study and a written information notice was handed out. Patients already discharged from hospital were called over the phone, and the information notice was sent at home. The study was registered at the National Institute for Health Data (French acronym INDS, No. MR0614010420) and was approved by an Institutional Review Board from the French infectious diseases ethics committee (CERC-MIT, No. 2020-043; N°IRB00011642). Collected data complied with the French data protection authority (CNIL MR-004). The review board approved this case series as minimal-risk research using data collected for routine clinical practice.

Consent to participate

An oral non-opposition to participate was obtained for each patient before inclusion in the study and a written information notice was handed out.

Availability of data and materials

The corresponding author (LB) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Funding

The authors did not receive any specific grant for this research from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure of interest

The authors declare that they have no competing interest. The corresponding author confirms that he had full access to all data in the study and had final responsibility for the decision to submit for publication.

References

[1] Mandereau-Bruno L. Prévalence du diabète traité pharmacologiquement (tous types) en France en 2015. Disparités territoriales et socio-éconmiques. BEH 2017:6.

[2] Muniyappa R, Gubbi S. COVID-19 Pandemic, Corona Viruses, and Diabetes Mellitus. Am J Physiol Endocrinol Metab 2020, http://dx.doi.org/10.1152/ajpendo.00124.2020 [Epub ahead of print 31 March].

[3] Simonnet A, Chetboun M, Poissy J, et al. High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. Obes Silver Spring Md 2020, http://dx.doi.org/10.1002/oby.22831 [Epub ahead of print 9 April].

[4] McMillan T, Wilson L, Ponsford J, et al. The Glasgow Outcome Scale - 40 years of application and refinement. Nat Rev Neurol 2016;12:477–85.

[5] Fang X, Li S, Yu H, et al. Epidemiological, comorbidity factors with severity and prognosis of COVID-19: a systematic review and meta-analysis. Aging 2020;12:12493–503.

[6] Pellaud C. Characteristics, comorbidities, 30-day outcome and in-hospital mortality of patients hospitalised with COVID-19 in a Swiss area–a retrospective cohort study 2020, http://dx.doi.org/10.4414/smw.2020.20314 [Epub ahead of print 14 July].

[7] Giacomelli A, Ridolfo AL, Milazzo L, et al. 30-day mortality in patients hospitalized with COVID-19 during the first wave of the Italian epidemic: A prospective cohort study. Pharmacol Res 2020;158:104931.

[8] De Vito A, Geremia N, Fiore V, et al. Clinical features, laboratory findings and predictors of death in hospitalized patients with COVID-19 in Sardinia, Italy. Eur Rev Med Pharmacol Sci 2020;24:7861–8.

[9] Une population vieillissante - Insee Analyses Réunion - 25, https://www.insee.fr/fr/statistiques/3047952.(accessed 10 November 2020).

[10] Ebert D, Bull JJ. Challenging the trade-off model for the evolution of virulence: is virulence management feasible? Trends Microbiol 2003;11:15–20.

L. Bruneau [a,b,*]
V. Lenclume [a,1]
A. Maillot [a,1]
A. Rousseau [b]
M. Lagrange-Xélot [c]
N. Allou [d]
P. Gérardin [a]

[a] *National institute of Health and Medical Research (INSERM) Center for Clinical Investigation (CIC) 1410 Clinical Epidemiology, Centre Hospitalier Universitaire, Saint Pierre, Reunion Island, France*

[b] *Department of Public health and Research Support, Methodological Support and Biostatistics Unit, Centre Hospitalier Universitaire, Saint Denis, Reunion Island, France*

[c] *Department of Infectious Diseases, Centre Hospitalier Universitaire, Saint Denis, Reunion Island, France*

[d] *Intensive Care Unit, Centre Hospitalier Universitaire, Saint Denis, Reunion Island, France*

* Corresponding author at: Department of Public health and Research Support, Methodological Support and Biostatistics Unit, Centre Hospitalier Universitaire, Saint Denis, Reunion Island, France.
E-mail addresses: lea.bruneau@chu-reunion.fr (L. Bruneau), victorine.lenclume@chu-reunion.fr (V. Lenclume), adrien.maillot@chu-reunion.fr (A. Maillot), alexandra.cagniant@lilo.org (A. Rousseau), marie.lagrange-xelot@chu-reunion.fr (M. Lagrange-Xélot), nicolas.allou@chu-reunion.fr (N. Allou), patrick.gerardin@chu-reunion.fr (P. Gérardin)

[1] Victorine Lenclume and Adrien Maillot contributed equally.

https://doi.org/10.1016/j.idnow.2021.10.005

High penetration of doravirine in the central nervous system: What are the benefits?

ARTICLE INFO

Keywords:
Doravirine
Central nervous system
CSF penetration
Pharmacokinetics

Neurocognitive disorders associated with HIV are caused by neurological damage secondary to viral replication and immune activation. Even if dementia-like syndromes have become rare, mild to moderate damage remains a particular concern, with a significant impact on quality of life [1,2].

Limited penetration of antiretrovirals in the central nervous system (CNS) may promote persistent viremia in the cerebrospinal fluid (CSF) with viral populations distinct from those observed in plasma, even during effective antiretroviral treatment (ART). The CNS penetration-effectiveness (CPE) score classifies antiretrovirals according to their physicochemical, pharmacokinetic and pharmacodynamic characteristics and may contribute to treatment optimization in patients with HIV-associated cognitive impairment [3,4].

Doravirine is a novel non-nucleoside reverse transcriptase inhibitor (NNRTI) for which pharmacokinetic data on CSF distribution have yet to be evaluated.

We report the case of a 48-year-old female patient infected with HIV-1 since 1989, treated since 1997, in whom doravirine levels in the CSF were monitored due to exacerbation of neurocognitive disorders. In her medical history, we observed an AIDS dementia syndrome with memory disorder sequelae and a chronic depressive syndrome with several suicide attempts and multiple addictions (alcohol, cannabis, benzodiazepines, tobacco). Treatment history was marked by poor observance and the absence of viral suppression from 1997 to 2009 under multiple ARTs containing either protease inhibitor or efavirenz. Adherence subsequently improved under raltegravir, maraviroc and lopinavir/ritonavir, enabling achievement of long-term virologic control. In October 2014, her treatment was switched to tenofovir disoproxil fumarate (TDF), emtricitabine and darunavir/ritonavir for reasons of simplification, and then, in September 2018, to TDF, emtricitabine and dolutegravir. After one year, however, dolutegravir was discontinued due to neuropsychiatric side-effects.

In October 2019, doravirine was initiated in combination with emtricitabine and TDF, and continued in November 2019 with lamivudine and TDF in a fixed-dose combination maintaining good virologic control. At the same time, the patient reported an increase in pre-existing memory disorders associated with exacerbation of her chronic depression, and was particularly concerned about a progressive relapse of her HIV encephalitis. Lumbar puncture and cerebral MRI were performed. MRI showed known advanced cortical atrophy, without additional lesions, corresponding to the former encephalitis lesions. The biological and pharmacological parameters of plasma and CSF are presented in Table 1. The latter was acellular and the results showed no alteration of the blood-brain barrier (BBB). Antiretroviral trough plasma concentrations at steady-state were within the ranges of expected values, thereby enabling control of viral replication, and were even higher for doravirine. This may be attributed to variability factors such as food intake, which was not recorded during sampling. Tenofovir and lamivudine CSF concentrations as well as the CSF/plasma ratio for both NRTI were in accordance with the literature [5]. Doravirine CSF concentration came to 97 ng/ml and the CSF/plasma ratio was 7.5%.

CSF penetration of antiretrovirals is highly variable, even within the same therapeutic class, driven mainly by their physicochemical and pharmacokinetic characteristics and depicted by the CSF/plasma ratio. Weak plasma protein-binding associated with low molecular weight and strong lipophilia promote better penetration [5]. Within the NNRTI class, due to its weak plasma protein-binding (60%), nevirapine presents the best CSF/plasma ratio (about 50%), unlike efavirenz, rilpivirine or etravirine, for which the CSF/plasma ratio ranges from 0.5 to 4%. [5,6].

In our patient's case, we report a doravirine concentration in the CSF that is substantially higher than the concentrations obtained with most other NNRTI and antiretrovirals, with a CSF/plasma ratio of 7.5%, which is consistent with the physicochemical and pharmacokinetic characteristics of doravirine, particularly as regards moderate plasma protein binding (76%), thereby exhibiting good diffusion through the BBB [7]. Moreover, our result was recently confirmed by a single prospective cohort study reporting a median CSF/plasma ratio of 13% (range: 9–19%) in 15 asymptomatic HIV-1 patients [8].

CNS efficacy is usually estimated by the inhibitory quotient (IQ), defined as the ratio between the CSF concentrations and the drug IC_{50}. An IQ greater than 1 has been established to ensure good antiviral activity and associated with a lower risk of virologic escape in the CSF [9]. In our patient, doravirine CSF concentration largely exceeded the IC_{50} value, ranging from 0.5 ng/ml to 4.3 ng/ml, i.e. an IQ of approximately 22 to 194. Among other NNRTIs, nevirapine and efavirenz have presented the highest IQ values, ranging from 38 to 55 and from 5.2 to 78, respectively, compared to rilpivirine (2.9) or etravirine (3 to 18). Moreover, taking into account the integrity of the BBB in our patient, as shown by CSF proteins and glucose levels, we can be sure that CSF doravirine concentration exclusively reflects the free fraction of the drug, thereby confirming not only its high diffusion but also the effective penetration of doravirine. Even if clinical signs do not always improve after use of CSF-penetrating drugs, the initiation of doravirine in our patient enabled long-term improvement in her neuropsychological status and mood disorders after several months of treatment. Since the symptoms occurred at the same time as when we initiated a doravirine-based regimen, we cannot rule out the causality of previous regimens, which means that the clinical improvement obtained in our patient after her