Bictegravir/FTC/TAF CSF Diffusion in HIV-Infected Patients with CNS Impairment

Antoine Chéret[1,2], Thibaut Gelé[1,3], Alicia Castro Gordon[1], Valérie Furlan[1], Coralie Pallier[1], Pierre-Hadrien Becker[1], Pilartxo Catalan[1], Cécile Goujard[1,4,5], Anne-Marie Taburet[1,3], Jacques Gasnault[1,3], Hélène Gouget[3], Aurélie Barrail-Tran[1,3,6]

[1]AP-HP. Université Paris Saclay, France~ [2]Université Paris-Descartes, Sorbonne Paris Cité, France~ [3]Université Paris-Saclay, Inserm, CEA, Centre de recherche en Immunologie des infections virales et des maladies autoimmunes, France~ [4]Université Paris-Saclay, UVSQ, Inserm, CESP, France~ [5]Université Paris-Saclay, Faculté de Médecine, France~ [6]Université Paris-Saclay, Faculté de Pharmacie, France~

CROI Conference on Retroviruses and Opportunistic Infections

ID 2327

Background

The penetration of antiretroviral drugs in deep compartments, like the central nervous system (CNS), is a crucial part of strategies toward HIV cure.

This study aimed to estimate cerebrospinal fluid (CSF) diffusion of bictegravir (BIC), that has high protein binding which could limit diffusion, emtricitabine (FTC) and tenofovir alafenamide (TAF) in patients with HIV-related CNS impairment (HCI) enrolled in a real-life observational study.

Patients and methods

Monocenter, prospective, single arm, open label, observational study

- **Inclusion criteria:**
  - Admitted to the Neuro-HIV Rehabilitation Care Unit, (AP-HP, Hôpital Bicêtre, France)
  - At least 1 HIV-related CNS impairment
  - Treated by an optimized antiretroviral therapy including BIC/FTC/TAF since at least 1 month
- **Enrolment:** 2019 January to 2020 January
- **Simultaneous samples in the setting of routine care:**
  - 1 blood sampling & 1 cerebrospinal fluid (CSF) sampling

Biologic parameters

- **HIV-RNA** (RT-PCR, Abbott Realtime®)
  - Plasma & cerebrospinal fluid
- **Albumin**
  - Plasma & cerebrospinal fluid

→ Quotient albumin Q_A

Q_A = CSF albumin *(mg/L)* / Plasma albumin *(g/L)*

→ Assess blood-brain barrier (BBB) integrity

Age	Damaged BBB
< 45 years	Q_A > 6.8
≥ 45 years	Q_A > 10.2

Antiretroviral assays

- **Bound and unbound plasma BIC separation**
  - Ultrafiltration (Centrifree® devices, Merck Millipore)

Biological fluid	Plasma		CSF
Antiretroviral concentration	Total	Unbound (BIC)	Total
Internal standard (IS)	Labelled IS for each antiretroviral		
Method	Simultaneous quality control validated method (LC-MS/MS)		



Centrifree® device
Cutoff: 30 kDa

Results

Baseline characteristics

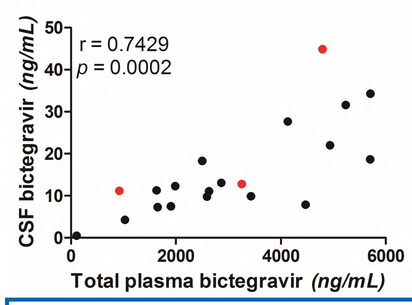
Sex – *M (♂) / F (♀)*	12 ♂ / 8 ♀
Median age (IQR) – *years*	45 (15)
Median CD4 cell count (IQR) – */µL*	204 (202)
Plasma HIV-RNA	
< 40 copies/mL – *n (%)*	14 (70)
Median (IQR) if > 40 copies/mL – *log_{10} copies/mL*	1.9 (2.2)
CSF HIV-RNA	
< 40 copies/mL – *n (%)*	18 (90)
Median (IQR) if > 40 copies/mL – *log_{10} copies/mL*	1.9 (1.2)
HIV-related CNS impairment – *n (%)*	
Progressive multifocal leukoencephalopathy (PML)	9 (45)
Cerebral toxoplasmosis (CT)	6 (30)
HIV encephalitis	2 (10)
CT combined with HIV encephalitis	1 (5)
Acute disseminated encephalomyelitis (ADEM)	1 (5)
VZV meningoencephalitis	1 (5)
Antiretroviral therapy (ART) – *n (%)*	
BIC/FTC/TAF	15 (75)
BIC/FTC/TAF + maraviroc	4 (20)
BIC/FTC/TAF + darunavir/ritonavir	1 (5)
Median (IQR) duration of the current ART regimen – *days*	32 (11)

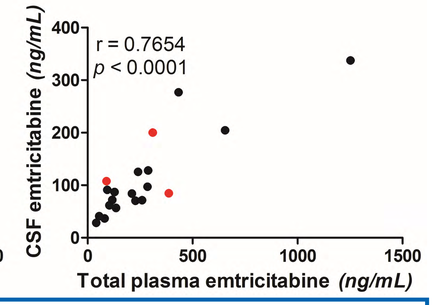
IQR: interquartile range

CSF antiretroviral diffusion

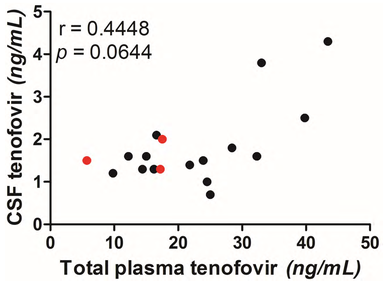
	BIC	FTC	Tenofovir
Total plasma – *ng/mL*	2630 (2854)	219 (193)	19.7 (12.2)
Unbound plasma – *ng/mL*	9.2 (9.8)	/	/
Total CSF – *ng/mL*	11.3 (12.2)	86.0 (57.8)	1.5 (0.7)
CSF IC50 – *ng/mL*	3.5	70	11.5
> CSF IC50 – *n (%)*	19 (95)	15 (75)	0 (0)
IQ50	3.4 (2.9)	1.2 (0.8)	0.1 (0.1)

Results are expressed as median (IQR)
IC50: *in vitro* 50% inhibitory concentration
IQ50: Inhibitory quotient
IQ50 = Total CSF / CSF IC50





- **There are correlations between:**
  - CSF and Total plasma concentrations for BIC and FTC



- **3 (15%) patients (● in red) had a damaged BBB**
  - HIV-related CNS impairment: PML (2), HIV encephalitis (1)
  - Not related with a higher CSF BIC/FTC/tenofovir diffusion.

Conclusion

Total plasma concentrations remained as previously reported. Almost all CSF BIC concentrations and most of CSF FTC concentrations were above the in vitro 50% inhibitory concentration (IC50). CSF tenofovir concentrations, administered as TAF, are even lower than administered as TDF. This suggests a limited effect of TAF in the CNS.

BIC with FTC/TAF backbone should be effective to target HIV replication in the CNS, which is a deep reservoir, even though BBB is undamaged.