Clinical Resolution and CSF Viral Suppression
Following Switching to a Genotype-guided South African Antiretroviral Third Line Regimen with Good CSF Penetration

Cerebrospinal Fluid HIV Viral Escape
Kabengele Kayembe D.; Nxele N.P.; Famoroti T.; Gordon M.
# Brain lives matter
Objective Neuro-symptomatic Cerebrospinal fluid Escape

Clinical and virologic outcomes

Individual and programmatic impact and management implications
The prevalence of CSF viral escape estimated at 4%–20% among ART-experienced HIV+ adults.

Figure 1. Geographic distribution of cohorts presented at the Global HIV-1 CSF Escape Meeting 2016.
The setting

Eshowe
District hospital

Deep rural Zulu Kingdom | KwaZulu-Natal province | South Africa
Neuro-symptomatic escape from cerebrospinal fluid

Clinical suspicion at the onset of new or progress of CNS symptoms

"With a high suspicion, every effort to obtain these assessments should be made since they are essential for diagnosis and rational management."

Neuro-symptomatic Cerebrospinal fluid Escape

- Plasma/CSF viral loads: September 2016
- Genotyping: October 2016* December 2016
- Magnetic resonance imaging: January 2017

*October 2016 plasma genotyping not reported (viral load 386 copies/mL)
The patient

55-year-old male
HIV infection diagnosis in February 2010
Baseline CD4 cell count (%) of 264 cells/μL (6%) and viremia of 156,162 copies/mL (cpm) (5.20 Log)

Shift worker process control officer
at a pulp and containerboard mill since 1987

Married (spouse optimally suppressed on NNRTI based ART) and father to six children
History of HIV care

- **adherence**
  - Intermittent
- **immune suppression**
  - Severe
- **viral suppression**
  - Suboptimal and labile

![Graph showing CD4 percentage and viral load levels over time.](image)

**Figure 2. Viremia & immune suppression levels**

- **Initiation**
  - March 2010
- **Switch**
  - July 2015
- **ART regimen exposure**
  - D4T, 3TC, NVP
  - TDF, FTC, ATV/r
  - TDF, FTC, LPV/r
  - TDF, FTC, ATV/r
  - TDF, FTC, LPV/r

**Figure 3. Antiretroviral therapy regimens**
History of HIV care

14 months

Ritonavir boosted protease Inhibitor based antiretroviral therapy
Insidious onset
Tremors & Unsteadiness
Progressive
Worsening
despite
viremia control
improvement
brain computed tomography
unremarkable

Spectrum & severity fluctuated with viremia
“Established” neurologic impairment
Insidious onset

Tremors & Unsteadiness

Progressive

Worsening

Incapacitation

Total dependence

Semi-consciousness

Neurogenic dysphagia

Culminated with **status epilepticus**

“Established” neurologic impairment
Definition criteria
Cerebrospinal fluid

Cerebrospinal fluid HIV-1 RNA higher than paired plasma levels

>0.5 Log***

>2 times**

≥1 Log*

Figure 4. CSF escape criteria


Figure 5. CSF/Plasma dissociation
Confirmation of Cerebrospinal fluid Escape

Meningeal inflammation

Neuro-Imaging

HIV encephalitis

Absence of alternative neuro-pathology diagnosis

Figure 5. CSF/Plasma dissociation
CNS drug resistance 
Cerebrospinal fluid 

Escape

Suggesting failure of the current treatment regimen in the central nervous system

some*, many**, majority***, all# cases had developed unique and significant resistance mutations in the CSF

CNS drug resistance Escape Cerebrospinal fluid

Compartmentalized, asynchronous, “discordant”? October 2016: Failure of boosted PI s based second-line ART regimen in the CSF

Reverse transcriptase (RT) gene
- D67N
- K70R
- T215F
- M184V
- K103N
- K238T

Protease (PR) gene
- M46I
- L10F
Plasma drug resistance escape

Cerebrospinal fluid

December 2016: Failure of boosted PIs based second-line ART regimen in the plasma

Reverse transcriptase (RT) gene
- D67N
- K70R
- T215F
- M184V
- K103N
- K238T

Protease (PR) gene
- M46I
- L10F
- V82A/V
Table 1. Reverse transcriptase (RT) gene drug resistance mutations & levels

<table>
<thead>
<tr>
<th>Mutations</th>
<th>Drugs</th>
<th>Mutation Scoring</th>
<th>Resistance Levels***</th>
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### Table 2. Protease (PR) gene drug resistance mutations & levels

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<td>M46I, V82A/V</td>
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Plasma PIs resistance one or two levels relatively higher
Rational management
Cerebrospinal fluid

What do you have to lose?!

Our Father

A CABBAGE !!!!!!!
Rational management of cerebrospinal fluid escape

Antiretroviral therapy alteration

Regimen switch and/or intensification

Patient’s adherence motivation, support & sustainment

Drug resistance* & previous exposure

Central nervous system drug penetration**

South African third line antiretroviral therapy
Cerebrospinal fluid Escape

Eligibility “criteria”
Protease inhibitor resistance mutations scoring ≥15 on the Stanford University HIV Drug resistance Database

two months earlier in the central nervous system than in the plasma

South African third line antiretroviral therapy 
Cerebrospinal fluid Escape 

Building the regimen according to the algorithm 

<table>
<thead>
<tr>
<th>Drug</th>
<th>CSF score</th>
<th>Plasma score</th>
<th>Third line option plasma</th>
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<tr>
<td>AZT</td>
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</table>

Additional InSTI and/or ETV not required with respectively TDF and DRV mutations scoring less than 29 and 15

South African third line antiretroviral therapy

Cerebrospinal fluid Escape

Building the regimen according to the algorithm

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<tr>
<th>Drug</th>
<th>CSF score</th>
<th>Plasma score</th>
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Application submitted 09/02/2017
Treatment started 09/04/2017
Authorization granted 09/05/2017

Central nervous system penetration effectiveness (CPE)
Neuro-symptomatic Cerebrospinal fluid Escape

Bettering the regimen penetration effectiveness

“CPE score > ... 7”

Controversies about improved neurocognitive scores or lower CSF HIV-1 RNA with higher CPE values

“Adjusted” CPE value thought to be a more accurate reflection of ART penetration in CSF

Bettering the regimen penetration effectiveness
The higher the score, the better the penetration into the CNS

Table 3. CNS penetration effectiveness score (CPE), updated according to Letendre 2014

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<th>3</th>
<th>2</th>
<th>1</th>
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<td>Abacavir Emtricitabine</td>
<td>Didanosine Lamivudine Stavudine</td>
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<td>Efavirenz Etravirine</td>
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<td>PI's</td>
<td>Indinavir/r</td>
<td>Darunavir/r Fosamprenavir/r Indinavir Lopinavir/r</td>
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<td>Entry/fusion inhibitors</td>
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Central nervous system penetration effectiveness (CPE)
Neuro-symptomatic Cerebrospinal fluid Escape

Bettering the regimen penetration effectiveness

<table>
<thead>
<tr>
<th>Drug</th>
<th>CSF score</th>
<th>Plasma score</th>
<th>From the committee</th>
<th>CPE “raw”</th>
<th>CPE “adjusted”</th>
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Regimen CPE score

Central nervous system penetration effectiveness (CPE)

Neuro-symptomatic Cerebrospinal fluid Escape

Bettering the regimen penetration effectiveness

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<th>Drug</th>
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<th>Plasma score</th>
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<th>CPE “adjusted”</th>
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</table>

Intensified Regimen CPE score

Clinical outcomes Neuro-symptomatic Cerebrospinal fluid Escape

Arrest and reversal of neurological deficits in the majority of reported cases

Clinical outcomes
Neurological deficits
Reversal

Day -7
Admission
Status epilepticus obtundation aphasia neurogenic dysphagia

Day 0
Indwelling feeding gastric tube
Crushed treatment

Day 8
Alert Seated Talking
Discharged in a wheelchair

Day 14
Unsteady gait
Gradual independency
ambulation activities of daily living

Escape
Virologic outcomes

Neuro-symptomatic

Cerebrospinal fluid

Viral suppression

8 days plasma HIV RNA
2 Log drop
From 162,000 cpm (5.2 Log) to 1550 cpm (3.2 Log)

4 months CSF HIV RNA
Complete suppression

Figure 5. CSF/Plasma viral suppression (Log HIV RNA)
Conclusion

Neuro-symptomatic Cerebrospinal fluid Escape

- “Real and emerging” clinical phenomenon
- Asynchronous and discordant emergence of resistance
- Significant impact and management implications
- Context-specific management clinical guidance
- Bi-compartmental suppression and neurological improvement
Acknowledgments

The patient & his family

Eshowe District Hospital management
Experts (local and international)
Ndlela LC & Mzilakazi S (students UKZN)

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Famoroti Temitayo
Gordon Michelle
Mathilda Classen