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Address: Dr. Atul K.Patel, Infectious disease clinic, 3rd floor, 'VEDANTA', Navrangpura, Ahmedabad-380 009, INDIA. Email: atulpatel65@gmail.com Telefax: 91 79 2644 0816

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Incidence of Symptomatic CSF Viral Escape in HIV Infected Adults Receiving Atazanavir/ritonavir (ATV/r) Containing ART: A Tertiary Care Cohort in Western India

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Atul Patel MD, FIDSA[1,2], Ketan Patel MD[2], Swati Gohel MD[2], A.Kumar MD, MPH[1], Scott Letendre MD[3]
[1]Departement of Internal Medicine, University of South Florida, Tampa, FL, USA; [2]Vedanta Institute of medical sciences, Infectious disease clinic, Ahmedabad- 380009, INDIA, [3]Department of medicine, University of California, San Diego, LaJolla, CA, USA.

Background

- A new onset of neurocognitive abnormality in a patient receiving suppressive ART regimen is increasingly being recognised [1,2]
- Many studies tried to correlate CSF viral escape (CSF-VE) with ART CNS penetration effectiveness (CPE) score with inconsistent results [1,3-5]
- Symptomatic CSF escape is not common phenomenon and its' incidence in patients receiving single ART regimen has not been studied
- Our study is intended to find out incidence and risk factors of symptomatic CSF-VE in patients receiving ATV/r containing regimen

Objectives

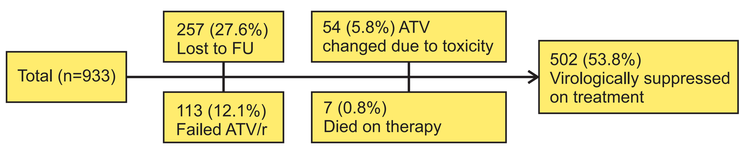
- Primary objective: To assess the incidence of symptomatic CSF-VE in patients receiving ATV/r containing ART in clinical practice
- Secondary objectives: To describe clinical presentation, risk factors and response to optimized ART in patients with CSF-VE

Materials & Methods

- Study Design & population: Retrospective observational cohort study of HIV-1 patients receiving ATV/r containing ART, diagnosed with Symptomatic CSF-VE from August 2013 to January 2017
- Study site: Infectious Disease Clinic, a tertiary care centre in western India
- Inclusion/exclusion criteria:
  →All symptomatic CSF-VE patients receiving ATV/r containing ART were included in the study
  →CSFVE was defined as either detectable CSF HIV RNA with undetectable plasma HIV RNA or CSF HIV RNA 1 log10 copies/mL > plasma HIV RNA
  →Patients with concomitant active CNS infection & other CNS etiologies were excluded from study
- Statistical Methods
  →Patient characteristics were reported as proportions (binary data) or means with accompanying 95% confidence intervals (95% CI) and standard error
  →The incidence rates (IR) were calculated by dividing the number of patients experiencing CSF-VE by the number of person-months at risk and summarized as per 10000 person–months at risk
  →The difference in IR according to factors associated with CSF escape was summarized as incidence rate ratio (IRR) along with 95% CI and the p-value for all comparisons was set at 5%
  →All analysis were done using STATA statistical analysis software

Results

- Detail of cohort receiving ATV/r containing treatment are shown in figure 1



- There were 933 patients on ATV/r based ART with a total of 36,068 person-months of follow up
- Total 26 patients diagnosed with CSF-VE during study period of which 16 (61.5%) were receiving ATV/r-containing regimen

Results

Table 1: Baseline characteristic of patients receiving ATV/r based therapy

Parameters	n=933
Age in years	41 (7-83) median (range) 41.39 ± 11.29 mean ± SD
Sex Male Female	 633 (67.84%) 300 (32.16%)
Weight in kg	65 (17.5-109) median (range) 56.96 ± 12.98 mean ± SD
Nadir CD4 count	199 (5-1730) median (range) 237.89 ± 197.61 mean ± SD
ATV therapy duration in months	30 (3-131) median (range) 38.46 ± 33.21 mean ± SD
HIV duration in months	77 (3-236) median (range) 85.47 ± 56.99 mean ± SD
ART naïve/experienced Naïve Experienced	 202 (21.65%) 731 (78.35%)
NRTI backbone TDF+FTC AZT+3TC ABC+3TC	 686 (73.53%) 235 (25.19%) 12 (1.29%)
Co infections HCV Syphilis HBV	 14 (1.50%) 15 (1.60%) 07 (0.75%)

- Incidence of CSF escape
  →Of the 933 patients 16-experienced CSF escapes resulting in incidence rate of 4.4 per 10,000 person-months (95% CI 2.7 to 7.2)
  →Patients receiving TDF/FTC as NRTI backbone are more likely to develope CSF-VE as compared to patients receiving ZDV/3TC

Table 3: Characteristics of patients with symptomatic CSF-VE

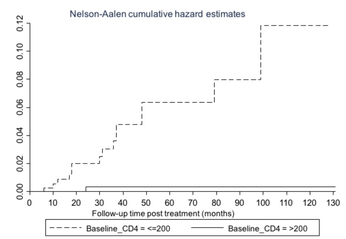
Parameters	n=16
Age in years median (range)	43 (17-58)
Sex Male Female	 12 04
Weight in Kg median(range)	55 (29-70)
HIV diagnosis in months median (range)	135 (17-216)
Current ART duration in months median (range)	30.5 (6-99)
ART status Naïve Experienced NNRTI exp NNRTI+PI exp	 02 14 14 1
Baseline CD4 count median(range)	91 (24-280)
CD4 at symptoms median (range)	435 (174-822)
Symptoms duration in weeks Median (range)	4 (1-17)
CSF examination Proteins mg/dL Sugar mg/dL Cells: /mm^3	 77.5 (44-640) 52 (42-100) 10 (1-70)
CSF VL copies/ml in median (range)	10934 (556-85200)
Plasma VL copies/ml Undetectable Detectable in median(range)	 n=6 n=10; 858.5 (28-6400)
Response to changed treatment in weeks	4 (1-8)
Follow up months after changed regimen	14.5 (1-48)
Comorbidities Syphilis ELISA HBsAg	 3 3

Table 2: Clinical features of patients developing CSF-VE are shown in table 2*

Symptoms	n (%)
Impaired Memory	9(56.25%)
Dizziness	8(50.00%)
Tremors	7(43.75%)
Gait disturbances	5(31.25%)
Psychiatric symptoms	3(18.75%)
Bradykinesia	3(18.75%)
Bladder bowel involvement	2(12.50%)
Slurred Speech	2(12.50%)
Convulsion	2(12.50%)
Visual disturbances	1(6.25%)
Headache	1(6.25%)
Encircling lower thoracic dermatome pain	1(6.25%)

*Except 2 patients all patients had multiple symptoms on presentation

Figure 2: Cumulative incidence of CSF escape in relation to baseline CD4 count in ATV/r cohort



Results contd.

- The difference in incidence of CSF escape was not significant for Age, Sex, Weight and ART status of the patient (naive vs experienced)
- The incidence of CSF escape was 9.5 (95% CI 5.7 to 15.7) in patients with a baseline CD4 ≤200 compared to 0.49 (95% CI 6.98e-02 to 3.5) in patients with a CD4 >200 per 10,000 person-months resulting in IRR of 0.05 (95% CI 0.001 to 0.34) which was statistically significant (p<0.0001)
- None of the patients receiving AZT/3TC or ABC/3TC backbone developed CSF escape, while 16 out of 686 receiving TDF/FTC developed CSF escape (Fisher's exact test two sided mid-*P* = 0.0086 is significant for TDF/FTC compared to AZT/3TC)
- Treatment: ART was optimized in all patients with a median CPE score of 10.5(7-13)
- New regimens were TDF/FTC/AZT/LPV/r (n=6), TDF/3TC/AZT/LPV/r (n=2), AZT/3TC/LPV/r (n=2), TDF/FTC/LPV/r (n=2) & TDF/FTC/LPV/r/RAL (n=1), AZT/3TC/LPV/r/RAL (n=1), AZT/3TC/LPV/r/IDV (n=1), TDF/FTC/IDV/r (n=1)
- All patients had rapid neurological improvement after change in ART & reported complete recovery at first follow up after 1 month

Discussion

- To our knowledge, this is the first study looking at the incidence of symptomatic CSF escape in patients receiving ATV/r containing ART in clinical practice
- Published literature so far reported CSF-VE in patients receiving different ART combinations with different CPE score
- Atazanavir (TDF/3TC/ATV/r with CPE score of 5 & TDF/FTC/ATV/r with CPE score 6) containing regimen is recommended 2nd line ART in India after failure on NNRTI based regimen (Naco guideline)
- Many researchers studied CSF penetration of ART and CSF-VE, evolution of HIV in CSF compartment, emergence of drug resistance in CNS compartment with neurocognitive abnormalities[1,2,6,7]
- Though incidence of symptomatic CSF escape in our cohort is low, but it is important for clinicians to recognize it early as it is associated with disturbed work performance, disturbed day-to-day activity and morbidity
- High CPE score ART is not associated with improved neurocognitive performance in randomized study but changing ART to higher CPE score in-patients with symptomatic CSF-VE escape showed good clinical response in published case reports and also in our study
- Limitations includes retrospective study & we might have missed many patients prior to current study

Conclusion

- Symptomatic CSF-VE with ATV/r containing regimen was a rare but clinically significant condition in this single-center study
- Nadir CD4 count ≤ 200 was associated with substantially increased risk of symptomatic CSF-VE, further strengthening efforts to diagnose and treat patients early in disease
- Clinicians should be more vigilant for symptomatic CSF-VE in patients with nadir CD4 count < 200

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