Poster 0708

Cryptococcal Antigenemia in ART-experienced HIV-infected Ugandans with Virologic Failure

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Abstract

Background: Detectable serum or plasma cryptococcal antigen (CrAg) precedes symptomatic cryptococcal meningitis (CM). World Health Organization recommends CrAg screening for those with CD4<100cells/µL initiating antiretroviral therapy (ART). However, the majority of CM patients are ART-experienced. We evaluated CrAg prevalence among ART-experienced persons with virologic failure in Uganda.

Methods: We retrospectively performed plasma CrAg testing among Ugandan adults with virologic failure (>=1000 HIV-1 copies/mL) using leftover plasma after viral load testing from September 2017 to January 2018. For those CrAg-positive, we obtained ART history, CM occurrence, and 6-month survival from medical record review.

Results: Among 1,186 subjects with viral loads >=1000 copies/mL, 35 (3.0%) were CrAg-positive with median ART duration of 41 months (IQR, 10-84 months). Among 25 subjects with 6-month outcomes, 16 (64%) were alive, 7 (28%) were dead, and 2 (8%) were lost. One survivor had a history of previous CM. Two others developed CM and survived. Five survivors were known to have received fluconazole. Thus, meningitis-free survival at 6-months was 56% (14/25). Overall, 91% (32/35) of CrAg-positive persons had viral loads ≥5000 copies/mL compared with 64% (735/1151) of CrAg-negative (Odds Ratio=6.0; 95%CI, 1.8-19.8, P=.001). CrAg prevalence was 4.2% (32/768) among those with viral loads ≥5000 copies/mL and 0.7% (3/419) among <5000 copies/mL. Among viral loads ≥5000 copies/mL, the real world cost to detect one CrAg-positive person was $96 (95%CI, $69 to $139).

Conclusion: In addition to the CD4 threshold, reflexive CrAg screening should be considered in persons failing ART with viral loads >=5000 copies/mL.

Introduction

- Detectable serum cryptococcal antigen (CrAg) precedes symptomatic cryptococcal meningitis.
- The World Health Organization recommends CrAg screening for ART naïve HIV patients with CD4<100 cells/µL, yet the majority of cryptococcal meningitis patients are ART-experienced.
- Prevalence of cryptococcal antigenemia in ART-experienced persons with virologic failure is unknown

Methods

- We retrospectively evaluated stored plasma samples of 1,186 ART-experienced HIV infected adults (>=18 years) with virologic failure with HIV viral loads above ≥1000 copies/mL.
- We used left over plasma samples after viral load testing from September 2017 to January 2018.
- CrAg testing was performed from March to July 2018.
- For the CrAg positive, retrospective chart review was done to determine CM occurrence and 6-month outcomes.
- This study was conducted at the Uganda National Health laboratory Services (UNHLS), which performs centralized viral load monitoring in Uganda (~95% of all HIV viral load testing).
- CrAg testing was performed using the CrAg LFA assay (CrAg LFA; IMMY Inc., Norman, Oklahoma, USA).
- Quantitative RNA viral loads on plasma were measured using the Roche Cobas assay on an Abbott m2000 Real Time System (Abbott Laboratories, Abbott Park, Illinois, USA).
- Additionally, clinicians were duly informed of the positive CrAg results.

Results

Prevalence of CrAg in ART-experienced HIV patients with virologic failure

- 368,174 adult HIV patients had viral load testing.
- 5,348 patients had viral loads ≥1000 copies/mL and left over plasma samples.
- We selected and CrAg tested 1186 ART-experienced persons with plasma viral loads ≥1000 copies/mL and available left over plasma
- We identified 35 CrAg positive persons:

  Prevalence of 3.0% (95%CI, 2.1%-4.1%)
  - For HIV RNA <5000 copies/mL, prevalence is 0.7%% (3/419)
  - For HIV RNA ≥5000 copies/mL, prevalence is 4.2% (32/768)

Table 1: Clinical characteristics of participants by CrAg status

Characteristic	CrAg Positive (N=35)	CrAg Negative (n=1151)	P-value
Age, years	35 (28-45)	36 (30-43)	0.92
Women	20 (57%)	704 (62%)	0.55
HIV-1 RNA, copies/mL	46,400 (17,300-56,000)	12,000 (3,020-69,800)	<0.001
HIV-1 RNA >5000 copies/mL	32 (91%)	735 (64%)	0.001
Duration of ART			
0.5-1 year	4 (12%)	69 (6.7%)	0.22
1-2 years	4 (12%)	144 (14%)	0.77
2-5 years	12 (36%)	400 (39%)	0.80
>5 years	13 (39%)	424 (41%)	0.86

Values are median (IQR) or n (%). P-Value from Wilcoxon rank-sum test for medians and Chi Square test for proportions. Abbreviations: CrAg, cryptococcal antigen; ART, antiretroviral therapy.

Outcomes

- Among the 35 CrAg-positive persons, we obtained 6-month survival data for 25 persons.
- Of these, 16 (64%) were known to be alive, 7 (28%) were confirmed dead, and 2 (8%) were lost to follow up.
- Of the 25 CrAg-positive, only 1 patient had a history of previous cryptococcal meningitis and was taking fluconazole for secondary prophylaxis.
- Five survivors were known to have received fluconazole.
- Two patients developed cryptococcal meningitis, were treated and survived.
- Meningitis-free survival at 6-months was 56% (14/25; 95%CI, 35% to 76%).
- Absent fluconazole receipt (n=19), 6-month meningitis free survival was 42% (8/19; 95%CI, 20% to 67%).

Distribution of HIV-1 RNA among CrAg-positive patients

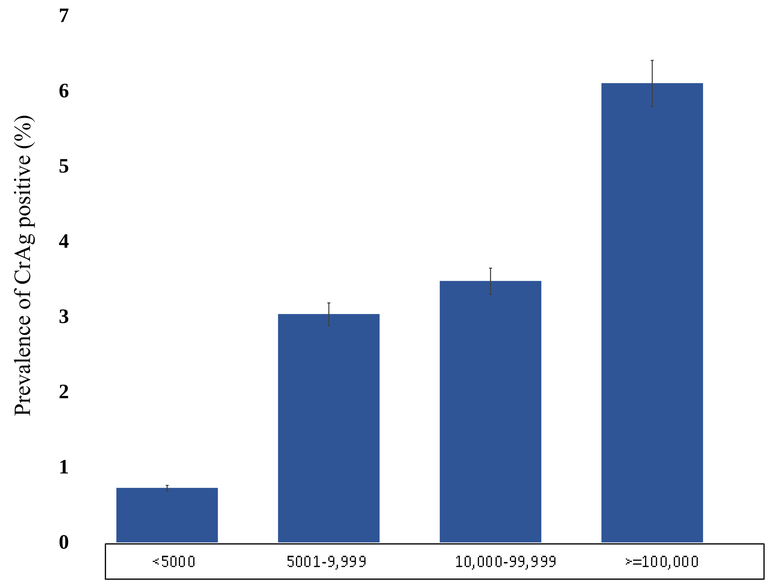


Figure 1: Cryptococcal Antigen (CrAg) prevalence by HIV-1 plasma viral load among Ugandans undergoing routine virologic monitoring on HIV therapy

- The number needed to test to detect one CrAg-positive given a prevalence of 4.2% (for HIV RNA ≥5000 copies/mL) is 24.0 (95%CI, 17.1-34.8).
- This corresponds to a cost of $96 (95%CI, $69-$139) assuming a real time cost of $4 per CrAg assay.
- This screening cost is well below the costs of cryptococcal meningitis hospitalization in Uganda.

Conclusions

- ART-experienced people failing HIV therapy are at risk for cryptococcal infection
- CrAg screening should be considered in persons with suspected virologic failure
- CrAg screening as part of routine viral load monitoring is feasible
- To maximize the efficiency, CrAg screening could be limited to persons with viral loads >5,000 copies/mL.
- Further prospective studies focused on CrAg screening among ART-experienced populations are warranted.

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