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HCV Ag core screening performance in mono-infected, HIV- and HBV-coinfected patients

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Introduction

Despite the shift occurring in HCV management thanks to the recent release of really efficient new oral antiviral drugs against HCV, it still remains some barriers to HCV treatment.

First of all, too few infected people are diagnosed: it is estimated that 90% of HCV-infected people are unaware of their infection[1]. In the low- and middle-income countries (LMIC), where 115 million of infected persons live, only 1% know their HCV status[2].

Thus, although early detection of HCV infection is of great importance it still remains challenging because of the complexity of the present HCV chronic infection diagnosis procedure which combines anti-HCV antibody (HCV-Ab) and HCV-RNA measurement, two technics barely available in LMIC.

Quantifying HCV core antigen (cAg), a marker of HCV viral replication, as a one-step procedure, could shorten this diagnosis procedure.

Objective

Principal objective

To assess the performance of HCV core antigen quantification as a diagnostic tool for chronic hepatitis C in Africa.

Secondary objective

To assess the impact of the demographic variables (age, gender), the HCV genotype and the HIV or HBV infection on the cAg diagnostic performance.

Material and methods

Patients

1009 serum samples from the Pasteur Center of Cameroon in Yaounde were included in the present study according to the following inclusion criteria:

- HCV positive samples:
  - HCV antibody (HCV Ab) positive serology
  - Quantifiable HCV RNA
- HCV negative samples:
  - HCV Ab negative serology
  - **OR** undetectable HCV RNA
- HIV status known
- HBV status known

Included samples:
- 465 HCV-
- 544 HCV+

Laboratory methods

- cAg quantification: Abbott ARCHITECT HCV Ag Assay
  - < 3 fmol/L : negative
  - ≥ 10 fmol/L: positive
  - 3 ≤ [cAg] < 10 fmol/L: « grey zone » ⇨ retested twice
- HCV RNA quantification by quantitative rt-PCR : gold standard
- Anti-HCV Ab
- Anti-HIV Ab
- Ag HBs

ELISA serologies

Statistical analysis

cAg quantification assay was compared to HCV RNA quantification by PCR and/or Ab anti-HCV detection as the gold standard. Sensitivity (Se), specificity (Spe), positive and negative predictive value (PPV and NPV respectively), positive and negative likelihood ratio (LR+ and LR- respectively) were estimated. Roc curves were also plotted and their corresponding Area under the curve (AUC) calculated. Statistical analysis was performed using STATA (v12.1, College Station, TX) and significance was determined using a *P*-value <0.05.

Results

1. Description of the study population

	Uninfected (n=335)	HCV-monoinfected (n=489)	HIV-infected (n=78)	HBV-infected (n=107)
HCV+ (n, %)	na	na	27 (34.6)	28 (59.6)
Gender, woman (n, %)	194 (57.9)	251 (51. 3)	42 (53.9)	55 (51.40)
Age (mean, sd)	40.8 (17.5)	59.8 (11.2)	46.4 (13.7)	40.6 (15.1)
HCV+	na	na	57.3 (8.8)	54.9 (11.9)
HCV-	na	na	40.6 (12.2)	35.5 (12.7)
Genotype (n, %)				
1	na	44	2	2
2	na	39	1	1
4	na	37	2	3
Virology (mean, sd)				
HCV RNA (IU/mL)	na	1 864 908 (2 339 039)	3 357 046 (4 613 890)	1 337 306 (1 676 788)
Undetectable HCV viral load	na	126	13	19
cAg HCV (fmol/L)	13.927 (251.28)	2063.24 (3073.74)		
HCV+	na	na	4637.09 (7780.75)	1602.69 (2742.27)
HCV-	na	na	2.336 (6.820)	5.477 (41.17)

2. Correlation between cAg and HCV RNA, by infection group

Figure 1a: HCV mono-infected sera

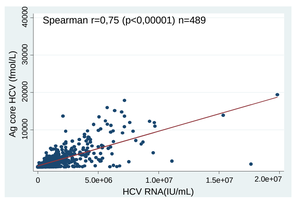


Figure 1b: HIV-HCV co-infected sera

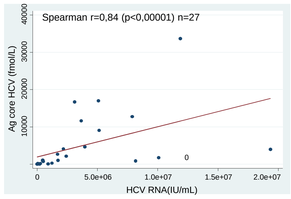
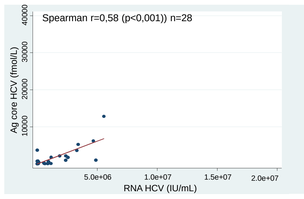


Figure 1c: HBV-HCV co-infected sera



3. Correlation between cAg and HCV RNA in mono-infected sera, by genotype

Figure 2a: genotype 1

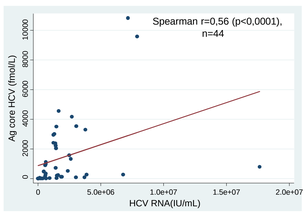


Figure 2b: genotype 2

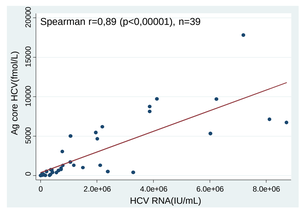
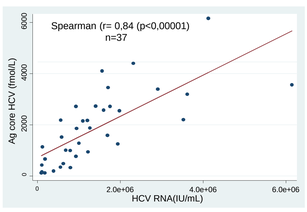


Figure 2c: genotype 4



4. Overall performance of cAg assay

Table 2: Performance of the cAg quantification by infection group

	n	Se [CI97.5%]	Spe [CI97.5%]	PPV*	NPV*	AUC [IC95%]	LR+	LR-
Mono	824	95.7 [93.2 ; 97.5]	99.7 [98.1 ; 100]	98.1	99.3	0.99 [0.98-1.0]	319	0.043
HIV	78	100 [85.0 ; 100]	88.2 [74.3 ; 96.2]	57.6	100	0.99 [0.97-1.0]	847	0
HBV	107	96.4 [79.2 ; 99.9]	96.2 [88.1 ; 99.4]	80.2	99.4	0.98 [0.95-1.0]	25	0.037

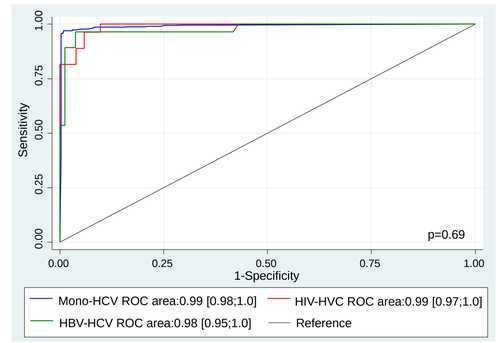
*Estimated HCV prevalence in Cameroon: 13.8%

Table 3: Performance of the cAg quantification by genotype among the mono-infected and uninfected sera group

	n	Se [IC 97.5%]	Spe [IC 97.5%]	PPV*	PPV*	AUC [IC95%]	LR+	LR-
Genotype 1	379	97.7 [86.4-1.0]	99.7[98.1-1.0]	98.1	99.6	0.9953 [0.9886-1.0]	327	0.023
Genotype 2	374	94.9 [80.7-99.6]	99.7 [98.1-1.0]	98.1	99.2	0.9891 [0.9740-1.0]	318	0,051
Genotype 4	372	100 [88.8-100]	99.7 [98.1-1.0]	98.1	100	0.9971 [0.9914-1.0]	335	0

*Estimated HCV prevalence in Cameroon: 13.8%

Figure 3: ROC curves of the performance of cAg quantification for the diagnostic of chronic hepatitis C in HCV mono-infected and HCV uninfected, HIV-infected and HBV-infected patients



5. Discordant results

- 32 wrong results (3.2%) : 22 false negative (FN) and 10 false positive (FP)
- FN compared to TP
  - HCV viral load significantly lower:
    => $\bar{m}$ =32 851 UI/mL vs $\bar{m}$ =1 992 335 UI/mL (p<0.00001)
  - Percentage of women significantly lower:
    ⇒ 22.7% vs 52.2% (p=0.007)
- FP compared to TN
  - Percentage of HIV-infected sera significantly higher:
    => 60% vs 11.8% (p<0.0001)

Conclusions

- The cAg quantification assay displayed high specificity and sensitivity; in addition neither genotype nor HBV-infection influenced its discrimination capacity.
- HIV infection did not affect its overall performance but its specificity was lower in sera with this infection.
- This assay represents a reliable HCV diagnosis tool and, being less costly than viral load tests, could ease HCV screening, notably in resource-limited settings.

Acknowledgements and References

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[1] Thomas DL. Curing hepatitis C with pills: a step toward global control. Lancet Lond Engl. 30 oct 2010; 376(9751):1441-2.
[2] Hepatitis-C_October-2013.pdf [Internet]. [cité 21 avr 2015]. Available on: http://www.unitaid.eu/images/marketdynamics/publications/Hepatitis-C_October-2013.pdf