BMJ Open

Relationship between estimated cardiovascular disease risk and insulin resistance in a black African population living with HIV: a cross-sectional study from Cameroon

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To cite: Noumegni SR, Bigna JJ, Ama Moor epse Nkegoum VJ, *et al*. Relationship between estimated cardiovascular disease risk and insulin resistance in a black African population living with HIV: a cross-sectional study from Cameroon. *BMJ Open* 2017;**7**:e016835. doi:10.1136/bmjopen-2017-016835

► Prepublication history for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2017-016835).

Received 13 March 2017
Revised 16 June 2017
Accepted 12 July 2017

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ABSTRACT

Objectives Cardiovascular disease (CVD) and metabolic diseases are growing concerns among patients with HIV infection as a consequence of the improving survival of this population. We aimed to assess the relationship between CVD risk and insulin resistance in a group of black African individuals with HIV infection.

Methods This cross-sectional study involved patients with HIV infection aged 30–74 years and followed up at the Yaoundé Central Hospital, Cameroon. Absolute CVD risk was calculated using the Framingham and the DAD CVD risk equations while the HOMA-IR index was used to assess insulin resistance (index ≥2.1).

Results A total of 452 patients (361 women; 80%) were screened. The mean age was 44.4 years and most of the respondents were on antiretroviral therapy (88.5%). The median 5-year cardiovascular risk was 0.7% (25th–75th percentiles: 0.2–2.0) and 0.6% (0.3–1.3) according to the Framingham and DAD equations respectively. Of all participants, 47.3% were insulin resistant. The Framingham equation derived absolute CVD risk was significantly associated with insulin resistance; while no linear association was found using the DAD equation.

Conclusion The relationship between cardiovascular risk and insulin resistance in black African patients with HIV infection seems to depend on the cardiovascular risk equation used.

Strengths and limitations of this study

- ► To the best of our knowledge, this is the first study which assessed the direct relationship between cardiovascular risk and insulin resistance as continuous variables among people with HIV infection in sub-Saharan Africa.
- ► Rigorous methodological and statistical procedures were used to examine our research questions.
- ► This study aptly highlighted that the relationship between cardiovascular risk and insulin resistance in patients with HIV infection in sub-Saharan Africa depends on the cardiovascular risk equation used.
- ► The sampling method was not random, perhaps hindering the external validity of our results.
- ► An indirect method was used to assess insulin resistance instead of the hyperinsulinemic euglycemic clamp which is the gold standard.

INTRODUCTION

In 2015, there were 36.7 million people living with HIV globally. As of June 2016, nearly 50% of them were accessing antiretroviral therapy (ART).[1] Since the advent and widespread use of continuous ART, the life expectancy of people living with HIV has considerably increased, with a concomitant significant reduction in related mortality. In fact, opportunistic illness associated with AIDS has drastically declined in this specific population, leading to an increase in life quality gain.[2] However, this is not without any drawback effect. Indeed, there is a body of evidence showing an increase in the burden of non-communicable diseases (NCDs) collectively with their risk factors among individuals with HIV infection.[3] Accordingly, the prevalence and burden of cardiovascular disease (CVD) and metabolic complications tend to grow within this population, occurring even at younger ages than in the general population.[3 4] In the last decade, despite the remarkable progress noted in the management of HIV infection worldwide, HIV/AIDS-related deaths, although in gradual decline, remain significant.[1] This is essentially the result of non-communicable

comorbidities led by cardiovascular and metabolic diseases.[4]

NCDs kill more than 36 million people each year and 80% occur in low and middle income countries, including most people in Africa. People infected with HIV therefore present a double burden of disease due to a close relationship between HIV, ART and CVD. For instance, HIV increases twofold the risk of coronary heart disease.[5] Moreover, HIV and ART are recognised as independent factors associated with metabolic complications.[6 7] The mechanism of the increased risk of CVD among people with HIV infection is multifactorial, mainly supported by two well described metabolic disorders, including dyslipidaemia and insulin resistance, both of which result from the probable complex interaction between the host's advancing age, the virus, the inflammatory process, and ART.[2] In this regard, evidence suggests a higher prevalence of insulin resistance in HIV-infected populations than in the general population.[8]

To better tackle the increasing burden of CVDs in patients with HIV infection, all mechanisms implicated in CVD occurrence should be clearly elucidated and subsequently attacked. However, studies investigating the existence of any association between insulin resistance and cardiovascular risk factors in HIV-infected black Africans are scarce. Therefore, we designed the present study, which aimed to examine the following question: what is the relationship between insulin resistance and absolute CVD risk in a group of black African people living with HIV?

METHODS

Ethical considerations

The study was approved by the Cameroon National Ethics Committee for Human Health Research (Ethical approval No 2015/12/710/CE/CNERSH/SP). All participants signed the informed consent form.

Study design and participants

This cross-sectional study was conducted from December 2015 to May 2016 at the HIV day-care unit of the Yaoundé Central Hospital. All apparently healthy patients aged 30–74 were included, unless they had a history of CVD, were pregnant or breastfeeding, or were on lipid-lowering therapy or hormone therapy.

Data collection

Socio-demographic characteristics, history of HIV infection, and cardiovascular risk factors were collected. Family history of early CVD was defined as CVD in a first-degree male relative before the age of 55 or in a first-degree female relative before the age of 65.[9] Smoking status was classified as never, former or current. Hazardous alcohol drinking was defined by an AUDIT-C (Alcohol Use Disorders Identification Test-Consumption) score ≥4 for men and ≥3 for women.[10] Lack of physical activity was defined as absence of walking or any other intense physical activity at least once a week.[11] Participants' stage of HIV infection was classified using the WHO clinical staging for HIV infection.[12]Body mass index (BMI) was classified as recommended by WHO.[13] Abdominal obesity was defined in accordance with the International Diabetes Federation (IDF).[14] High blood pressure was defined as a systolic blood pressure (SBP) ≥140 mmHg and/or a diastolic blood pressure (DBP) ≥90 and/or self-reported history of antihypertensive medication.[15] Insulin was indirectly estimated by measuring the C-peptide level, using the sandwich immunoassay method (ELISA method). Dyslipidaemia was considered as an elevated level of total cholesterol (TC) (>6.2 mmol/L) and/or an elevated level of low-density lipoprotein cholesterol (LDL-C) (>4.1 mmol/L) and/or a low level of high-density lipoprotein cholesterol (HDL-C) (<1.04 mmol/L in men and 1.29 mmol/L in women) and/or hypertriglyceridaemia (≥1.7 mmol/L).[16] We considered any patient as having diabetes when there were at least 2 fasting plasma glucose (FPG) levels ≥7.0 mmol/L on two occasions at least 48 hours apart, or self-reported ongoing use of antidiabetes medications following a diagnosis made in a health facility.[17] Metabolic syndrome was defined using the International Diabetic Federation criteria.[14]

CVD risk assessment

The 5-year risk of CVD was calculated using two equations: a non-specific equation (the FraminghamAnderson equation)[18] and a specific equation applied to people living with HIV (the DAD equation).[19]

Insulin resistance evaluation

The HOMA-IR index served to assess the insulin sensitivity; it was determined by the formula: fasting blood glucose (mmol/L) x fasting Insulin (mU/L or µUl/mL)/22.5.[20] Insulin resistance was defined by any value of the HOMA-IR index equal or above 2.1; this threshold was defined in an HIV-infected population in Peru.[5]

Statistical analysis

Data were analysed using the Statistical Package for Social Sciences (SPSS) software, version 23.0 (IBM SPSS Inc, Chicago, Illinois, USA). Results are presented as frequency (percentage) for categorical variables; and mean ±SD deviation (SD) or median (25th–75th percentiles) for continuous variables. Qualitative variable comparisons used the χ^2 test. Likewise, the Student *t*-test or non-parametric equivalents served for quantitative variable comparisons. Univariable and multivariable linear regression analyses were undertaken to investigate the relationship between CVD risk and insulin resistance. We introduced in the multivariable model all variables with a p-value<0.25 in the univariable model as recommended by the purposeful selection process,[21] in addition to the HOMA-IR index regardless of its p-value obtained in univariable analysis. We used backward elimination to retain the final significant predictors in the model. A p-value<0.05 was considered of statistical significance.

RESULTS

Characteristics of the study population

Overall, we included 452 patients among whom 361 (79.9 %) were women. The mean age was 44.4±9.8 years. Of the 452 participants, 400 (88.5%) were on continuous ART. The study population's characteristics are presented in table 1.

Assessment of the 5-year risk of CVD and insulin resistance

Calculated with the DAD equation, the 5-year risk of CVD ranged from 0.1% to 13.3%, with a median of 0.6% (0.3–1.3). The 5-year risk of CVD estimated by the Framingham equation ranged from 0.0% to 20.7% with a median of 0.7% (0.2–2).

The median HOMA-IR index was 2.1 (1.4–3.2).

Relationship between CVD risk and insulin resistance

The CVD risk (estimated using the Framingham equation) of participants with insulin resistance was higher than that of participants without this condition: 4.1% (2.5–5.6) versus 2.2% (1.7–3.7); p<0.001. But using the DAD equation, there was no difference between CVD risk of participants with insulin resistance and those without: 1.9% (1.4–2.9) versus 1.5% (1.1–2.5); p=0.102.

In univariable analysis, there was no linear significant association between the CVD risk (estimated using the DAD equation) and the HOMA-IR index (β=0.03; p=0.717) as well as between this risk and categorical insulin resistance (β=0.12; p=0.156); however, using the CVD risk assessed with the Framingham equation, this relation became statistically significant: HOMA-IR (β=0.28; p=0.002); categorical insulin resistance (β=0.17; p=0.033) (table 2). The regression equations of these associations are presented below. In multivariable analysis, the association between the CVD risk (assessed using the DAD equation) and the HOMA-IR index remained non-significant (β=0.18; p=0.429) (table 3). On the contrary, this association using the Framingham equation remained statistically significant (β=0.64; p=0.001) (table 3).

Relationship between CVD risk (DAD score based) and HOMA-IR index:

$Y=0.0069x+1.8324$ ($R^2=0.001$).

Relationship between CVD risk (Framingham score based) and HOMA-IR index:

$Y=0.01052x+2.7622$ ($R^2=0.0774$).

DISCUSSION

The general objective of this study was to evaluate the relationship between CVD risk and insulin resistance among patients with HIV infection in Cameroon. As key findings, we observed that the relationship between CVD risk and insulin resistance varied depending on the risk equation used. Indeed, using the Framingham risk equation, participants with insulin resistance had a higher risk of CVD compared with their counterparts without insulin resistance. Additionally, the relationship between CVD risk and the HOMA-IR index was significant in univariable analysis as well as in multivariable linear regression analysis after adjusting for confounders. By contrast, all these linear associations were insignificant when the CVD risk was estimated with the DAD risk equation.

Calculated using the Framingham equation or the DAD equation, the median CVD risk was lower in our study population. This can be explained by the relatively young age of our participants and the high proportion of females (80%). Indeed, the male sex is recognised as an independent risk factor for CVD.[22] Using either the Framingham or the DAD equations, we found that the proportion of subjects decreased progressively with increasing degree of cardiovascular risk. These results are similar to those already reported.[23 24] and are probably due to the relative young age of the majority of our study population.

In this study, insulin resistance had a higher prevalence than that found by Guillen *et al* in a population of 219 people with HIV infection in Peru (34.2%) while using the same HOMA-IR definition threshold.[5] Moreover, Guillen *et al* reported a mean value of HOMA-IR index of 2.6±3 less than that found in our study (3.85±5.87). This difference may be due to the fact that the basal insulin secretion is high in African populations.[25]

We found no significant relationship between insulin resistance and CVD risk calculated using the DAD equation. Indeed, there was no significant association between HOMA-IR index and CVD risk calculated using this equation. Considering the Framingham equation, we found a significant association between CVD risk and insulin resistance in univariate analysis and after adjustment for other factors in the multivariate analysis. These results were the same when considering the linear association between CVD risk and HOMA-IR index as a continuous variable or a categorical one (defining insulin resistance). Thus, based on our results, there was a significant linear relationship between CVD risk of people with HIV infection assessed by a non-specific equation (the Framingham risk equation) while this relationship was not significant when considering the specific CVD risk equation (the DAD risk equation). This discrepancy may be related to the fact that the DAD and Framingham risk scores do not measure exactly the same parameters.[23 24] Indeed, contrary to the Framingham risk equation, the DAD risk equation includes the use or not of some ART which is a specific parameter of HIV-infected populations. Notwithstanding, this difference is not sufficient enough to explain the discrepancy observed. Therefore, longitudinal studies need to be conducted in African populations to derive local CVD risk assessment tools, not only for the general population, but also for specific populations such as the HIV-infected population.

Unfortunately, we found no reason to explain these discrepant results. To the best of our knowledge, no previous study has investigated the relationship between the risk of CVD and insulin resistance as continuous variables in people living with HIV, especially those residing in Africa. However, evidence accumulated from systematic reviews, cross-sectional and prospective cohort studies point in favour of an increased risk of developing

Table 1 Characteristics of the study population

	Overall (n=452)	Women (n=361)	Men (n=91)	p
General characteristics				
Mean age (years)	44.4±9.8	43.7±9.9	47.2±8.8	0.001
Unmarried, n (%)	251 (55.5)	227 (62.9)	24 (26.4)	<0.001
Secondary education or higher, n (%)	289 (63.9)	227 (62.9)	62 (68.1)	0.351
Urban residence, n (%)	381 (84.3)	305 (84.5)	76 (83.5)	0.820
Unemployed, n (%)	219 (48.5)	196 (54.3)	23 (25.3)	<0.001
Family past history of premature CVD, n (%)	46 (10.2)	36 (10.0)	10 (11.0)	0.774
Tobacco use, n (%)	27 (6.0)	10 (2.8)	17 (18.7)	<0.001
HIV infection				
ART use, n (%)	400 (88.5)	328 (90.9)	72 (79.1)	0.002
Median duration of ART in months (25th–75th percentile)	72 (35–108)	72.0 (34.0–108.0)	74.0 (36.0–106.5)	0.971
First-line treatment, n (%)	373/400 (93.3)	304/328 (92.7)	69/72 (95.8)	0.442
NVP, n (%)	78/373 (20.9)	67/304 (22.0)	11/69 (15.9)	0.261
EFV, n (%)	295/373 (79.1)	237/304 (78.0)	58/69 (84.1)	0.261
PI, n (%)	27/400 (6.8)	24/328 (7.3)	33/72 (4.2)	0.442
Clinical characteristics				
Mean systolic blood pressure (mmHg)	123.4±22.5	122.6±23.0	126.5±20.3	0.120
Mean diastolic blood pressure (mmHg)	81.3±13.5	81.3±13.6	81.1±13.2	0.909
Hypertension, n (%)	60 (13.3)	48 (13.3)	12 (13.2)	0.978
Mean body mass index (kg/m^2)	25.8±5.3	26.2±5.5	24.0±3.9	<0.001
Obesity, n (%)	218 (48.0)	188 (52.1)	29 (31.9)	0.001
Mean waist circumference (cm)	82.1±11.6	82.3±11.9	81.0±10.5	0.303
Abdominal obesity, n (%)	195 (43.1)	185 (51.2)	10 (11.0)	<0.001
Mean hip circumference (cm)	95.1±11.2	96.0±12.0	91.4±8.8	0.001
Mean waist/hip ratio	0.86±0.07	0.88±0.07	0.89±0.06	<0.001
Biological characteristics				
Median CD4 count (cells/mm^3)	375 (245–532)	375 (245–532)	365 (257–504)	0.926
Mean fasting glycaemia (mmol/L)	5.1±0.9	5.1±0.7	5.2±1.3	0.236
Diabetes, n (%)	9 (2.0)	6 (1.7)	3 (3.3)	0.318
Mean total cholesterol (mmol/L)	4.5±1.0	4.5±1.0	4.3±1.1	0.238
Hypercholesterolaemia, n (%)	26 (5.8)	22 (6.1)	4 (4.4)	0.534
Mean HDL-C (mmol/L)	1.7±0.6	1.7±0.6	1.5±0.6	0.003
Low HDL-C, n (%)	106 (23.5)	85 (23.5)	21 (23.1)	0.925
Mean triglycerides (mmol/L)	1.0±0.5	1.0±0.4	1.1±0.6	0.012
Hypertriglyceridaemia, n (%)	35 (7.7)	25 (6.9)	10 (11.0)	0.195
Mean LDL-C (mmol/L)	2.3±0.9	2.3±0.9	2.3±1.0	0.788
High LDL-C, n (%)	17 (3.8)	13 (3.6)	4 (4.4)	0.722
Any dyslipidaemia, n (%)	153 (33.8)	122 (33.8)	31 (34.1)	0.961
Median 5-year CVD risk				
DAD equation	0.6% (0.3–1.3)	0.5% (0.3–0.9)	1.4% (0.8–2.7)	<0.001
Framingham equation	0.7% (0.2–2)	0.5% (0.2–1.5)	1.8% (0.9–4)	<0.001

Values are count (percentages), mean±SD deviation or median (25th–75th percentiles).
ART, antiretroviral therapy; CVD, cardiovascular disease; EFV, efavirenz; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NVRP, nevirapine; PI, protease inhibitor.

Table 2 Relationship between HOMA-IR index, others factors and CVD risk, univariable analysis

	CVD risk with DAD equation		CVD risk with Framingham equation	
Variables	Unadjusted β	p	Unadjusted β	p
HOMA-IR index	0.03	0.717	0.28	0.002
Socio-demographic characteristics				
Occupation (employed/unemployed)	−0.08	0.105	−0.08	0.109
Education (secondary or high/primary or less)	−0.12	0.013	−0.10	0.042
Place of residence (urban/rural)	−0.01	0.868	−0.06	0.231
Physical activity (yes/no)	0.07	0.155	0.06	0.202
Hazardous alcohol consumption (yes/no)	0.03	0.513	−0.05	0.311
Clinical characteristics				
Past history of CVD (yes/no)	/	/	0.04	0.463
Body mass index	0.01	0.9	0.15	0.002
Waist circumference	0.13	0.008	0.25	<0.001
Hip circumference	0.01	0.794	0.15	0.002
WHO clinical stages (3 or 4/1 or 2)	0.01	0.797	0.00	0.993
Duration of HIV infection	0.12	0.014	0.10	0.035
ART (yes/no)	/	/	0.01	0.783
ART line (second /first)	/	/	−0.07	0.193
ART duration	/	/	0.15	0.003
NRTIs (yes/no)	/	/	0.01	0.783
NNRTIs (yes/no)	/	/	0.05	0.287
PIs (yes/no)	/	/	−0.07	0.193
PI duration	/	/	0.21	0.294
Biological characteristics				
Virus serotype (2 and 1+2/1)	0.01	0.726	−0.23	0.650
CD4 count	−0.04	0.507	0.01	0.853
Viral load (detectable/undetectable)	0.59	0.042	0.56	0.061
LDL-C	0.22	<0.001	0.28	<0.001
Triglycerides	0.09	0.059	0.10	0.043
Any dyslipidaemia (yes/no)	0.05	0.302	0.17	<0.001
Metabolic syndrome (yes/no)	0.03	0.481	0.31	<0.001

*β, Regression coefficient.
ART, antiretroviral therapy; CVD, cardiovascular disease; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; NNRT, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

CVD among subjects without diabetes presenting insulin resistance, despite some discrepancies between studies.[26 27] Indeed, partly corroborating our findings, Schmiegelow *et al* demonstrated a significant association in a univariable analysis between CVD risk estimated using the Framingham equation and insulin resistance assessed by the HOMA-IR index in a population of 15 288 postmenopausal US women; but this association became non-significant in multivariable analysis after adjusting for HDL-C.[28] Moreover, Howard *et al* did not find a significant relationship between insulin resistance and atherosclerosis in African Americans, which on the contrary was significant among Euro-Americans.[29]

Our study presents some limitations. The sampling method was not random, perhaps hindering any generalisation of our results. In the absence of locally-developed tools we used equations which were developed in Caucasian populations though the pattern of CVD may be different between Caucasians and black Africans.[30] The cut-off used to define insulin resistance in our study was first used in a Peruvian HIV-infected population,[5] this may have perhaps overestimated the prevalence of insulin resistance in our study given that basal insulin secretion may be higher in Africans.[25] However, the results of the association between CVD risk and categorical insulin resistance (based on the HOMA-IR index cut-off) were confirmed by the results of the linear association between CVD risk and HOMA-IR. Finally, we used an indirect method to assess insulin resistance instead of the hyperinsulinemic euglycemic clamp which is the gold

Table 3 Relationship between CVD risk, HOMA-IR index and other factors, multivariable analysis

	CVD risk with DAD equation		CVD risk with Framingham equation	
Variables	Adjusted β*	p	Adjusted β**	p
HOMA-IR index	0.18	0.429	0.64	0.001
Socio-demographic characteristics				
Occupation (employed/unemployed)	0.09	0.616	–0.11	0.512
Education (secondary or high/primary or less)	0.01	0.976	0.20	0.216
Place of residence (urban/rural)	/	/	0.14	0463
Physical activity (yes/no)	0.23	0.217	0.05	0.809
Hazardous alcohol consumption (yes/no)	/	/	/	/
Clinical characteristics				
Past history of CVD (yes/no)	/	/	/	/
Body mass index	/	/	–0.34	0206
Waist circumference	0.14	0.532	0.32	0.066
Hip circumference	/	/	0.14	0.894
WHO clinical stages (3 or 4/1 or 2)	/	/	/	/
Duration of HIV infection	0.54	0.022	–0.10	0.702
ART (yes/no)	/	/	/	/
ART line (second /first)	/	/	–0.18	0.331
ART duration	/	/	–0.20	0.971
NRTIs (yes/no)	/	/	/	/
NNRTIs (yes/no)	/	/	/	/
PIs (yes/no)	/	/	/	/
PI duration	/	/	/	/
Biological characteristics				
Virus serotype (2 and 1+2/1)	/	/	/	/
CD4 count	/	/	/	/
Viral load (detectable/undetectable)	–0.31	0.117	0.14	0.393
LDL-C	–0.01	0.994	–0.12	0.628
Triglycerides	–0.06	0.752	–0.13	0.469
Any dyslipidaemia (yes/no)	/	/	/	/
Metabolic syndrome (yes/no)	/	/	/	/

*Adjusted for: occupation, level of education, physical activity, waist circumference, duration of HIV infection, viral load, LDL-C and triglycerides.
**Adjusted for: occupation, level of education, place of residency, physical activity, body mass index, waist circumference, hip circumference, duration of HIV infection, ART duration, ART line, viral load, LDL-C and triglycerides.
‡β, Regression coefficient.
ART, antiretroviral therapy; CVD, cardiovascular disease; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; NNRT, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

standard.[31] Nevertheless and to the best of our knowledge, this study is the first one which evaluated the direct relationship between CVD risk and insulin resistance as a continuous variables in sub-Saharan Africans. Furthermore, our sample size was large and we used rigorous methodological and statistical procedures to examine our research questions.

CONCLUSION

The relationship between insulin resistance and CVD risk may depend on the risk equation used. Further prospective cohort studies are warranted to better assess the relationship between CVD and insulin resistance in black African patients with HIV infection. In the meantime, preventing CVD in this population may call for implementation of a programme aiming to reduce, delay or prevent the occurrence of insulin resistance.

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Acknowledgements Our gratitude goes to the physicians and nurses of the HIV outpatient clinic of the Yaoundé Central Hospital, to the personnel of the biochemistry laboratory of the Yaoundé University Teaching Hospital and that of the Laboratory of Molecular Medicine and Metabolism of the University of Yaoundé 1 Biotechnology Centre for their assistance during recruitment of participants and/or biochemical measurements. The authors are also grateful to all those who have volunteered to take part in this study.

Contributors Conception and design: SRNN, ES, APK, FKA, VJAM. Participant recruitment and data collection: SRNN. Data analysis: SRNN, ES, APK, FKA, JJRB. Manuscript drafting: SRNN. Manuscript revision: APK, MYD, ES, JJRB, JRNN, VJAM, FKA, LKM, JAM, JCK, SL, MGF. Final approval of the version to be submitted: all authors.

Competing interests None declared.

Patient consent Obtained.

Ethics approval The study was approved by the Cameroon National Ethics Committee for Human Health Research (Ethical approval N° 2015/12/710/CE/CNERSH/SP). All participants singed a consent form.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement All available data are included in this manuscript.

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