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Safety of lumbar puncture procedure in an international research setting during acute HIV infection

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Abstract

Background: Cerebrospinal fluid (CSF) sampling at the time of acute HIV infection (AHI) is crucial in understanding NeuroAIDS pathogenesis. Here, we report on the safety of performing a lumbar puncture (LP) during untreated AHI and follow-up after initiation of combination antiretroviral therapy (cART).

Methods: We reviewed clinical records of participants who took part in an AHI protocol in Bangkok, Thailand, including untreated AHI subjects (baseline), and longitudinal visits following immediate initiation of cART to assess rates and risk of post-lumbar puncture headaches (PLPH). A cerebrospinal fluid (CSF) volume of 10–20 mL was collected using standard cutting-edge or atraumatic needles.

Results: From April 2009 to February 2016, 195 LPs were performed, of which 89 (46%) were at baseline. The LP procedures at baseline were not associated with an additional PLPH risk as compared to repeat LPs after cART initiation (26/89 [29%] *vs* 4/27 [15%], respectively; *P*=0.134). Higher body mass index (BMI) at baseline (*P*=0.070) and use of an atraumatic needle (*P*=0.058) had trend-level associations with reduced PLPH. A higher CSF volume collection (20 mL) was independently associated with a lower PLPH frequency (*P*=0.024). This association was similar in a subgroup analysis with the use of atraumatic needles. The CD4+ T lymphocyte count, blood and CSF HIV viral load, Fiebig staging, and the presence of an acute retroviral syndrome did not correlate with risk for PLPH (all *P*>0.05).

Conclusion: The frequency of PLPH during AHI was similar to that seen in the setting of cART-treated HIV infection and not higher with a larger CSF volume collection. Our study adds to the existing evidence that atraumatic needles should be used to minimise the risk of PLPH.

Keywords: Lumbar puncture headache, acute HIV infection, cerebrospinal fluid, atraumatic spinal needle, RV254

Introduction

Cerebrospinal fluid (CSF) collection by lumbar puncture (LP) is essential for the evaluation of central nervous system (CNS) disorders. In the setting of neurological complications in HIV, CSF examination is critical to exclude viral escape and opportunistic infections in this compartment. It provides invaluable information about HIV neuropathogenesis, including about the factors associated with cognitive impairment, which is reported in up to 20% of treatment-naïve individuals with CD4+ T lymphocyte counts of >500 cells/mm^3 [1] and ranges from 18% to 63% in treated patients on combination antiretroviral therapy (cART) [2,3]. Measurement of CSF markers such as neopterin and neurofilament light chain provides insight into CNS inflammation and neuronal injury [4-6], which are incompletely normalised despite systemic virological suppression, particularly among those with cognitive impairment [7].

Although a LP is safe and rarely causes life-threatening complications, a post-LP headache (PLPH) is common and develops in up to 40% of individuals undergoing this procedure [8-11]. The reduction in intracranial pressure following LP is believed to cause PLPH, which typically presents with an orthostatic pattern characterised by worsening pain when moving from supine to an erect position. A smaller needle size [12,13], use of an atraumatic (non-cutting edge) spinal needle [14,15] and replacement of the stylet in the atraumatic needle before needle withdrawal [16] are approaches that tend to reduce PLPH. In 2005, the American Academy of Neurology released a statement supporting the use of atraumatic needles to reduce PLPH [17].

Although HIV infection is known to alter coagulation and hence may affect the sealing of an LP wound [18], a recent report on LP safety has stated that HIV status does not alter the risk of PLPH [11]. To date, information has not been published on the safety of LP during AHI, nor have studies been performed in a research setting outside a World Bank-classified high-income country. This may limit our understanding of the cultural acceptance of LP [19] and its uptake in the absence of medical expertise required for treating cases of persistent CSF leakage. Intrathecal immune activation is substantial during AHI [20] and clinically recognised neurological symptoms occur [21], including meningitis [22], leading us to consider whether the frequency and characteristics of adverse events related to LP are altered during AHI. Additionally, although infrastructure exists for clinical research in an array of settings outside high-income countries, there are no reports on the safety of CSF collection in low- or middle-income research settings. We have examined the frequency and risk factors for PLPH, backache and wound infection in AHI from the SEARCH010/RV254 cohort, a prospective longitudinal AHI study under way in Bangkok, Thailand that characterises participants longitudinally before and after initiation of cART during AHI.

Methods

Participants

In our analysis, we included all individuals enrolled into the SEARCH010/RV254 study from its initiation in April 2009 until February 2016. Details of enrolment have been described

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elsewhere [20]. Briefly, specimens from participants seeking HIV voluntary counselling and testing services at the Anonymous Clinic of the Thai Red Cross AIDS Research Center in Bangkok, Thailand were systematically screened for AHI and enrolled during Fiebig stages I to V, as defined by a hierarchical algorithm from pooled nucleic acid and sequential immunoassay (IA) testing [23]. After completion of the initial research assessments and an optional LP performed by research physicians, nearly all participants initiated cART, this typically commenced within 48 hours of AHI confirmation. An optional LP was also performed during the post-cART follow-up to determine the longitudinal outcome of treating HIV at the earliest stage of the infection, using CSF marker analyses. All subjects provided written informed consent to participate in the study. The consent form was approved by the institutional review boards of Chulalongkorn University, Bangkok, Thailand, and the Walter Reed Army Institute of Research, Silver Spring, MD, USA. The study protocol was also approved by the institutional review boards of both institutions.

Lumbar puncture and clinical data

Participants underwent an optional LP at various study time-points such as baseline during untreated AHI (n=89), and at 24, 96 and 240 weeks following enrolment. A subset of participants (n=9) also underwent LP at week 48 as part of a co-enrolment into a separate sub-study (106 follow-up LPs). Demographic and procedure-specific data collected for each LP included age, sex at birth, body mass index (BMI), type of spinal needle used (i.e. cutting edge [Quincke] *vs* atraumatic [Sprotte®, 22-gauge, PAJUNK Medizintechnik]), volume of CSF collected, any same-day invasive study procedure performed (e.g. lymph node biopsy, sigmoid colon biopsy, leukapheresis) and previous exposure to LP. Additional clinical parameters collected at baseline included CD4+ T lymphocyte cell count, plasma and CSF HIV RNA level, Fiebig stage, and the presence or not of an acute retroviral syndrome (ARS), defined as ≥3 qualifying symptoms using a standardised checklist.

Two alterations in the LP standard operating procedure took place during the study period. First, in July 2010 the spinal needle used was changed from a cutting edge to an atraumatic needle. There was a simultaneous emphasis to encourage fluid replacement through the intravenous or oral route to reduce the chance of a dehydration headache. Second, at the beginning of April 2015, the standard operating procedure for CSF volume collection increased from 10 mL to 20 mL.

Adverse events recording and grading

Adverse events (AE), including headache, backache and wound infection, were collected by trained physicians and extracted from the research adverse event database. Designation as an LP-related AE was considered for symptoms with an onset within 3 days after an LP. All events were self-reported by participants or collected by research nurses during the research follow-up visits. Treatment and hospital admission records, if applicable, were retrieved from the research clinical notes. Adverse events were graded from I to IV according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adults and Pediatric Adverse Events (Version 2.0, Nov 2014).

Statistical analysis

In order to minimise the selection bias that participants who experienced PLPH at week 0 were less likely to consent for a repeated LP, as suggested by fewer episodes of PLPH in subjects with LP experience (P<0.01, odds ratio [OR]: 0.32, 95% confidence interval [CI]: 0.14–0.75), we decided to restrict our analysis to first ever LP. Results are reported as mean and standard deviation or frequencies and percentage, as appropriate. All demographic data and clinical factors were linked to the procedure dates. Factors associated with PLPH were examined using logistic regression models that included factors of significance to P<0.05 in individual univariate analyses. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp, Armonk, NY, USA).

Results

During the study period, 347 participants were enrolled into this cohort and 116 participants underwent one or more LPs, accounting for a total of 195 LPs. Nearly all (94%) were undergone by male participants who had a mean age of 29 (range 18–50) years. The participant age and sex of those undergoing an LP or not were similar (mean age 28.5 *vs* 28.1 years, P=0.294 and male 95% *vs* 97%, P=0.746, respectively). Atraumatic needles were used in 88% (169/195) of procedures and a volume of 20 mL CSF was collected in 29% (57/195) of participants. Among all enrolees undergoing an LP, 33% (64/195) had other invasive procedures on the same day taking place among participants with an ARS and pre-existing headache, respectively.

Frequency of post-lumbar puncture complications

A PLPH was recorded in 19% (38/195) of participants undergoing an LP with 68% (n=26) occurring in untreated AHI (i.e. baseline). The PLPH frequency was 29% (26/89) for LPs at baseline and 11% (12/106) during follow-up (week 24: 14% [9/63], week 48: 11% [1/9], week 96: 6% [2/31], and week 240: 0% [0/3]). Among them, 47% (18/38) were grade I (mild), 37% (14/38) grade II (moderate) and 16% (6/38) grade III (severe), defined as an inability to perform usual social and functional activities. All PLPH resolved after conservative management and none required epidural blood patch. There were no grade IV (life-threatening) events. No cases of wound infection were reported, and backache occurred in 8% (15/195) with 12 (80%) grade I and 3 (20%) grade II. All resolved without consequence.

Factors associated with post-lumbar puncture headache

The use of an atraumatic needle (OR 0.22, 95% CI 0.07–0.68, P=0.010) and a higher CSF volume (20 mL *vs* 10 mL) collection (OR 0.13, 95% CI 0.03–0.57, P=0.002) were associated with a reduced PLPH frequency (Table 1). We noted no association between PLPH and age, sex or BMI (P>0.05). Neither an LP during untreated AHI (baseline, P=0.134) nor multiple invasive procedures on the day of LP (P=0.981) were associated with PLPH. In multivariate analysis, the use of an atraumatic needle (P=0.058) and a higher CSF volume collection (P=0.024) remained associated with reduced PLPH frequency.

Analyses limited to untreated AHI

During untreated AHI, the use of an atraumatic needle (OR 0.25, 95% CI 0.08–0.79, P=0.024), CSF collection of 20 mL *vs* 10 mL (OR 0.09, 95% CI 0.01–0.68, P=0.005) and a higher BMI (OR 0.85, 95% CI 0.71–1.01, P=0.070) were associated at trend level with a reduced PLPH frequency (Table 2). In multivariate analyses that included needle type and volume of CSF collected, the use of an atraumatic needle (P=0.094) and higher CSF volume collection (P=0.047) remained associated with a reduced PLPH frequency. Levels of blood and CSF HIV RNA, CD4+ T cell count, Fiebig stage I/II *vs* III–V, presence of an ARS at enrolment, pre-existing headache (in the context of an ARS) and other ARS symptoms (not shown) were not associated with PLPH (P-values >0.05).

Table 1. Participant demographics and procedure-related conditions

	LP without PLPH (*n*=86)	LP with PLPH (*n*=30)	Univariate OR (95% CI)	*P*-value	Multivariate OR (95% CI)	*P*-value
Age (mean, SD) at LP	28.7 (7.05)	27.9 (7.35)	0.98 (0.93–1.05)	0.600		
Sex, *n* (%)						
Male (Ref)	84 (98%)	28 (93%)	1.00	0.275		
Female	2 (2%)	2 (7%)	3.00 (0.40–22.30)			
Body mass index mean (SD)	21.8 (3.02)	20.9 (2.56)	0.89 (0.76–1.05)	0.161		
Volume of CSF collected, *n* (%)						
10 mL (Ref)	55 (64%)	28 (93%)	1.00	0.002	0.17	0.024
20 mL	31 (36%)	2 (7%)	0.13 (0.03–0.57)		(0.04–0.79)	
Type of needle used[a], *n* (%)						
Cutting edge (Ref)	7 (8%)	8 (29%)	1.00	0.010	0.33	0.058
Atraumatic	79 (92%)	20 (71%)	0.22 (0.07–0.68)		(0.10–1.04)	
Multi-procedures on the same day, *n* (%)						
No (Ref)	60 (70%)	21 (70%)	1.00	0.981		
Yes	26 (30%)	9 (30%)	0.99 (0.40–2.45)			
LP at baseline, *n* (%)						
No (Ref)	23 (27%)	4 (13%)	1.00	0.134		
Yes	63 (73%)	26 (87%)	2.37 (0.75–7.54)			

LP: lumbar puncture; PLPH: post-lumbar puncture headaches.
[a] Two LP records (both at week 0) were excluded due to uncertaint type of needle used (*n*=114).

Additional analyses were performed to examine whether the systematic use of an atraumatic needle and the CSF volume collected confounded each other (Table 3). After unification of needle type and CSF volume drawn, both 20 mL CSF collection (all first-ever LP, *P*=0.013; baseline, *P*=0.028) and atraumatic needle use (all first-ever LP, *P*=0.068; baseline, *P*=0.087) remained significant or trend level associated with a reduced occurrence of PLPH.

Discussion

Among our AHI participants, the overall PLPH frequency was 19%, compared to 2–40% in the literature. None of the PLPH events required an invasive medical intervention and all resolved after analgesia and intravenous fluid replacement. No cases of wound infection were reported and local back pain occurred transiently in 8% of participants.

Participant characteristics, including low BMI [11,24], female sex [25–28] and younger age [28–30] have been reported as risk factors of PLPH. This is consistent with our observation of a trend for low BMI associated with PLPH. We did not observe the effect of sex and age in our cohort, probably due to the restricted age range (mean age below 30 years) and a high percentage of male participants (97%).

In a previous report, which compared PLPH incidence between chronic HIV-infected individuals and healthy participants, the authors reported an absence of increased risk in the HIV-infected group [11]. The overall PLPH frequency was 5.6% compared with 19% in our study. However, all LPs were completed using an atraumatic needle in that study, whereas a portion (12%) of our LP procedures were completed with standard cutting-edge spinal needles, which may contribute to PLPH. By comparing the PLPH incidence before and after the use of atraumatic needles, we have confirmed the beneficial effect of atraumatic needle use as described in previous reports [9,29].

Our study is also unique in that it is the first to report LP safety during AHI, with nearly half of LPs performed at study baseline. The higher frequency of PLPH at baseline in comparison with subsequent time-points after cART initiation (29% *vs* 11%) may be related to the selection bias as discussed above. After adjusting for this bias, neither AHI nor individual clinical factors during AHI correlated with PLPH. Multiple invasive procedures on the day of the LP, or a pre-existing headache, did not increase the PLPH risk. Nonetheless, headaches that developed after a baseline LP may be secondary to other factors, including the side-effects of immediate cART initiation that included efavirenz (87/89 of baseline LP participants) and, potentially, a heightened awareness of symptoms associated with anxiety in AHI [21]. Importantly, our experience suggests that a research LP can be carried out safely in a middle-income setting.

The paradoxical relationship between PLPH and volume of CSF collection is unexpected. Traditionally, the orthostatic feature of intracranial hypotension headache is thought to be caused by the traction and distortion of pain-sensitive intracranial venous structures [31]. While persistent CSF leakage is likely to contribute to delayed PLPH, immediate PLPH is probably linked with an abrupt pressure change related to the CSF volume loss. The study design may have contributed to our findings. All LPs completed with the standard cutting-edge needle withdrew only 10 mL of CSF, whereas those with a 20 mL CSF sample were performed with an atraumatic needle. However, we have managed to demonstrate the protective effect of the atraumatic needle use regardless of the amount drawn and a lack of AEs with a higher CSF volume drawn. To date, research LP procedures seldom collect a volume above 20 mL [11,24,29]. One recent Alzheimer's disease study found that collection of a greater CSF volume was associated with higher rates of immediate post-procedural headache, but with a trend towards a lower rate of delayed PLPH at 24 hours of follow-up with a lower risk of therapeutic blood patch [10]. A volume <17 mL compared to >30 mL had a significantly higher rate of PLPH and blood patch intervention [10]. The authors have

Table 2. Subgroup analysis at week 0 (*n*=89)

	LP without PLPH (*n*=63)	LP with PLPH (*n*=26)	Univariate OR (95% CI)	*P*-value	Multivariate OR (95% CI)	*P*-value
Age at LP, mean (SD)	28.9 (6.84)	27.6 (6.92)	0.97 (0.90–1.04)	0.408		
Sex, *n* (%)						
Male (Ref)	61 (97%)	24 (92%)	1.00	0.577		
Female	2 (3%)	2 (8%)	2.54 (0.34–19.09)			
BMI, mean (SD)	22.0 (3.15)	20.7 (2.50)	0.85 (0.71–1.01)	0.070		
CD4 cell count, mean (SD) (cells/mm^3)	434 (172)	437 (178)	1.00 (0.997–1.003)	0.944		
Blood HIV RNA (Log_{10} copies/mL), mean (SD)[b]	5.78 (1.08)	5.41 (1.26)	0.75 (0.50–1.12)	0.155		
CSF HIV RNA (Log_{10} copies/mL), mean (SD)	3.50 (1.22)	3.08 (1.19)	0.74 (0.50–1.11)	0.137		
Fiebig stage I/II, *n* (%)			1.00			
No (Ref)	39 (62%)	14 (54%)	1.39 (0.55–	0.481		
Yes	24 (38%)	12 (46%)	3.51)			
Type of needle used, *n* (%)						
Cutting edge (Ref)	7 (11%)	8 (33%)	1.00	0.024	1.00	0.094
Atraumatic	56 (89%)	16 (67%)	0.25 (0.08–0.79)		0.36 (0.11–1.19)	
Vol of CSF collected, *n* (%)						
10 mL (Ref)	43 (68%)	25 (96%)	1.00	0.005	1.00	0.047
20 mL	20 (32%)	1 (4%)	0.09 (0.01–0.68)		0.12(0.01–0.98)	
Multi-procedures, same day, *n* (%)						
No (Ref)	40 (63%)	17 (65%)	1.00	0.866		
Yes	23 (37%)	9 (35%)	0.92 (0.35–2.40)			
ARS, *n* (%)						
No (ref)	22 (35%)	8 (31%)	1.00	0.706		
Yes	41 (65%)	18 (69%)	1.21 (0.45–3.22)			
Pre-existing headache, *n* (%)						
No (Ref)	28 (44%)	14 (54%)	1.00	0.419		
Yes	35 (56%)	12 (46%)	0.69 (0.27–1.72)			

ARS: acute retroviral syndrome; LP: lumbar puncture; PLPH: post-lumbar puncture headaches.
[a] Two LP records were excluded due to uncertain type of needle used (*n*=87)
[b] 20/89 of CSF sample showed undetectable HIV RNA VL

Table 3. Non-confounding analysis on LP needle type and volume of CSF drawn on PLPH development

Type of LP performed		All first ever LP		Baseline only	
		OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
LP performed with atraumatic needle only	Vol of CSF drawn:				
	10 mL (Ref)	1.00	0.013	1.00	0.028
	20 mL	0.17 (0.04–0.19)		0.12 (0.02–0.98)	
LP with 10 mL CSF drawn only	Needle used:				
	Cutting edge (Ref)	1.00	0.068	1.00	0.087
	Atraumatic	0.33 (0.10–1.04)		0.365 (0.11–1.19)	

CSF: cerebrospinal fluid; LP: lumbar pucture; PLPH: post-lumbar puncture headaches.

suggested that a lower intracranial pressure after high volume CSF collection may facilitate the dural closure and decrease the risk of persistent leakage [10]. As we have only collected PLPH data at 3 days post LP, we are unable to confirm whether the reduction is in immediate PLPH, delayed PLPH or both.

Our study is limited by the fact that orthostatic characteristics of PLPH were not systematically collected during the early phase of our study. This may have led to an over-estimation of PLPH, especially at baseline due to the combined effect of the ARS and ART initiation. Moreover, there could be selection bias as participants who developed PLPH after their first LP at week 0 may not have undergone further LPs. Additionally, we did not have consistent data regarding the CSF white cell count and information on CSF/serum albumin ratio was not collected, each of which could clarify the level of CNS inflammation and may correlate with PLPH development. We did not have sufficient information to analyse the number of LPs, which may increase the risk of PLPH. Lastly, the protective effect of the atraumatic needle may be potentiated by simultaneous introduction of vigorous fluid replacement,

although a protective role of fluid replacement on PLPH is controversial [32]. As information on route and amount of fluid replacement was not specifically captured, we are unable to analyse the effect of fluid replacement on PLPH development.

Conclusion

We found no additional risk in development of PLPH or other post-procedural complications during the acute phase of HIV infection as compared to prior studies of chronic HIV. We noted a protective effect from a higher BMI and the use of an atraumatic needle, with an assumption of insignificant effect of fluid replacement in reducing PLPH from available literature. Finally, a higher volume of CSF collection (20 mL) was not associated with a higher risk of PLPH or required medical interventions. In short, lumbar puncture can be carried out safely in a middle-income research setting during acute HIV infection.

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The RV254 study has been registered in ClincalTrials.gov of NIH and the identifier number is NCT00796146.

Competing interests

The authors have no competing interests to declare

Authors' contributions

Contributions to conception and design: PC, JH, SP, VV, JA, SS

Acquisition, analysis and interpretation of data: PC, JH, DC, EK, CS, JF, PP, SP

Drafting the manuscript or revising it critically: PC, JH, DC, EK, CS, JF, PP, SP, JA, VV, SS

All authors listed have read and agreed to the content of the manuscript

Disclaimer

The views expressed are those of the authors and do not necessarily represent the views of the US Army, the Department of Defense, or the US National Institutes of Health.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

References

1. Wright EJ, Grund B, Cysique LA *et al.* Factors associated with neurocognitive test performance at baseline: a substudy of the INSIGHT Strategic Timing of AntiRetroviral Treatment (START) trial. *HIV Med* 2015; **16 Suppl 1**: 97–108.
2. Cysique LA, Brew BJ. Prevalence of non-confounded HIV-associated neurocognitive impairment in the context of plasma HIV RNA suppression. *J Neurovirol* 2011; **17**: 176–183.
3. Tozzi V, Balestra P, Bellagamba R *et al.* Persistence of neuropsychologic deficits despite long-term highly active antiretroviral therapy in patients with HIV-related neurocognitive impairment: prevalence and risk factors. *J Acquir Immune Defic Syndr* 2007; **45**: 174–182.
4. Anderson AM, Harezlak J, Bharti A *et al.* Plasma and cerebrospinal fluid biomarkers predict cerebral injury in HIV-infected individuals on stable combination antiretroviral therapy. *J Acquir Immune Defic Syndr* 2015; **69**: 29–35.
5. McGuire JL, Gill AJ, Douglas SD *et al.* Central and peripheral markers of neurodegeneration and monocyte activation in HIV-associated neurocognitive disorders. *J Neurovirol* 2015; **21**: 439–448.
6. Peterson J, Gisslen M, Zetterberg H *et al.* Cerebrospinal fluid (CSF) neuronal biomarkers across the spectrum of HIV infection: hierarchy of injury and detection. *PLoS One* 2014; **9**: e116081.
7. Eden A, Marcotte TD, Heaton RK *et al.* Increased Intrathecal Immune Activation in Virally Suppressed HIV-1 Infected Patients with Neurocognitive Impairment. *PLoS One* 2016; **11**: e0157160.
8. Zetterberg H, Tullhog K, Hansson O *et al.* Low incidence of post-lumbar puncture headache in 1,089 consecutive memory clinic patients. *Eur Neurol* 2010; **63**: 326–330.
9. Castrillo A, Tabernero C, Garcia-Olmos LM *et al.* Postdural puncture headache: impact of needle type, a randomized trial. *Spine J* 2015; **15**: 1571–1576.
10. Monserrate AE, Ryman DC, Ma S *et al.* Factors associated with the onset and persistence of post-lumbar puncture headache. *JAMA Neurol* 2015; **72**: 325–332.
11. de Almeida SM, Shumaker SD, LeBlanc SK *et al.* Incidence of post-dural puncture headache in research volunteers. *Headache* 2011; **51**: 1503–1510.
12. Carson D, Serpell M. Choosing the best needle for diagnostic lumbar puncture. *Neurology* 1996; **47**: 33–37.
13. Halpern S, Preston R. Postdural puncture headache and spinal needle design. Metaanalyses. *Anesthesiology* 1994; **81**: 1376–1383.
14. Sprotte G, Schedel R, Pajunk H, Pajunk H. [An "atraumatic" universal needle for single-shot regional anesthesia: clinical results and a 6 year trial in over 30,000 regional anesthesias]. *Reg Anaesth* 1987; **10**: 104–108.
15. Hart JR, Whitacre RJ. Pencil-point needle in prevention of postspinal headache. *J Am Med Assoc* 1951; **147**: 657–658.
16. Strupp M, Brandt T, Muller A. Incidence of post-lumbar puncture syndrome reduced by reinserting the stylet: a randomized prospective study of 600 patients. *J Neurol* 1998; **245**: 589–592.
17. Armon C, Evans RW, Therapeutics, Technology Assessment Subcommittee of the American Academy of N. Addendum to assessment: Prevention of post-lumbar puncture headaches: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2005; **65**: 510–512.
18. Funderburg NT. Markers of coagulation and inflammation often remain elevated in ART-treated HIV-infected patients. *Curr Opin HIV AIDS* 2014; **9**: 80–86.
19. Thakur KT, Mateyo K, Hachaambwa L *et al.* Lumbar puncture refusal in sub-Saharan Africa: A call for further understanding and intervention. *Neurology* 2015; **84**: 1988–1990.
20. Valcour V, Chalermchai T, Sailasuta N *et al.* Central nervous system viral invasion and inflammation during acute HIV infection. *J Infect Dis* 2012; **206**: 275–282.
21. Hellmuth J, Fletcher JL, Valcour V *et al.* Neurologic signs and symptoms frequently manifest in acute HIV infection. *Neurology* 2016; **87**: 148–154.
22. Newton PJ, Newsholme W, Brink NS *et al.* Acute meningoencephalitis and meningitis due to primary HIV infection. *BMJ* 2002; **325**: 1225–1227.
23. De Souza MS, Phanuphak N, Pinyakorn S *et al.* Impact of nucleic acid testing relative to antigen/antibody combination immunoassay on the detection of acute HIV infection. *AIDS* 2015; **29**: 793–800.
24. Kuntz KM, Kokmen E, Stevens JC *et al.* Post-lumbar puncture headaches: experience in 501 consecutive procedures. *Neurology* 1992; **42**: 1884–1887.
25. Leibold RA, Yealy DM, Coppola M, Cantees KK. Post-dural-puncture headache: characteristics, management, and prevention. *Ann Emerg Med* 1993; **22**: 1863–1870.
26. Vilming ST, Schrader H, Monstad I. The significance of age, sex, and cerebrospinal fluid pressure in post-lumbar-puncture headache. *Cephalalgia* 1989; **9**: 99–106.
27. Tourtellotte WW, Henderson WG, Tucker RP *et al.* A randomized, double-blind clinical trial comparing the 22 versus 26 gauge needle in the production of the post-lumbar puncture syndrome in normal individuals. *Headache* 1972; **12**: 73–78.
28. Khlebtovsky A, Weitzen S, Steiner I *et al.* Risk factors for post lumbar puncture headache. *Clin Neurol Neurosurg* 2015; **131**: 78–81.
29. Duits FH, Martinez-Lage P, Paquet C *et al.* Performance and complications of lumbar puncture in memory clinics: Results of the multicenter lumbar puncture feasibility study. *Alzheimers Dement* 2016; **12**: 154–163.
30. Evans RW, Armon C, Frohman EM, Goodin DS. Assessment: prevention of post-lumbar puncture headaches: report of the therapeutics and technology assessment subcommittee of the american academy of neurology. *Neurology* 2000; **55**: 909–914.
31. Mokri B. Spontaneous intracranial hypotension. *Continuum (Minneap Minn)* 2015; **21**: 1086–1108.
32. Arevalo-Rodriguez I, Ciapponi A, Roque i Figuls M *et al.* Posture and fluids for preventing post-dural puncture headache. *Cochrane Database Syst Rev* 2016; **3**: CD009199.