Report on the 8th IAS Conference on HIV Pathogenesis, Treatment & Prevention (19–22 July 2015, Vancouver, Canada)

Specific area: HIV & the central nervous system

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A sizeable amount of novel research was presented regarding the central nervous system (CNS) involvement of the HIV infection. The CNS was mentioned in several presentations in the context of direct HIV pathogenesis, combined antiretroviral treatment (cART) in the CNS, psychiatric comorbidities, neurocognitive impairment in people living with HIV, opportunistic CNS infections and HIV reservoirs in the CNS.
Despite substance abuse being out of scope in this report, the use of illegal drugs is repeatedly mentioned as part of the confounders involved in the assessment of neurocognitive impairment in HIV-infected patients. Moreover, illegal drug injection is identified as a risk factor for HIV infection and remains a major problem in British Columbia and Vancouver in particular. Hence, it is worthwhile mentioning that a significant amount of research work on this field was also presented during the conference starting with the opening session where Dr Volkow discussed the use of buprenorfin, opioid substitution and other approaches to control addictions and parenteral injection practices in order to increase antiretroviral adherence and reduce HIV transmission risks.

The morning of the 20th of July was dominated by the presentation of the design, conduct and main results of the Strategic Timing of AntiRetroviral Treatment (START) study by J Lundgren on behalf of the INSIGHT START study team, due to the wide implications of the results for the HIV community. This trial supports the immediate commencement of cART in all individuals diagnosed with HIV infection regardless of their CD4 cell count, as this reduces the risk of death and illnesses with respect to those patients delaying ART start. The main reference to the CNS within this study was the description as end points of 'depressed mood disorder or disturbance' and 'suicidal or self-injurious behaviour' as part of the most common grade 4 events with no statistically significant differences in incidences between the immediate-initiation arm and the deferred-initiation arm [1].

During the conference, the abstracts (oral and poster presentations) were presented in four separate categories: basic science, clinical science, prevention science and implementation science. However, they are presented according to the fields mentioned at the beginning of this report.

Direct HIV pathogenesis

Regarding basic science and direct HIV pathogenesis, Capoferri *et al* presented a case of HIV rebound and meningoencephalitis following ART interruption after allogeneic hematopoietic stem cell transplant which suggested that recipient cells persist and that a single latent viral population can re-establish infection with elevated CSF viremia and CNS involvement [2]. On a slightly different note, associating peripheral blood and

CNS compartments, Merlini *et al* described an association between CSF and peripheral markers of immune-activation/inflammation (such as TNF-a, IL-6, sCD14, IFNg, MCP-1, IP-10, neopterin, S100beta and activated CD8+ T-cells) and elevated intrathecal HIV-RNA levels in a cohort of HIV-infected antiretroviral-naïve individuals suggesting that both compartments cooperate in maintaining the inflammation within the CNS [3].

Antiretroviral treatment in the CNS

When referring to clinical science, the report of CNS side effects and adverse events (AEs) related to antiretrovirals is of paramount importance for the HIV clinician and so it was reported in the following studies. Lombaard *et al* reported somnolence as an AE possibly related to rilpivirine in 14% of the HIV-infected treatment-naïve adolescents included in the PAINT Phase II trial [4]. In a larger trial assessing doravirine (DOR) 100mg QD vs efavirenz (EFV) 600mg QD in ART-naive HIV-infected patients at week 24, Gatell *et al* reported significantly fewer CNS adverse event in the doravirine group. The most common CNS AEs (all causality) were dizziness (DOR 9.3%; EFV 27.8%), insomnia (7.4%; 2.8%), abnormal dreams (6.5%; 17.6%), and nightmares (6.5%; 8.3%) [5]. On a similar note, Lepik *et al* assessed the proportion of adverse drug reactions (ADR) leading to discontinuation associated with integrase strand transfer inhibitors (INSTI) in clinical practice, which overall was greater in patients on elvitegravir/cobicistat 26/301 (8.64%) vs raltegravir 24/522 (4.60%), and dolutegravir 9/299 (3.01%). However, the proportion of CNS-related ADR was greater in patients on dolutegravir than the other two INSTI at around 2.7% [6].

In order to assess the efficacy of antiretroviral regimens in the CSF, we presented a novel CNS pharmacodynamic end-point measurement whereby we assess the antiretroviral efficacy of CSF collected from subjects on antiretroviral therapy. This assay showed feasibility and will be proven as a tool for future research studies [7].

Psychiatric comorbidities

Psychiatric disorders play a relevant role during HIV infection starting with the potential drug interactions between psychiatric drugs and antiretroviral therapy. Knobel *et al* presented data relating these drug interactions with adherence and clinical outcomes in a hospital cohort in Barcelona. They concluded that a fifth of HIV patients were taking psychiatric drugs and, among them, 87% had at least one drug interaction with almost 10% of psychiatric patients presenting contraindicated interactions, which seemed to affect interruption of antiretroviral treatment and the effectiveness of antiretroviral treatment [8].

Depression was a frequent subject of discussion. Higher rates were reported among men who have sex with men (MSM) in India who had experienced STI symptoms in the past 6 months (59%, AOR: 3.1, 95% CI: 1.9–5.0) and those who knew their HIV-positive status (51%, AOR: 2.4, 95% CI: 1.2–4.7) [9].

As a factor leading to worse outcomes and HIV-infection, prevalence of maternal depression among HIV infected mothers was reported as high and was extremely high among women with HIV-infected infants in a study from Kenya. Maternal depression was associated with lower rates of exclusive breastfeeding and with higher rates of infant symptoms [10]. In Tanzania, mental health, including depression, was also reported to be associated to higher risk of HIV infection [11]. Likewise, in Nigeria decreased quality of life was reported to be associated with depressive symptoms in a cohort of people living with HIV [12]. Interestingly, a study from Lesotho found depression significantly associated with lower self-reported adherence to ART without evidence of association with lower rates of viral suppression [13].

As a consequence of the HIV infection, depression was also reported to be associated with fewer years of schooling and being bullied for taking medications and stigma among adolescents living with HIV in Malawi [14]. Likewise, HIV-related stigma was positively associated with higher depression among newly diagnosed HIV-infected MSM in China [15] and in Cambodia [16]. Moreover, in Thailand female gender, poor adherence, poor/fair quality of life and efavirenz use was associated with symptoms of anxiety and depression [17]. This highlights the intimate relationship between depression and HIV infection outcomes as a cause and a consequence. Most of these studies suggest that a brief screening test to evaluate anxiety and depression symptoms prior to and during cART can help to identify those most at risk so that interventions can be implemented early. In this context, a group from Mexico showed the utility of Beck Depression Inventory HIV-adapted for screening adjustment or depressive symptoms in this clinical population [18].

Regarding other neurological symptoms, a study from Taiwan reported 25.5% of patients with HIV infection were diagnosed with sleep disturbances and that this was associated with higher risk of depression (aHR: 2.52; 95% CI: 2.35–2.71) and use of antiretroviral therapy (aHR: 1.26; 95% CI: 1.17–1.36) [19].

Neurocognitive impairment in people living with HIV

The wide range of neurocognitive disorders presented by people living with HIV is usually described with the umbrella term HIV-associated neurocognitive disorders (HAND). The milder of these disorders is known as asymptomatic neurocognitive impairment (ANI) and was reported to be associated with almost a two-fold increased risk of progression to symptomatic HAND in a Canadian study. The study authors advocated for early treatment with cART in order to delay or lower the risk for the development and progression to symptomatic HAND [20].

Aimed at clarifying the extent and nature of neurocognitive impairment among patients on cART in resource-limited countries, Robertson *et al* presented normative comparison data for seven countries, we provided training for site personnel on the conduct of neurological and neurocognitive assessments. We collected normative comparison data on high-risk HIV-negatives from 10 sites in seven countries (Brazil, India, Malawi, Peru, South Africa, Thailand and Zimbabwe) finding considerable between-country differences in the

neurocognitive test scores. Despite these country variations (attributed to cultural and socioeconomic factors among others), these data provide infrastructure for future neurocognitive studies in resource-limited countries [21]. In the quest to characterise and quantify neurocognitive impairment Brouillette *et al* presented two studies. The first identified several areas of cognitive concerns in persons living with HIV, many of which were not captured by any of the existing questionnaires [22]. The second aimed at estimating the extent to which raw scores from multiple neuropsychological tests can be combined on a single calibrated measurement scale across a range of ability, suitable for cross-population comparisons [23].

On a similar note, to characterise HAND and to differentiate it from other neurocognitive disorders occurring in the ageing population (such as Alzheimer's Disease), Pohl *et al* presented a novel method (iMap) that acknowledges the anatomical heterogeneity of HIV+/- by grouping brain magnetic resonance imaging (MRIs) according to common image patterns [24].

Opportunistic CNS infections

Little was presented about opportunistic infections affecting the CNS. One study from Uganda described the association of cryptococcal immune reconstitution inflammatory syndrome (CM-IRIS) with memory T cell phenotype and increased cryptococcal glucuronoxylomannan (GXM) capsule-specific cytokine responses, suggesting that distinct functional T cell cytokine responses to GXM may predict CM-IRIS [25].

On the same subject of cryptococcal meningitis, a study in Lesotho proved the feasibility of point-of-care screening for cryptococcal antigen by lay counsellors in remote primary care settings. This would allow pre-emptive treatment or referral by nurses [26].

HIV reservoirs in the CNS

During the Monday plenary session Dr Chomont from the University of Montreal highlighted the involvement of CNS tissue as a site for persistence of HIV reservoirs in his presentation 'From Care to Cure'.

Several other presentations highlighted the importance of characterising the latent reservoir and measuring DNA HIV reservoirs in the CNS in order to assess outcomes in future HIV cure studies. However, no original research related to the CNS was presented to this respect.

In conclusion, no specific session or major breakthrough related to 'HIV & the CNS' was presented during this conference. However, the amount of original evidence transversally presented throughout the conference contributed significantly to shed light about the complex field of HIV pathogenesis and treatment in the CNS. For the rest of the conference, the results of the START study and the sessions about HIV cure and vaccine strategies were the most prominent subjects of discussion.

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