Central Nervous System Penetration of Antiretroviral Therapy in HIV-Infected Children

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BACKGROUND
Suboptimal suppression of viral replication within the central nervous system may be a driver of neurocognitive deficits in perinatally HIV-infected children on combination antiretroviral therapy (cART). Pediatric data on central nervous system (CNS) penetration of antiretroviral drugs are scarce.

This study aimed to evaluate antiretroviral (ARV) drug penetration into CNS in perinatally HIV-infected children, and to compare this to available data in adults. As a secondary objective, we evaluated whether ARV drugs reached effective CNS concentrations, by comparing them to the IC50.

METHODS
The current study is part of the NOVICE study, which focuses on cognitive and central deficits in perinatally HIV-infected children between 6-18 years of age from the Academic Medical Center in Amsterdam. We included participants who were on long-term cART, and of which paired cerebrospinal fluid (CSF) and blood samples were available.

Total plasma and total CSF drug concentrations were measured using liquid chromatography-mass spectrometry (LC-MS). Of note, lopinavir was always boosted with ritonavir, but not measurable in CSF and thus not included in our analysis. For each drug, the CSF-to-plasma ratio was calculated as a surrogate marker of CNS penetration. Plasma drug concentrations were adjusted for protein binding, by calculating protein bound concentrations (Table 1). CNS ARV concentrations were compared to half maximal inhibitory concentrations (IC50). The CNS-to-plasma ratio was calculated as a measure of blood-brain barrier permeability, to assess for possible confounding.

RESULTS
STUDY PARTICIPANTS
We included 15 boys and 8 girls with a median age of 12.8 (IQR 10.3-17.5) years, who had been using cART for a median duration of 10.7 (IQR 7.2-14.4) years, and were virologically suppressed in blood and CSF. The most frequently prescribed regimen was abacavir/lamivudine/efavirenz (n=15). The dose-to-sampling interval ranged from 2.7-193 hours. The median CSF-to-plasma albumin ratio was 2.9 (IQR 2.4-3.3, n=20) and did not vary with age (<0.24, P=0.75).

CNS PENETRATION OF ANTIRETROVIRAL DRUGS
After adjusting for protein binding, the highest CNS penetration was seen for nevirapine, abacavir, zidovudine and efavirenz (Table 1, Figure 1). Lopinavir and tenofovir showed the poorest CNS penetration. Overall, the CNS-to-plasma ratios from our study showed reasonable agreement with reports from adult studies, although limited data with correction for protein binding was available for comparison.

CNS CONCENTRATIONS AND EFFECTIVITY (IC50)
CSF concentrations of lopinavir, zidovudine, efavirenz, and nevirapine were all above the reported IC50, similar to reports in adults (Table 2, Figure 2). The CSF concentrations of abacavir, emtricitabine, and tenofovir were lower as compared to studies in adults, and did not reach IC50 in all cases. Notably, while lamivudine concentrations were similar to that in an adult study, all concentrations fell below the reported IC50 from another study.

CONCLUSIONS
In a group of perinatally HIV-infected children on long-term cART, CNS penetration of ARV drugs was overall similar to adults. The majority of the ARV drugs showed good CNS penetration, except for tenofovir and lopinavir, which had the lowest CNS-to-plasma ratios.

High CNS penetration did not always correspond to effective CNS concentrations. As compared to adults, the proportion of CNS concentrations that reached the IC50 was lower for tenofovir, lamivudine, emtricitabine, and abacavir.

As these four ARV drugs were used in combination with at least one other ARV drug that reached effective CNS concentrations (nevirapine, efavirenz, lamivudine, or abacavir), virological suppression was achieved in all children.

Table 1. CNS-to-plasma ratio is presented as uncorrected median (IQR). Lopinavir and tenofovir showed the poorest CNS penetration. Overall, the CNS-to-plasma ratios from our study showed reasonable agreement with reports from adult studies, although limited data with correction for protein binding was available for comparison.

Table 2. CSF concentration is reported as concentration (ng/mL) with concentration reported as IC50 (ng/mL) for each drug. CNS concentrations were compared to half maximal inhibitory concentrations (IC50). The CNS-to-plasma ratio was calculated as a measure of blood-brain barrier permeability, to assess for possible confounding.

With the current regimens, all participants achieved virological suppression in blood and cerebrospinal fluid.

KEY POINTS
Most antiretroviral drugs showed good central nervous system penetration, except for lopinavir and tenofovir.

Tenoforv, emtricitabine, abacavir, and lamivudine did not reach IC50 in all participants.

With the current regimens, all participants achieved virological suppression in blood and cerebrospinal fluid.