HIV-1 Infection of the Central Nervous System (CNS) and the AIDS Dementia Complex (ADC)

Introduction & Some Issues for Africa
CSF Studies of HIV and the CNS: Outline

- Introduction (Quick Overview)
  - Major issues of CNS Infection and ADC
  - Pathology & pathogenesis
  - Clinical diagnosis and evaluation
  - Antiretroviral treatment effects

- Extending these Issues to Africa
  - Pathogenetic variables
  - Evaluatation strategy for clinical trial
The Brain in HIV Infection and ADC: Salient Observations

- The CNS HIV is exposed early and continuously to HIV
- Late in systemic disease some patients develop HIV encephalitis and ADC
- Major pathological substrate of ADC is HIV encephalitis
  - HIV productively infects macrophages (and microglia) but not neurons or oligodendrocytes, and likely insignificantly astrocytes
The Brain in HIV Infection and ADC: Fundamental Questions of Pathogenesis

- How does HIV infection cause both:
  - Innocent exposure early in all?
    - Chronic infection with meningeal inflammation
  - Damaging encephalitis late (in some)?

- How are the ‘functional elements’ of the brain perturbed or killed in the absence of direct infection?
ADC & HIV Encephalitis: Neuropathology
ADC: Multinucleated-Cell (HIV) Encephalitis
ADC: Vacuolar Myelopathy
The Brain in HIV Infection: Basic Elements

HIV ↔ Immune System ↔ CNS
Importance of Macrophages in CNS HIV Infection and Clinical Disease (ADC)

- **Infection**
  - Macrophages are principal cells supporting HIV encephalitis
    - Perivascular macrophage has primary role in seeding and sustaining infection
    - Develops in late infection
  - CNS infection (and ADC) is associated with macrophage-tropic variants using CCR5

- **Injury**
  - Macrophage infection produces pathogenic mediators
    - Infected & uninfected cells
    - Chemotactic and other signals
    - Neurotoxins
ADC: Some Clinical Aspects
ADC: Character & Diagnosis

- Clinical syndrome of ‘subcortical dementia’
  - Cognitive
  - Motor
  - Behavioral

- Diagnosis
  - Inclusion
    - Clinical recognition
  - Exclusion
    - Neuroimaging
    - Laboratory evaluations
ADC: Exercise of Differential Diagnosis

- **Stage 0.5 & 1**
  - Is ADC present?
    - Or depression?
    - Non-neurological disease?

- **Stage 2-4**
  - Is impairment caused by another condition?
    - CNS OI?
    - Non-AIDS CNS disease, eg metabolic encephalopathy?
The Brain in HIV Infection and ADC: Some Issues of Treatment

- Can systemic treatment effectively suppress CNS HIV infection despite variable drug penetration?
  - Impact on ADC
    - To prevent ADC?
    - To treat manifest ADC?
  - Impact on viral persistence
    - To eliminate ‘reservoir’?
    - To eliminate incubator of resistant virus?
CSF as a Reflection/Model of CNS Infection

- **Variable relationship of CSF to brain infection**
  - Directly reflect brain processes
    - Leak/exchange of brain interstitial and perivascular fluid
  - Parallel formation
    - Similar barriers & selection
  - Independent meningeal processes

- **LP allows easy & serial sampling**
Response of CSF HIV to treatment

CSF HIV responses to HAART

- Initial rates of CSF response frequently slower than plasma
- But may be equal
- And longterm CSF outcomes as good as or better than plasma
CSF HIV can decay as quickly as plasma during acute phase of response

- **Observation**
  - CSF fell proportionally or actually as rapidly as plasma
  - Seen with or without pleocytosis

- **Implication**
  - Either drug(s) equally effective in CSF compartment
  - Or, rapid virus turnover so that systemic treatment rapidly reduced CSF virus

**Graphs:**
- CSF HIV and Plasma HIV decay rates
- ADC0, CD40, WBC0 values for each comparison
- WBCs and HIV RNA levels over time for nelfinavir, combivir, sustiva, zidovudine, lamivudine
ADC Treatment Response: Example
ADC treatment responses, anecdote 2
More favorable CSF response

- All 5 treatment experienced
  - Persistent plasma viremia due to resistance
- 4/5 switching drugs
  - Represents 4 of the 8 (50%) switching in treatment group of 27 treated
Simple Models of CNS Infection

1. PUSH

2. PULL

3. AMPLIFIED/MIXED
Simple Models of CNS Infection: Implications for Treatment

1. PUSH
2. PULL
3. AMPLIFIED/MIXED

- Transitory
- Autonomous

No treatment

Non-penetrating treatment

Penetrating treatment
ViroLogic Chemokine Receptor Assay

Transfection

HIV genomic luc vector + HIV env expression vector

Infection

virus entry inhibitors added

CD4 + CXCR4 +

CD4 + CCR5 +
HIV-1 Chemokine Receptor (CCR) Utilization in Plasma & CSF

- **Survey of CCR Use**
  - 46 paired plasma & CSF specimens
  - Convenience sample
  - HIV RNA in both samples near or >1,000 copies/mL
  - Range of blood CD4 counts
    - Greater X4 with lower CD4
  - 4 ADC subjects
HIV-1 Chemokine Receptor (CCR) Utilization in Plasma & CSF

- **Sorted by Concordance:** Discordance of CCR use
  - **Concordant**
    - 36 R5
    - 5 dual/mixed (D/M)
  - **Discordant**
    - 3 D/M plasma, R5 CSF
    - 2 R5 plasma, D/M CSF

(increasing CD4 counts w/in each group)
Clonal Analysis of 3 Plasma:CSF Pairs with D/M CCR Use

7069: Treatment naïve
CD4 124; CSF WBC 5
HIV: Pl 63,400, CSF 4,550
Discordant: plasma -D/M, CSF -R5

7047: Treatment naïve
CD4 228; CSF WBC 73
HIV: Pl 62,900, CSF 17,200
Concordant -D/M

7120: Off ART 4 yrs
CD4 102; CSF WBC 12
HIV: Pl 10,200, CSF 14,000
Discordant: plasma -R5, CSF -D/M
Neurological Disease: Variables in Pathogenesis

HIV
- Dose
- Gene variation
  - Clade

Host
- Genetics
- Epigenetics
  - Other diseases
  - Nutrition

Treatment

Systemic Disease
- HIV replication
- Immune perturbation
- OIs

Neurological Disease
- HIV encephalitis/ADC
- OIs
Neurological Disease in HIV: Approaches to Evaluation in Clinical Trials

**Neurological Evaluation**
- History
- Examination
- Laboratory

**Quantitative Neurological Performance**
- Change over time

**Specific Diagnosis**
- Inclusion Criteria
- Exclusion Criteria
- Clinical Endpoints

**Functional Status**
- Neurological Morbidity
- Group Effect