Antiretroviral Therapy (ART): Impact, Limitations and Strategies in Treating CNS HIV Infection

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Disclosure of Potential Conflicts

- Honorarium and travel reimbursement:
  - Abbott Laboratories
- Research support:
  - Investigator-initiated study support Merck & Co.

ART & CNS HIV Infection: Outline

- Treating systemic infection
  - Objectives
  - When to treat?
  - How to treat?
- Effectiveness & shortcomings treating CNS infection
  - Objectives
  - Neurological impact
  - Virological impact
- Targeting CNS infection
  - Objectives
  - Theoretical rationale
  - Empirical approach
- Recommendations for approach to new CNS disease

Systemic ART: Objectives

Patient rationale
- ART aims to reduce the risk of disease progression through:
  - Suppression of systemic HIV infection
  - Restoration/preservation of immune competence
  - Reduction of immune activation and thereby
  - Prevent OIs and other complications of immunosuppression and HIV (including CNS OIs)
  - Prevent non-AIDS complications (including CNS diseases)

Community rationale
- ART also aims to reduce the risk of sexual transmission of HIV
Systemic ART: When to Initiate Treatment

**DHHS Guidelines for starting therapy (2012)**

- Antiretroviral therapy (ART) is recommended for all HIV-infected individuals. The strength of this recommendation varies on the basis of pretreatment CD4 cell count:
  - CD4 count <350 cells/mm³ (AI)
  - CD4 count 350 to 500 cells/mm³ (AII)
  - CD4 count >500 cells/mm³ (BII)
- Antiretroviral therapy (ART) is recommended for all HIV-infected individuals to reduce the risk of:
  - Disease progression (patient rationale)
  - Sexual transmission of HIV (community rationale)

Rating of Recommendation Statements:  
A = Strong; B = Moderate; C = Optional
Rating of Evidence:  
I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

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Systemic ART: What to Start

**Initial drug selection**

**DHHS Guidelines for starting therapy (2012)**

- Criteria for treatment selection
  - Efficacy in reducing viral burden and restoring/sustaining immune function: antiviral potency, pharmacokinetics
  - Factors affecting tolerability and adherence: dosing frequency, pill burden, side effects, toxicities, and drug interactions
  - Strength of evidence: based on large body of evidence, including particularly randomized clinical trials
  - Resistance is greatest pitfall to enduring treatment success
    - Pretreatment drug-resistance testing
- Classification of initial regimens
  - Preferred (AI)
  - Alternative (BI & BIII)
  - Other (Acceptable) (CI & CIII)

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Systemic ART: Drug Targets

**Drug classes**

- Nucleoside/tide reverse transcriptase inhibitors (NRTIs)
- Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- Protease inhibitors (PIs)
- Integrase strand transfer inhibitors (INSTIs)
- CCR5 antagonists
- Fusion inhibitors

**General principles**

- 3 active drugs, some with 4th to boost exposure
  - Most common: 2 NRTIs + NNRTI or PI or INSTI
  - Boosting drugs: ritonovir (r), cobicistat

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Systemic ART: What to Start

**Initial drug selection**

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CNS ART: Objectives

- **Treatment:**
  - Suppress CNS HIV infection
  - Stop progression of and reverse CNS dysfunction
- **Prevention:**
  - Prevent late effects: HIV-associated dementia (HAD)
  - Prevent milder CNS dysfunction
  - Eliminate viral reservoir (barrier to viral eradication)

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Neurological Effects of ART

- **Impact on HAD**
  - Treatment: reversal of dysfunction (variable but often substantial)
  - Prevention: marked reduction in incidence
  - Similar to impact on CNS OIs
- **Shortcomings**
  - Persistence of milder CNS impairment in treated patients
  - Symptomatic CNS escape

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Treatment of HAD: Example

- **Study design:**
  - Nationwide, population-based cohort study using Danish registries of severe neurocognitive disorders (SNCD)
- **Findings:**
  - 32 cases per 4,452 HIV+
  - 120 cases per 62,328 controls
  - Relative risk 10.1 when CD4 <350
  - Relative incidence in HIV+ approached HIV- in 2005-2008
  - Mortality higher in HIV+ SNCD
  - Age younger in HIV+ SNCD

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Prevention of HAD: Example

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CNS Shortcomings of ART: HIV-Associated Neurocognitive Disorders (HAND) Definitions

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CNS Shortcomings of ART: Milder CNS Impairment

- **Study of 200 subjects with treatment-induced plasma viral suppression**
  - 27% Cognitive complaints
- **50 with neurological complaints (84% impairment)**
  - 24% asymptomatic neurocognitive impairment (ANI)
  - 52% mild neurocognitive disorder (MND)
  - 8% HAD
- **50 without neurological complaints (64% impairment)**
  - 60% ANI
  - 4% MND
  - 0% HAD


CNS Shortcomings of ART: Milder CNS Impairment

- **Heaton et al. Charter Study Cohort**
  - Cross-sectional study of 1,555 subjects, 6 centers, extensive NP testing
    - CD4 420 (IQR 49-300); 71% on cART; 59% with detectable plasma HIV (44% on cART); 34% detectable in CSF (16% on cART)
    - 52% neuropsych (NP) test impairment in those cases ‘not severely confounded’:
      - 33% asymptomatic (ANI)
      - 12% mild NP impairment (MND)
      - 2% severe (HAD)
    - Low CD4 nadir strong predictor of impairment


Causes of Mild Impairment (ANI/MND) in Treated Patients

- Confounding conditions
  - Amenable to CNS-directed ART
- Past (static) HIV-related injury
  - With residual damage
  - Reduced reserve, additive with other conditions (e.g., aging)
- Active immune activation-related injury without CNS infection
  - Related to systemic immune activation
  - Sustained local CNS immune activation?
- Active CNS HIV-related injury
  - With detectable CSF virus
  - With level or type or infection below detection?
CNS Virological Effects of ART

- CNS (CSF) infection is nearly ubiquitous facet of systemic HIV infection
- In most patients who achieve plasma virus suppression, CSF HIV is also suppressed
  - In most of these CSF HIV RNA levels <1 copy/ml
- Exceptions
  - Asymptomatic CSF escape
  - Symptomatic CNS escape

Asymptomatic CSF Escape: Eden et al

- Retrospective case series of patients on contemporary therapies with:
  - HIV in CSF (>50 cpm) with suppressed (<50 cpm) plasma
  - Neurologically asymptomatic or clinically static
- 69 total subjects
  - 7 with detectable CSF (10%)
  - Median CSF HIV 121 cpm (54 – 213)
  - CSF pleocytosis: no different from non-escape
  - CSF neopterin in escape (median 9.2) > controlled (median 5.1, p=0.03)
  - Resistance mutations not done
  - No relation to cpe score
  - Only ZDV-treated without CSF escape
- Preliminary data suggest most do not evolve to symptomatic disease

Symptomatic CSF Escape: Canestri et al

- Retrospective case series patients with neurological symptoms and HIV in CSF with suppressed plasma
  - CSF > 200 cpm, plasma <50 cpm, or
  - CSF > 10x plasma in treated patients
- 11 patients
  - Acute or subacute neurological disease
  - 10/11 CSF pleocytosis
  - Median CSF HIV 880 cpm (588 – 12,885)
  - Resistance mutations in 7/8
  - All improved after optimization of treatment with respect to:
    - Resistance
    - CNS drug entry
- Relative incidence
  - 2 centers, 6000 patients/year
  - Review over 5 year period

Favorable CSF HIV RNA Suppression in Most Patients

- Price RW & Spudich S. Antiretroviral therapy and central nervous system HIV type 1 infection. JID 2008; 197 Suppl 3:S294-306.
Symptomatic CSF Escape: Peluso et al

- Retrospective case series patients with neurological symptoms and HIV in CSF with suppressed plasma
- 10 patients
  - Acute or subacute neurological disease
  - 10/10 CSF pleocytosis
  - Median plasma HIV 62 cpm (<50 – 380)
  - Median CSF HIV 3900 cpm (134 - 9056)
  - Median CD4 482 (290 – 660)
  - Resistance mutations in 6/7
  - 8/9 improved after optimization of treatment with respect to:
    - Resistance
    - CNS drug entry
- Relative incidence
  - 4 centers (SF, Milan, New Haven, Gothenburg)
  - Denominator uncertain


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Symptomatic CSF Escape


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Symptomatic CSF Escape: Peluso et al

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Symptomatic CSF Escape: Imaging Changes

MRI findings at the time of cerebrospinal fluid escape and following modification of antiretroviral regimen. Panels (a-j) show selected MRI images for patients 2000 and 7000. Panels (a-d) show imaging at the time of neurologic worsening when cerebrospinal fluid (CSF) escape was detected for patients 2000 (a, b) and 7000 (c, d), demonstrating diffuse T2 prolongation (a, b) and suggesting focal lesions (d) at the time of CSF ‘escape’. Panels (e-h) show follow-up imaging for patient 2000 at 111 days and patient 7000 at 62 days. Even though neurologic symptoms had resolved in both cases, imaging still shows diffuse leukoencephalopathy (a, d) and hyperintense, diffuse signal alteration of bilateral white matter (a, d), despite improvement of previous focal lesions (b). Panels (i) and (j) show imaging for patient 2000 at 567 days follow-up, demonstrating significant interval decrease in T2 prolongation.

Symptomatic CSF Escape: Pathogenesis

- Compartmentalized CNS infection
- Local resistance to one or more drugs
- Suboptimal drug concentrations of one or more drugs
- Partially functional anti-HIV immunity?
  - Local anti-viral inflammatory reaction (IRIS)
  - But failure to eradicate infection

Targeting CNS HIV Infection: Rationale for Drug Choice

- Character of infection
  - CNS HIV infection can be compartmentalized
- Drug pharmacology
  - ART drugs achieve variably lower concentrations in CNS (CSF) than in blood
- Efforts to develop systems to optimize CNS drug exposure of combinations
  - CPE scores
- Conflicts with preferred systemic recommendations

CNS Pharmacological Limitations

## CNS Penetration Effectiveness (CPE) 1:
### Original 2008, Modified 2010

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*Letendre et al. Arch Neurol 2008 & Smurzynski et al. AIDS, 2010*

## CNS Penetration Effectiveness (CPE) 2: 2010

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*From Letendre et al, CROI 2010*

## CNS ART: What to Start
### Conflicts with DHHS Guidelines (2012)

- Theoretically highest CNS exposure in **Acceptable** and **Alternative** groups

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>CNS Priority</th>
<th>CNS Penetration Effectiveness (CPE) 2010</th>
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<td>TDF FTC DRV/r</td>
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<td>TDF FTC RAL</td>
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<tr>
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*DHHS Rating | CNS Priority | CNS Penetration Effectiveness (CPE) 2010*
If CNS Penetration is Generally Poor, Why Do Common Regimens Work So Well?

- Major action is through systemic therapy?
  - Enhance immune control
  - Reduce CNS viral reseeding
  - Reduce immune activation
  - Reduce traffic of activated target cells
- Current methods underestimate CNS effects
  - Most regimens actually above threshold for CNS efficacy (e.g., equivalent to CPE 7)
  - PK and CPE scores are limited indicators of CNS efficacy
    - CSF is not equivalent to brain
    - Intracellular concentrations and effects paramount for most drugs, particularly NNRTIs

Recommendations: CNS ART Targeting on Initiating Therapy

- New onset or progressive HAD
  - Most ‘CNS effective’ of Preferred
    - TDF/FTC/DRV/r
    - TDF/FTC/EFV (side effect, lower genetic barrier)
    - TDF/FTC/RAL (lower genetic barrier)
- New onset or uncertain milder CNS symptoms and signs
  - History of nadir CD4 <200 cells/µL – as above
  - Otherwise, standard Preferred
- Neurologically asymptomatic
  - Standard Preferred

Recommendations: CNS Evaluation and Treatment in Patients Already on ART

- New onset or progressive disease
  - Diagnostic evaluation: MRI, CSF
  - If case of symptomatic CNS escape
    - Adjust according to CSF & plasma HIV drug resistance
    - Favor drugs with greater CNS exposure
- Static or uncertain MND
  - Systemic drug failure: adjust salvage regimen based on systemic resistance
  - Systemic viral suppression: MRI, CSF as indicated
    - If CSF escape, as above
    - If no escape, no indication for adjusting ART

Treating CNS HIV Infection: Conclusions

- Systemically tailored ART is generally very effective in preventing CNS disease
  - Particularly if started early in infection
- Neurosymptomatic CNS escape is an important, though uncommon, exception
- The pathogenesis of more common impaired test performance in well-treated patients is heterogeneous and often uncertain
- Adjusting ART in treated patients should be based on presence and character of CSF HIV
Acknowledgements

• Clinical/CSF
  - Magnus Gisslen
  - Serena Spudich
  - Arvid Eden
  - Paola Cinque
  - Aylin Yilmaz
  - Lars Hagberg
  - Evelyn Lee
  - Julia Peterson

• Biomarkers
  - Henrik Zetterberg
  - Sheila Keating
  - Jon Jacobs
  - Dick Smith
  - Joe Brown

• Virology
  - Ron Swanstrom
  - Gretja Schnell
  - Sarah Joseph
  - Teri Liegler
  - Sarah Palmer
  - Victor Dahl

• Immunology
  - Dietmar Fuchs
  - Elizabeth Sinclair
  - Barbara Shacklett

Key to Abbreviations:
Drug classes: INSTI = integrase strand transfer inhibitor, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleos(t)ide reverse transcriptase inhibitor, PI = protease inhibitor,
Drugs: 3TC = lamivudine, ABC = abacavir, APV = amprenavir, ATV/r = atazanavir/ritonavir, COBI = cobicistat, d4T = stavudine, ddI = didanosine, DRV/r = darunavir/ritonavir, EFV = efavirenz, EVG = elvitegravir, FPV/r = fosamprenavir/ritonavir, FTC = emtricitabine, LPV/r = lopinavir/ritonavir, MVC = maraviroc, NVP = nevirapine, RAL = raltegravir, RPV = rilpivirine, RTV = ritonavir, SQV/r = saquinavir/ritonavir, TDF = tenofovir, ZDV = zidovudine