Cerebral Small Vessel Disease and HAND in ARV-treated Subjects

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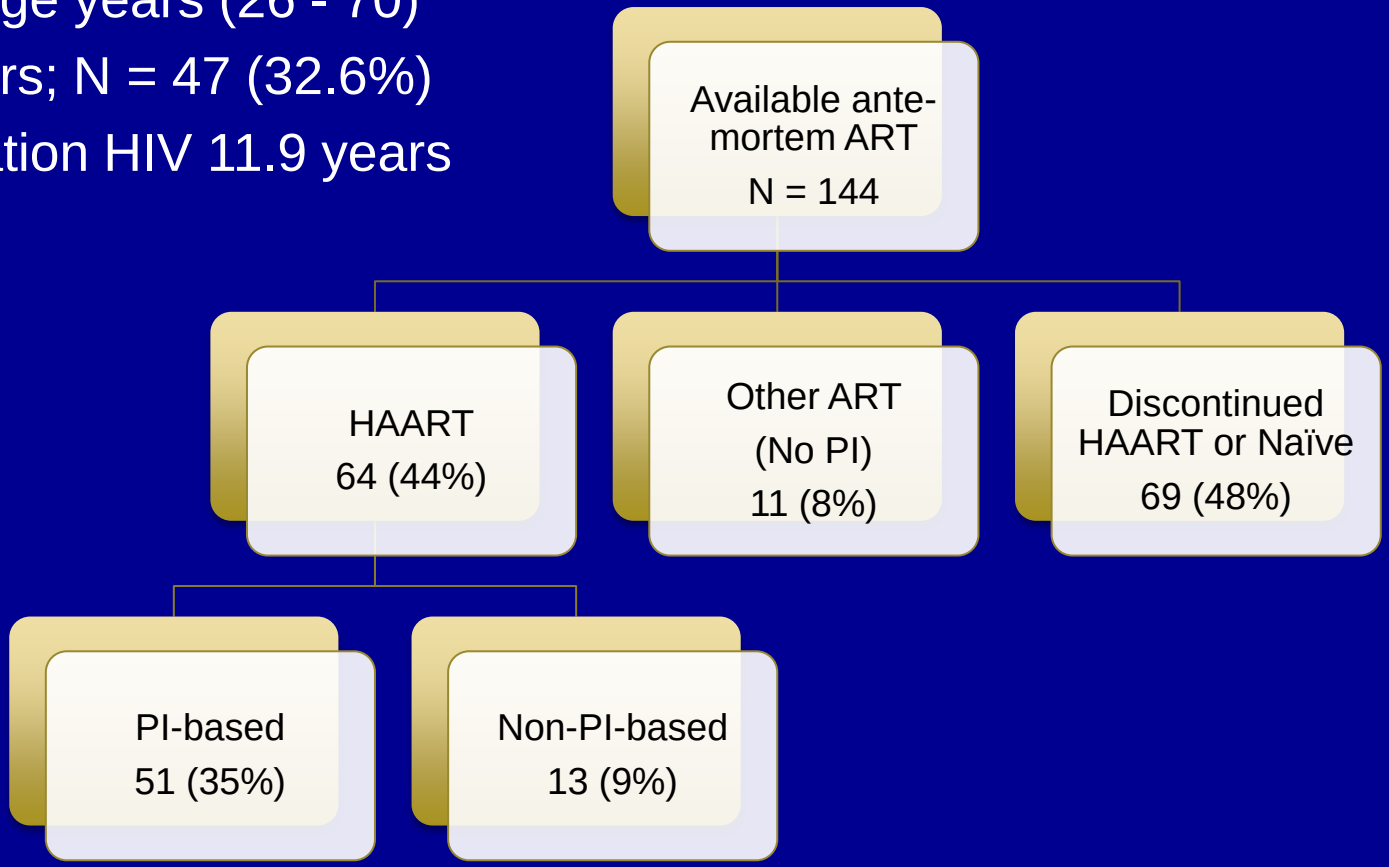
ARROW, Bucharest, Romania
October 5-6, 2015

Rationale and Study Design

- Chronic toxic effects of antiretroviral drugs could contribute to cerebral small vessel disease (CSVD), underlying HAND
- Clinicopathological correlation study: HIV+ adults in the California NeuroAIDS Tissue Network (CNTN)
- 144 HIV+ decedent tissue donors (1999−2011) with detailed antemortem data on ARV medications
- cART was defined as regimens containing three or more ARV medications from at least two different drug classes
- CSVD standard histopathology: moderate/severe, mild, or absent

Participants (N = 144)

- 120 men (83.3%)
- median 45 age years (26 - 70)
- age ≥50 years; N = 47 (32.6%)
- median duration HIV 11.9 years



Results and Conclusions

- H&E-stained paraffin-embedded formalin-fixed tissue slides from the following brain regions: frontal (Brodmann's area [BA] 8 and BA4), parietal (BA1−3 and BA7), temporal (BA21−22), hippocampus, basal ganglia (anterior and posterior), anterior cingulate and corpus callosum, occipital (BA17−18), hemispheric cerebellum, midbrain, pons, and medulla.

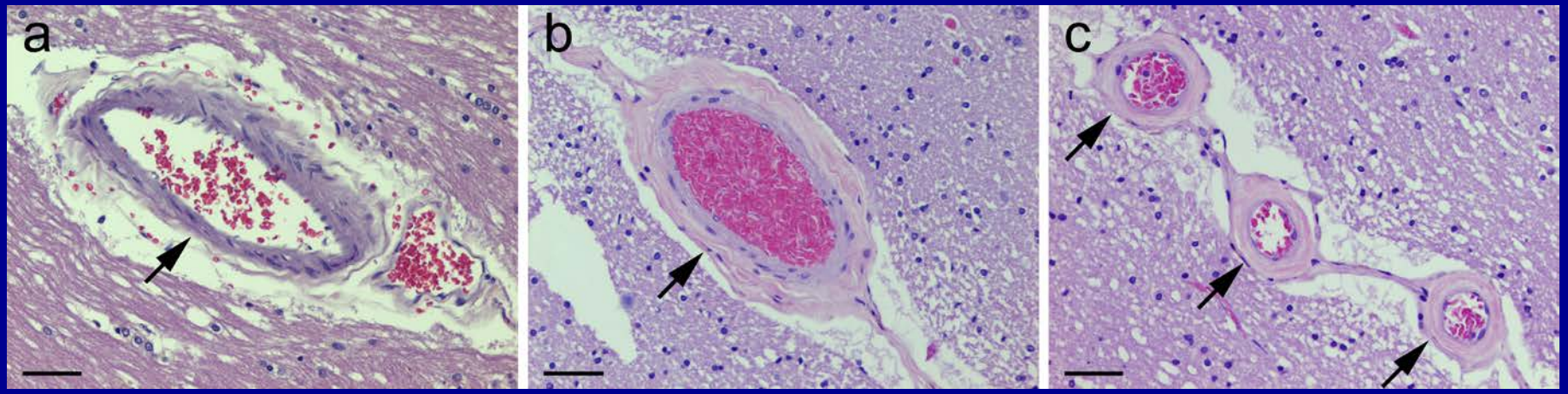
- Moderate/severe CSVD was associated with diabetes after adjusting for HAART exposure which remained statistically significant after adjusting for vessel mineralization, HIV encephalitis, microglial nodular lesions, white matter lesions, or older age

- Both mild and moderate/severe CSVD were associated with PI based cART exposure after adjusting for diabetes

- PI-based cART exposure may increase the risk of CSVD and neurocognitive impairment in HIV-infected adults

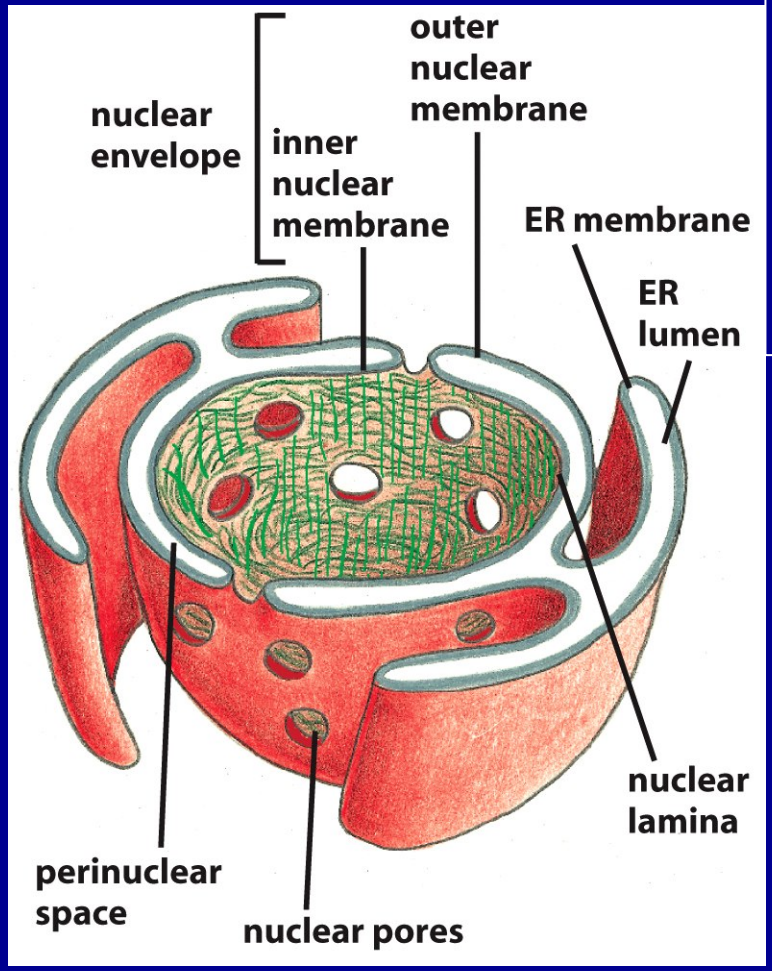
- Beside the possible direct toxicity to cerebral small vessels, PI-based cART may contribute indirectly to CSVD by inducing metabolic abnormalities

HIV PI exposure predicts CSVD

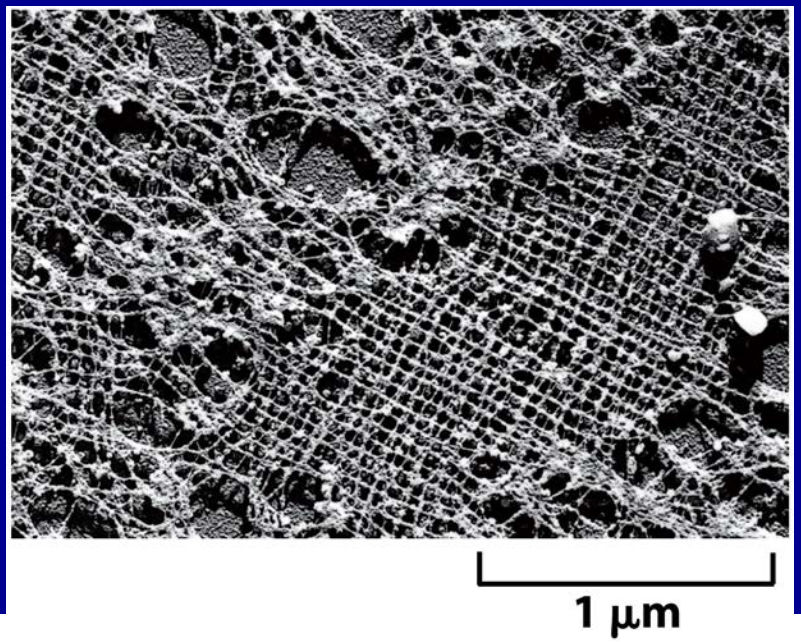


- **Histopathology of cerebral small vessel disease (CSVD) in the forebrain white matter of HIV-infected adults.** On hematoxylin and eosin staining, CSVD is defined as concentric intramural hyalinization of small arteries or arterioles and graded as absent [normal] (a, arrow), mild [partial-thickness involvement] (b, arrow), or moderate/severe [full-thickness involvement] (c, arrows); scale bars 50 μm.

Nuclear Lamina



Nuclear Lamins (A, C; B1; B2): Intermediate filament proteins that form a 2-D lattice for the nuclear lamina, providing shape and stability to the nuclear envelope

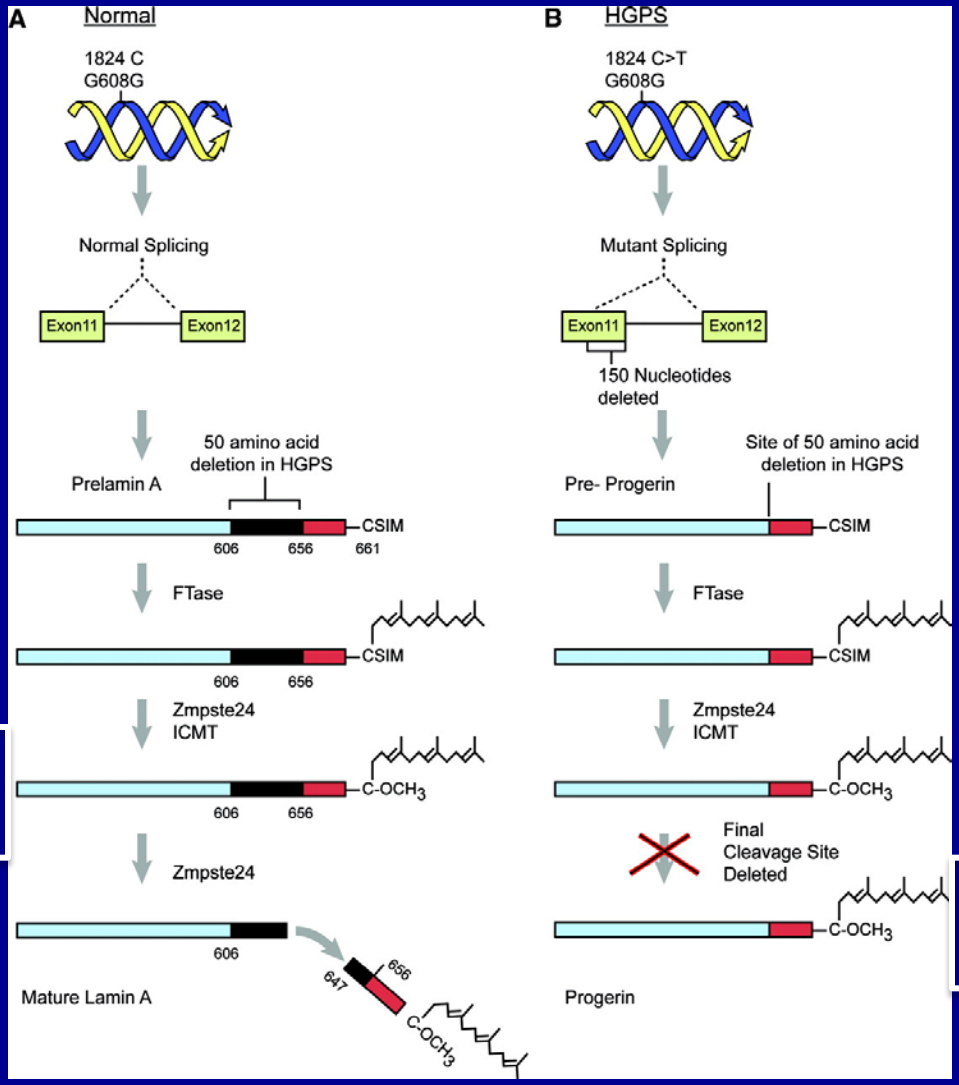


Hutchinson-Gilford Progeria Syndrome (HGPS)
Mutation in *LMNA* gene (Lamins A/C)
'premature aging'

- Predominantly affect mesenchymal cells (VSMC).
- Fatal myocardial infarction or ischemic stroke in 2nd decade.

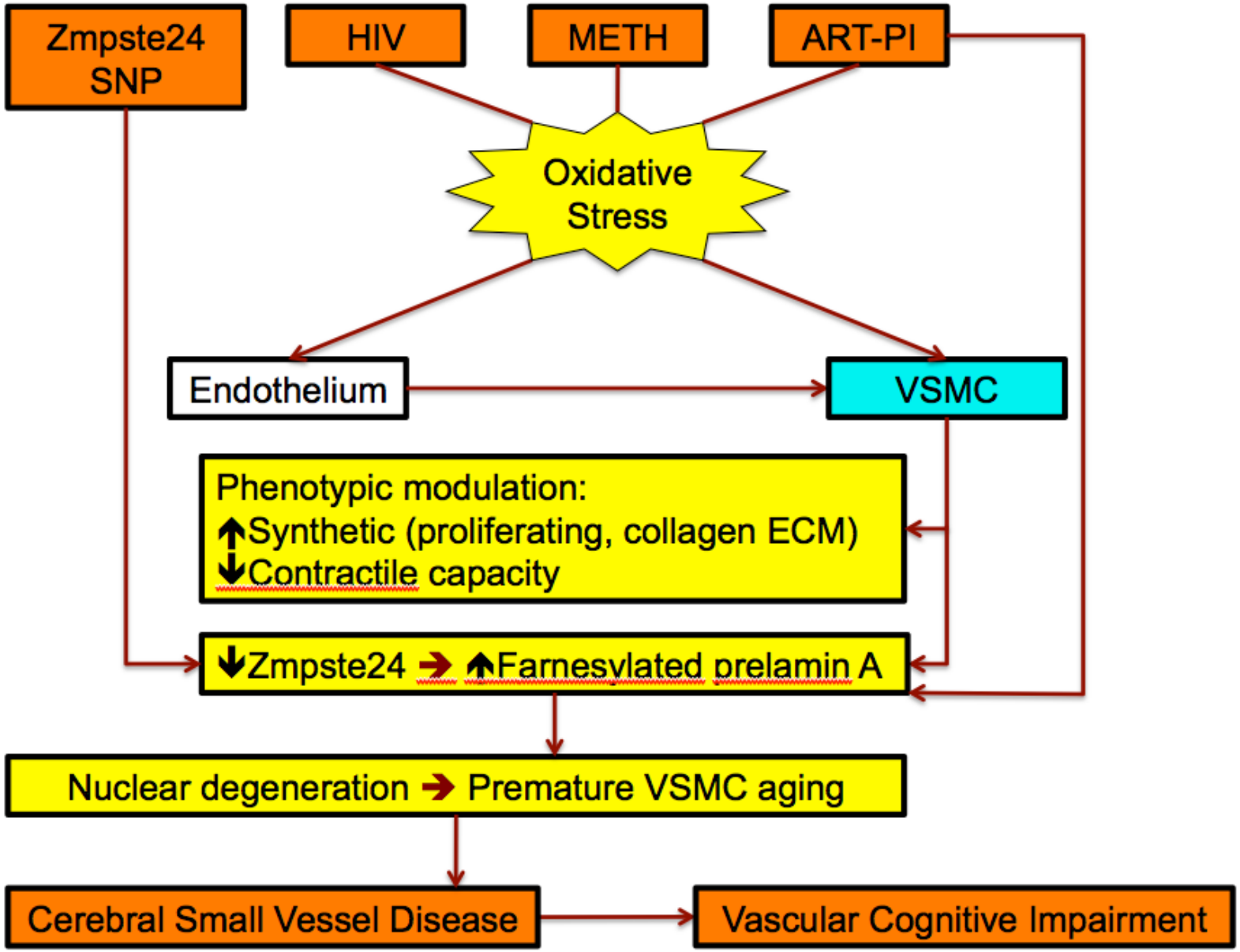
Lamin-A Processing

Farnesylated prelamin-A



Progerin

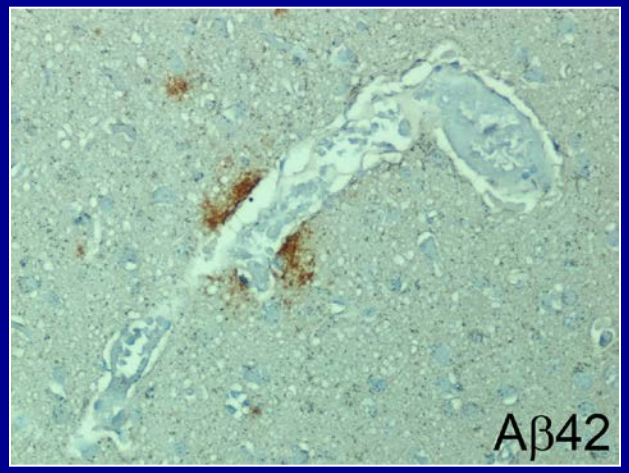
Capell BC et al, Circulation Research 2007;101:13-26

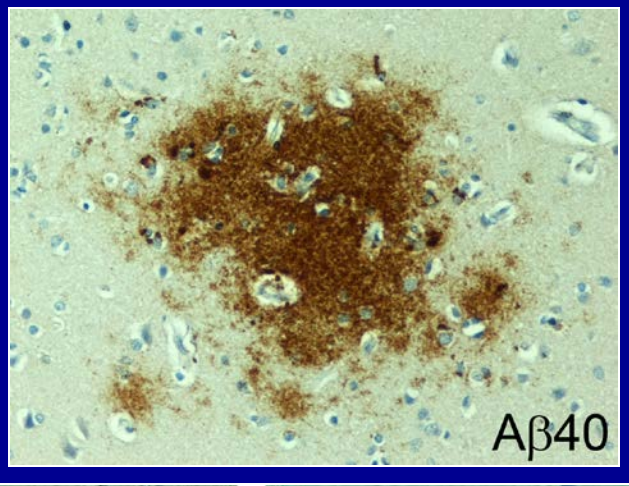

Zmpste24 SNP
HIV
METH
ART-PI
Oxidative Stress
Endothelium
VSMC
Phenotypic modulation:
↑Synthetic (proliferating, collagen ECM)
↓Contractile capacity
↓Zmpste24 → ↑Farnesylated prelamin A
Nuclear degeneration → Premature VSMC aging
Cerebral Small Vessel Disease
Vascular Cognitive Impairment

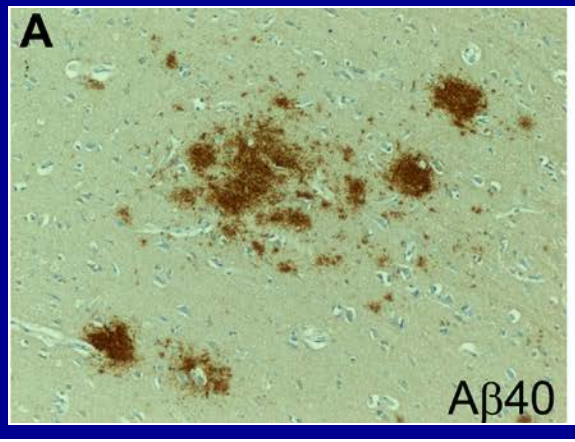
Future Directions

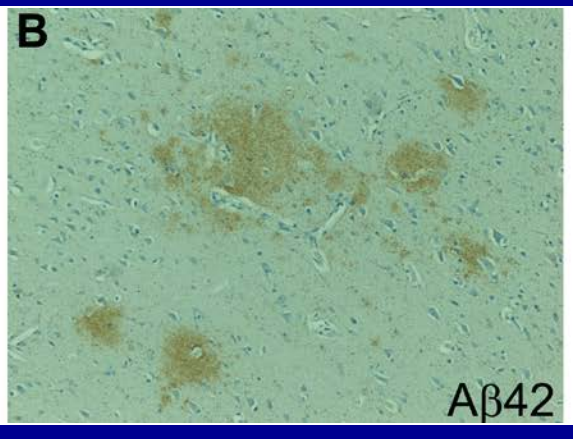
- The clinical significance of CSVD in our study was substantiated by the finding that mild CSVD was predictive of HAND, even after statistically adjusting for each of other potential predictors and covariates:
  - » older age, HIV encephalitis, microglial nodular lesions, white matter lesions, and vessel mineralization
- Detect CSVD at stages earlier than arteriolosclerosis
- In vivo assessment of cerebral vascular integrity and function
  - » CSF measurements of amyloid and vascular markers
  - » Brain imaging
- cART vascular toxicity as index of HAND risk factor
- Neuroprotective interventions in CSVD: e.g. rescue treatments in Lamin A processing

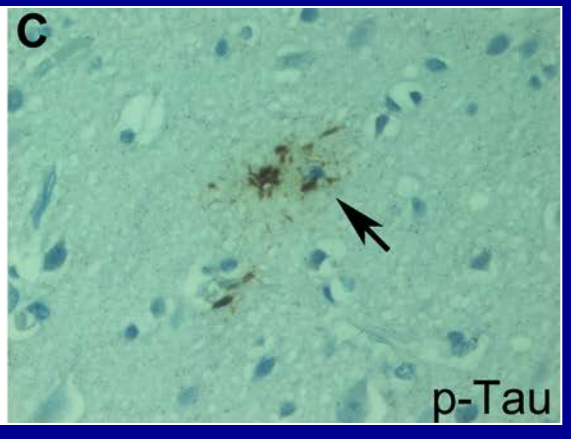
Perivascular and diffuse A-beta deposits and neuritic plaques in the HIV brain



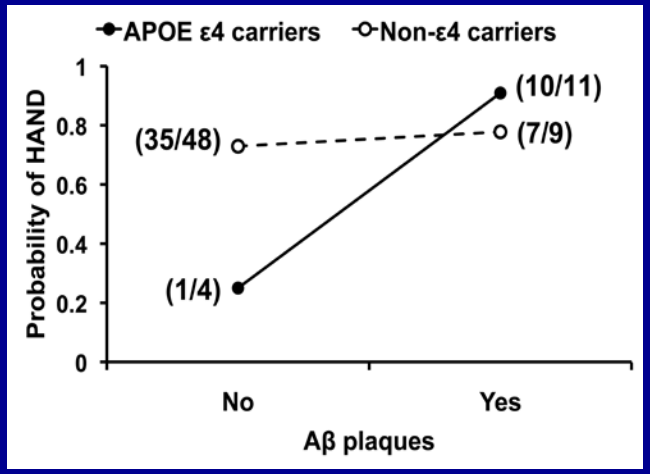








The interaction effect of apolipoprotein E (*APOE*) ε4 genotype and cerebral β-amyloid (Aβ) plaques on HAND



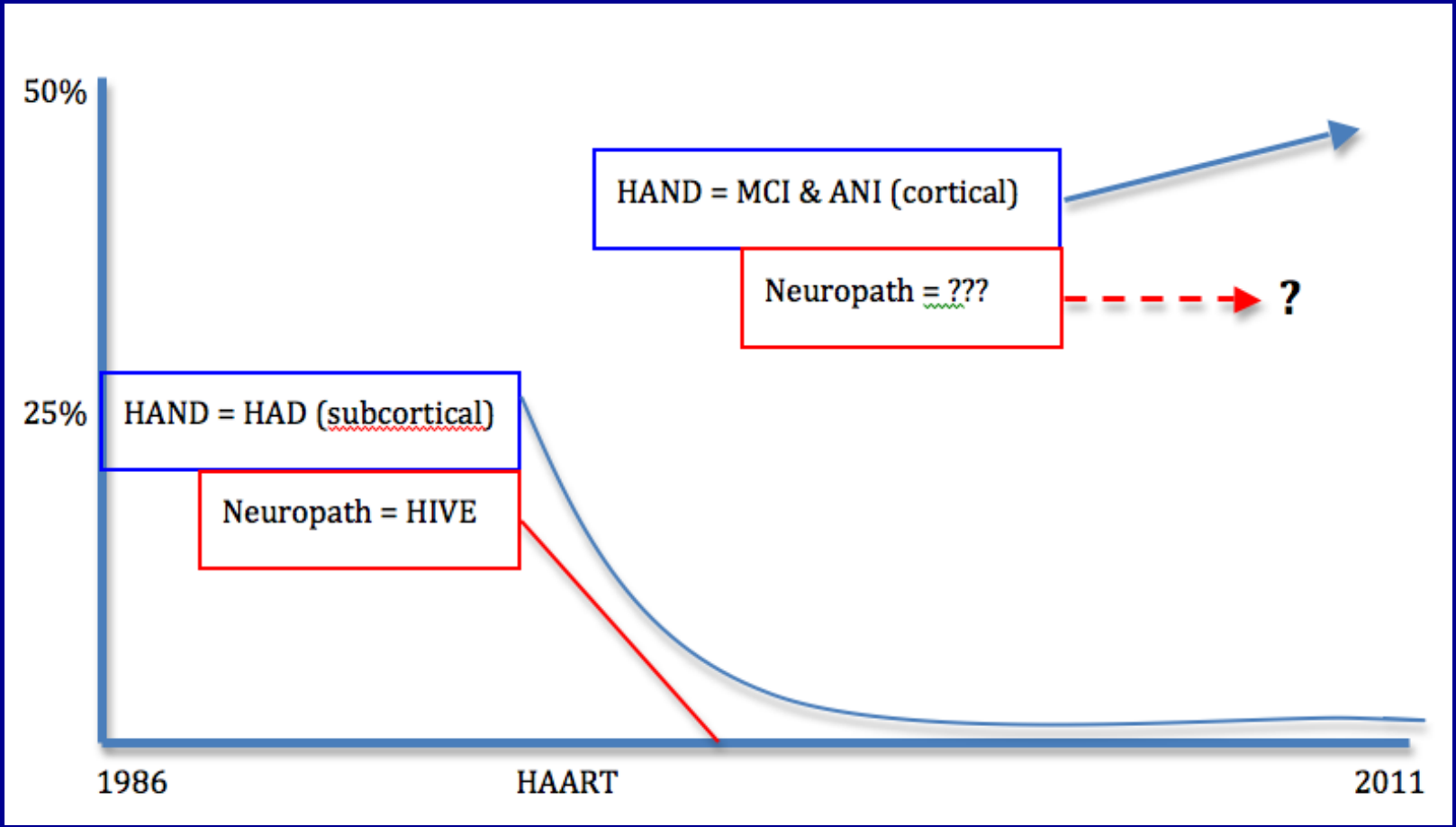
The probability of HAND is increased in the presence of Aβ plaques among *APOE* ε4 carriers (adjusted odds ratio [OR] 30.00 [95% confidence interval (CI) 1.41−638.63], *P*=0.029), but not in non-ε4 carriers (adjusted OR 1.30 [95% CI 0.24−7.09], *P*=0.76). Shown in parentheses is the number of HAND cases out of the total number of HAND cases and cases with normal cognition in each of the four *APOE* ε4−Aβ plaque subgroups.

1) *APOE* ε4 increased the likelihood of cerebral Aβplaque deposition in HIV infected adults.
2) These plaques were associated with HAND in *APOE* ε4 carriers.
3) Detection of *APOE* ε4 genotype and markers of cerebral amyloid deposition may be useful in identifying living HAND subjects who could benefit from Aβ targeted therapies.

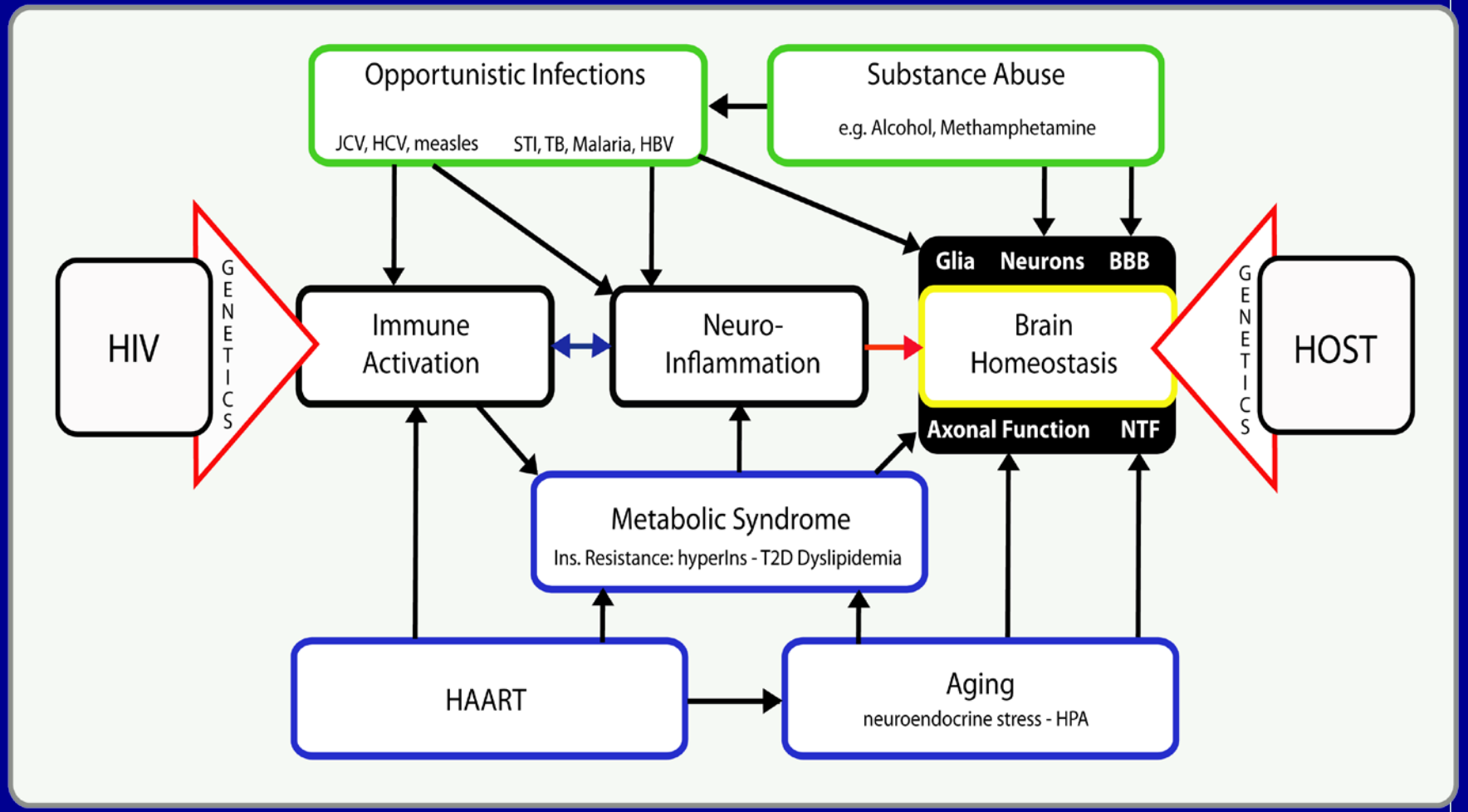
Questions

- How will CSVD and aging intersect in long term survivors on cART?
  - » Are PI the only culprits?
- Comorbidities and CSVD: accelerated aging?
  - » HCV: we have no evidence yet for an association with CSVD
  - » METH: we hypothesize that in may lead to CSVD via vascular smooth muscle cell senescence; i.e. nuclear membrane dystrophy via prelamin A accumulation (Soontornniyomkij)
- Can CSVD lead to amyloid accumulation through deficient perivascular clearance?
  - » We do not have evidence yet that this is the case
  - » CAA is not prevalent in the HIV+ subjects on cART
  - » We hypothesize that brain amyloid accumulation is mediated by reduced macrophage phagocytosis

The present…HAND spectrum



The future…potential pathways leading to HAND in the cART era



Acknowledgments

ACHIM LAB

- Virawudh Soontornniyomkij
- Benchawanna Soontornniyomkij
- Sandra A. Chung
- Megan Cochran

HNRC & CNTN

- Igor Grant
- Ron Ellis
- David More
- Ben Gouaux
- Anya Umlauf
- Eliezer Masliah
- Will Toperoff
- Scott Letendre

- NIMH
  - MH100928
  - MH062512
  - MH096648
  - MH097589
  - MH094159
- NIDA
  - DA026306
- HNRP
- TMARC
- NNTC


Thank you!