Design, implementation, and findings of next generation stroke adjudication in HIV

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Background
- There are many unanswered questions regarding the risk of stroke among persons living with HIV (PLWH).
- Most prior studies used unadjudicated stroke outcomes or composite outcomes with death and cardiovascular disease (CVD), were early in the antiretroviral treatment (ART) era or preART, and could not differentiate subtype risk.
- Most prior studies were single site, and eliminated women or hemorrhagic strokes.
- To address questions regarding stroke in HIV, we developed a stroke adjudication protocol for HIV cohort research that enables comparisons with traditional cohort studies, addresses issues specific to HIV, and allowed us to examine factors associated with stroke in HIV.

Methods
- CNICS is a U.S multisite cohort of PLWH in clinical care.
- CNICS stroke protocol was based on and expanded from a well-established protocol (Multi-Ethnic Study of Atherosclerosis).
- Potential events at 5 CNICS sites were identified using stroke diagnosis codes such as ICD9 code 434.9 (embolic occlusion of cerebral arteries with infarction) as well as a range of possibly related diagnosis or procedure codes to increase sensitivity.
- For each potential event, the site assembled de-identified packets with provider notes, imaging results, Antiretroviral medication exposure was redacted to allow blinded review.
- Using standardized criteria in the setting of ongoing quality control, two neurologists reviewed each packet, followed by a 3rd reviewer when discrepancies occurred.
- Strokes were categorized as Definite, Probable, or Possible.
- Stroke types and subtypes and whether the event was related to infection or illicit drug use were determined.
- Multivariable Cox regression analyses were used to determine traditional and HIV-specific risk factors for stroke comparing PLWH with and without stroke (N=16,924).

Results
- Sensitivity analysis repeated multivariate Cox model limiting outcome to Ischemic strokes.
- Multiple imputation (10 imputations) was used to handle missing covariate data.
- Traditional risk factors examined were age, sex, race, smoking, diabetes.
- HIV-specific risk factors examined were CD4 count and HIV viral load.
- Strokes occurred in the setting of illicit drug use in 19% and infection in 20%.
- The case-fatality rate was 9%.

Conclusions
- Standard adjudication protocols facilitate cross-cohort comparisons but require modification to address issues such as identification of strokes related to infection or illicit drug use that is more common in PLWH.
- Strokes were predominantly ischemic and were associated not only with traditional risk factors but with lower CD4 count and higher viral load suggesting potential benefits of earlier ART initiation.

Acknowledgments
Funding for this study came from the American Heart Association and National Institute of Allergy and Infectious Diseases.

Table 1. Demographic and clinical characteristics of PLWH with and without an adjudicated stroke

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Adjusted Hazard Ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1.07</td>
<td>0.99-1.15</td>
<td>0.080</td>
</tr>
<tr>
<td>White</td>
<td>0.79</td>
<td>0.67-0.92</td>
<td>0.003</td>
</tr>
<tr>
<td>Black</td>
<td>1.54</td>
<td>1.34-1.76</td>
<td>0.000</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.51</td>
<td>1.35-1.70</td>
<td>0.000</td>
</tr>
<tr>
<td>Other</td>
<td>1.46</td>
<td>1.34-1.59</td>
<td>0.000</td>
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Table 2. Factors associated with stroke in adjusted analyses

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