## ON-LINE APPENDIX

### *Materials and Methods*

Of the 82 records retrieved, 28 were excluded for the following reasons: 1) They studied participants not infected with HIV[1-4]; 2) they were performed in animal models[5-9]; 3) they were review articles[4,10-24]; 4) they were case reports[25,26]; or 5) they examined participants with perinatal HIV exposure who were not infected.[27] Given the variability in the ROIs in which FA and MD were measured, we chose to focus on the corpus callosum because it is the largest WM fiber tract in the brain and was the most frequent measurement target. Of the 54 eligible full-text articles, 16 studies were included in the meta-analysis, with 12 studies reporting both FA and MD values and 4 studies reporting only FA values from HIV-infected patients and controls by using a cross-sectional design. While 3 of the aforementioned 12 studies did not include FA and MD values in the published article, the values were obtained from the corresponding authors. The remaining studies were excluded for the following reasons: 1) Numeric values for FA and MD were not reported for seropositive individuals or seronegative controls[28-40] (corresponding authors of these articles were contacted to obtain the values); 2) only whole-brain FA or MD or both were reported[41-44]; 3) the studies examined the relationships of clinical variables, biomarkers, or treatment on DTI parameters without including a seronegative control group[45-51]; 4) FA and MD were not measured in the corpus callosum[38,52-54]; 5) they used prior published DTI data to determine selection of ROIs for fMRI connectivity analysis[55]; 6) they reported results of a single case-control pair using a new glyph design[56]; 7) the study focused on imaging measures other than diffusion parameters[57-62]; or 8) they reported a new processing algorithm that was applied to the DTI data.[63]

In addition, interpretation of many of these studies was confounded by reporting of mixed cohorts of treated and untreated participants with HIV infection[30,32-34,36-38,45,47,64,65] or participants with HIV infection treated solely with cART.[39,42,44,66]

### *Results*

**Callosal Regional Heterogeneity in WM Measures.** The observed between-study heterogeneity in mean callosal FA and MD group differences might also have resulted from sampling of different callosal segments in the included studies. To more closely examine regional variations in callosal FA and MD related to serostatus, we used repeated-measures multilevel models with region and serostatus as fixed effects and study as a random effect in the 8 studies providing all 4 diffusion measures for 3 callosal subregions. For this analysis, comparison data from the present study were included in the meta-analysis. For FA, we found no effect of serostatus [$F(1,26) = 1.36$, $P = .25$], but a significant effect of region [$F(2,26) = 51.9$, $P < .001$], with the splenium having higher FA than the body. For MD, we found a significant effect of serostatus [$F(1,26) = 6.51$, $P = .017$], with the HIV-positive group having higher MD and a significant effect of region [$F(2,26) = 4.06$, $P = .029$], with the splenium having the lowest MD. For RD, we found significant effects of serostatus [$F(1,26) = 4.35$, $P = .047$] and region [$F(2,26) = 8.58$, $P < .0014$], with the splenium having the lowest RD. For AD, we found a significant effect of serostatus [$F(1,26) = 5.55$, $P = .026$], with the HIV-positive group exhibiting overall higher AD, and no effect of region [$F(2,26) = 0.30$, $P < .97$]. Thus, the callosal region selected for sampling appears to have a strong effect on group estimates of WM microstructure.

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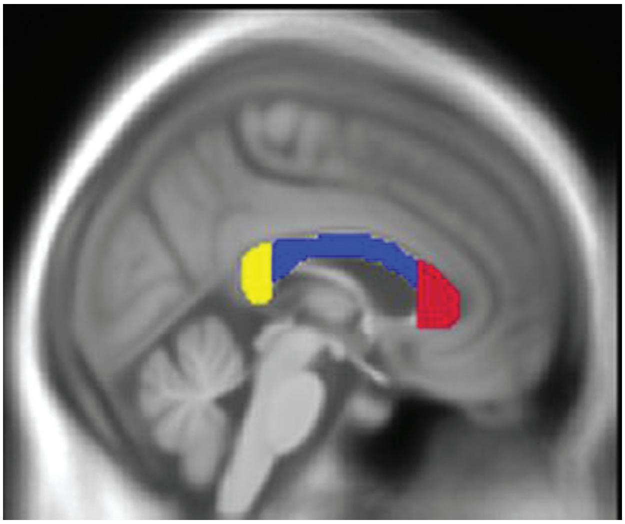
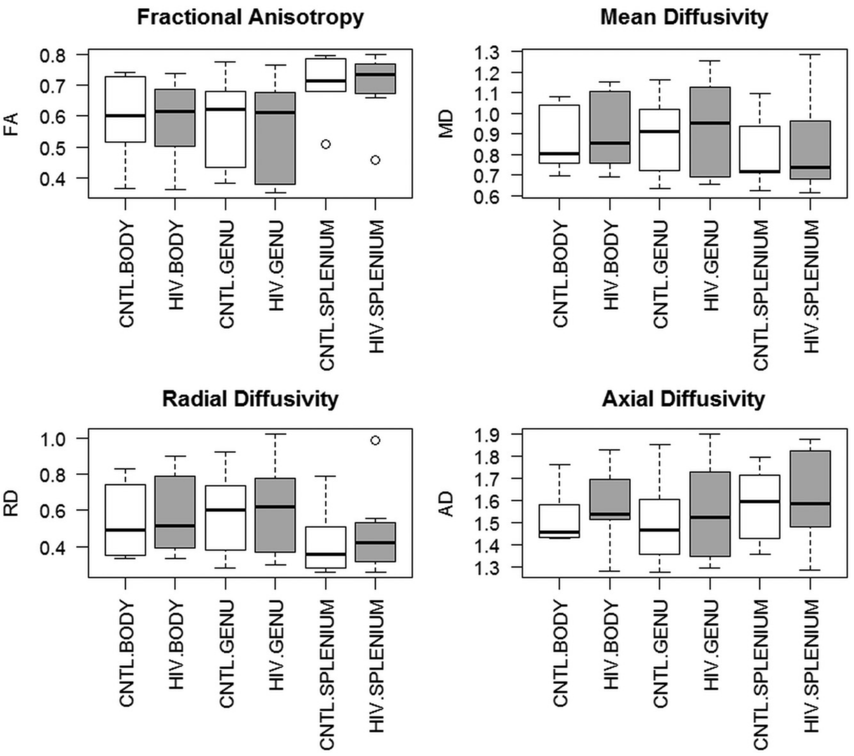


**ON-LINE FIG 1.** Callosal subregions sampled in the comparison study, with the genu shown in red, the body in blue, and the splenium in yellow.




**ON-LINE FIG 2.** Boxplots of FA, MD, RD, and AD values for midline corpus callosum regions (body, genu, and splenium) for both seropositive (HIV) and seronegative (CNTL) participants. Results are aggregated from the 8 studies reporting callosal subregions. For both groups, diffusivity differs across callosal subregions.

**On-line Table 1: Variation in technical parameters of DTI studies performed in HIV-infected subjects**

| Study | DTI Processing Program | Field Strength (T) | Gradient Directions | Voxel Dimensions (mm) |
|---|---|---|---|---|
| Seider et al, 2016[35] | FSL | 3 | 64 | 1.77 × 1.77 × 1.8 |
| Wright et al, 2015[32] | Custom software | 4 | 6 | 2.0 × 2.0 × 3.0 |
| Tang et al, 2015[59] | FSL | 3 | 16 | 2.0 × 0.875 × 0.875 |
| Ragin et al, 2015[24] | SIENAX[a] | 3 | 64 | 2.0 × 2.0 × 2.0 |
| Kamat et al, 2014[25] | FSL | 1.5 | 51 | 2.5 × 2.5 × 2.5 |
| Leite et al, 2013[23] | FSL | 1.5 | 30 | 2.10 × 2.13 × 2.10 |
| Zhu et al, 2013[26] | FSL | 1.5 | 21 | 2.0 × 2.0 × 5.0 |
| Stubbe-Drager et al, 2012[27] | Münster Neuroimaging Evaluation System | 3 | 20 | 1.8 × 1.8 × 3.6 |
| Wright et al, 2012[34] | Custom software | 3 | 23 | 2.0 × 2.0 × 2.0 |
| Hoare et al, 2011[28] | FSL | 3 | 30 | 2.0 × 2.0 × 2.2 |
| Chang et al, 2008[33] | DTIStudio, Version 2.03[b] | 3 | 12 | 1.7 × 1.7 × 4.0 |
| Pfefferbaum et al, 2007[29] | FSL | 1.5 | 6 | 1.88 × 1.88 × 4.0 |
| Wu et al, 2006[40] | DPTools[c] | 1.5 | 6 | 1.875 × 1.875 × 7 |
| Thurnher et al, 2005[21] | ? | 1.5 | 7 | 1.80 × 1.80 × 5.0 |
| Pomara et al, 2001[30] | ? | 1.5 | 6 | 1.875 × 1.875 × 5.0 |
| Filippi et al, 2001[31] | ? | 1.5 | 7 | 1.72 × 1.72 × 5.0 |

**Note:**—? indicates unknown.
[a] FSL SIENAX (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/SIENA).
[b] Johns Hopkins University, Baltimore, Maryland.
[c] INFORMAG, Paris, France.

**On-line Table 2: Regional variation in diffusion measures in the corpus callosum in 4 studies**

| Treatment Status | O'Connor et al, 2017 (current study) cART | Seider et al, 2016[35] Mixed | Wright et al, 2015[32] cART-, cART-infected <1 yr, >1 yr | Tang et al, 2015[59] Mixed |
|---|---|---|---|---|
| FA CNTL | | | | |
| Genu | .686 (.026) | .719 (.049) | .622 (.036) | .384 (.025) |
| Body | .595 (.047) | .726 (.043) | .517 (.041) | |
| Splenium | .736 (.031) | .785 (.037) | .679 (.056) | |
| FA HIV+ | | | | |
| Genu | .720 (.048) | .730 (.057) | .610 (.035) .552 (.072) | .352 (.029) |
| Body | .678 (.055) | .738 (.064) | .513 (.056) .493 (.078) | |
| Splenium | .775 (.029) | .797 (.050) | .683 (.046) .660 (.040) | |
| MD CNTL | | | | |
| Genu | .713 (.020) | .637 (.069) | 1.017 (.056) | .910 (.054) |
| Body | .815 (.031) | .698 (.084) | 1.081 (.083) | |
| Splenium | .744 (.032) | .626 (.053) | .938 (.098) | |
| MD HIV+ | | | | |
| Genu | .694 (.053) | .655 (.083) | 1.025 (.066) 1.129 (.160) | .951 (.039) |
| Body | .765 (.056) | .725 (.095) | 1.103 (.157) 1.153 (.170) | |
| Splenium | .708 (.036) | .647 (.068) | .946 (.085) .981 (.104) | |
| AD CNTL | | | | |
| Genu | 1.399 (.036) | 1.274 (.169) | 1.853 (.089) | 1.283 (.071) |
| Body | 1.452 (.079) | 1.427 (.205) | 1.762 (.021) | |
| Splenium | 1.541 (.043) | 1.358 (.150) | 1.794 (.122) | |
| AD HIV+ | | | | |
| Genu | 1.407 (.063) | 1.345 (.174) | 1.840 (.097) 1.899 (.157) | 1.301 (.047) |
| Body | 1.483 (.047) | 1.508 (.211) | 1.783 (.167) 1.829 (.170) | |
| Splenium | 1.535 (.050) | 1.427 (.156) | 1.814 (.131) 1.831 (.170) | |
| RD CNTL | | | | . |
| Genu | .370 (.031) | .319 (.041) | .600 (.059) | .723 (.052) |
| Body | .406 (.076) | .333 (.046) | .741 (.091) | |
| Splenium | .346 (.041) | .260 (.029) | .510 (.106) | |
| RD HIV+ | | | | |
| Genu | .337 (.061) | .317 (.069) | .617 (.066) .744 (.177) | .775 (.046) |
| Body | .406 (.076) | .333 (.079) | .763 (.159) .815 (.184) | |
| Splenium | .294 (.041) | .257 (.060) | .512 (.086) .556 (.085) | |

**Note:**— HIV+ indicates seropositive; CNTL, seronegative participants; cART−, seropositives not taking cART.

**On-line Table 3: Regional variation in diffusion measures in the corpus callosum in 5 studies**

| Treatment Status of HIV+ | Kamat et al, 2014[25] Mixed | Leite et al, 2013[23] Mixed | Zhu et al, 2013[26] Mixed | Wright et al, 2012[34] cART+ | Wright et al, 2012[34] cART− |
|---|---|---|---|---|---|
| FA CNTL | | | | | |
| Genu | .47 (.09) | .775 (.0626) | .396 (.205) | .6373 (.125) | .637 (.125) |
| Body | | .739 (.0298) | .367 (.153) | .6013 (.103) | .601 (.103) |
| Splenium | | .796 (.0198) | .509 (.225) | .7128 (.098) | .713 (.098) |
| FA HIV+ | | | | | |
| Genu | .38 (.11) | .764 (.632) | .379 (.195) | .625 (.095) | .676 (.056) |
| Body | | .721 (.629) | .361 (.152) | .614 (.088) | .649 (.060) |
| Splenium | | .792 (.617) | .457 (.223) | .735 (.061) | .745 (.042) |
| MD CNTL | | | | | |
| Genu | 1.02 (.28) | .678 (.035) | 1.165 (.539) | .766 (.087) | .766 (.087) |
| Body | | .760 (.025) | 1.038 (.390) | .806 (.097) | .806 (.097) |
| Splenium | | .717 (.023) | 1.096 (.572) | .713 (.096) | .713 (.096) |
| MD HIV+ | | | | | |
| Genu | 1.20 (.29) | .693 (.047) | 1.256 (.575) | .837 (.097) | .675 (.160) |
| Body | | .789 (.0336) | 1.113 (.478) | .853 (.071) | .693 (.161) |
| Splenium | | .717 (.000023) | 1.284 (.660) | .740 (.063) | .614 (.155) |
| AD CNTL | | | | | |
| Genu | 1.56 (.25) | 1.468 (.0536) | 1.650 (.556) | 1.425 (.202) | 1.425 (.202) |
| Body | | 1.582 (.0557) | 1.456 (.491) | 1.431 (.167) | 1.431 (.167) |
| Splenium | | 1.595 (.0625) | 1.715 (.629) | 1.429 (.169) | 1.429 (.169) |
| AD HIV+ | | | | | |
| Genu | 1.70 (.27) | 1.478 (.0583) | 1.730 (.591) | 1.524 (.185) | 1.292 (.313) |
| Body | | 1.606 (.0403) | 1.539 (.569) | 1.520 (.164) | 1.279 (.286) |
| Splenium | | 1.586 (.0484) | 1.877 (.701) | 1.530 (.140) | 1.283 (.340) |
| RD CNTL | | | | | |
| Genu | .75 (.30) | .288 (.0369) | .922 (.577) | .437 (.116) | .437 (.116) |
| Body | | .349 (.0353) | .829 (.385) | .493 (.119) | .493 (.119) |
| Splenium | | .279 (.0286) | .787 (.595) | .355 (.119) | .355 (.119) |
| RD HIV+ | | | | | |
| Genu | .97 (.32) | .301 (.0485) | 1.018 (.609) | .494 (.105) | .367 (.102) |
| Body | | .380 (.0418) | .899 (.469) | .515 (.094) | .400 (.112) |
| Splenium | | .283 (.0245) | .987 (.687) | .350 (.055) | .422 (.104) |

**Note:**—HIV + indicates seropositive; CNTL, seronegative participant.

**On-line Table 4: Longitudinal clinical data including viral load (No. of copies/mL) and CD4 (cells/uL) measured prior to initiation of cART and at 3 and 6 months after the initiation of cART[a]**

| Participant | Visit | Viral Load | CD4 | Age (yr) |
|---|---|---|---|---|
| 1 | Start cART | 7015 | 600 | 30 |
| | | – | – | |
| | | – | – | |
| 2 | Start cART | 5124 | 283 | 26 |
| | Month 3 | <75 | 402 | |
| | Month 6 | 3423 | 359 | |
| 3 | Start cART | >500,000 | 126 | 23 |
| | Month 3 | <75 | 305 | |
| | Month 6 | <75 | 458 | |
| 4 | Start cART | 265,071 | 73 | 22 |
| | Month 3 | 22,149 | 149 | |
| | Month 6 | 112 | 231 | |
| 5 | Start cART | 185,966 | 5 | 43 |
| | Month 3 | <75 | 88 | |
| | Month 6 | <75 | 106 | |
| 6 | Start cART | <75 | 187 | 40 |
| | Month 3 | <75 | 257 | |
| | Month 6 | <75 | 384 | |
| 7 | Start cART | 7366 | 386 | 48 |
| | Month 3 | <75 | 672 | |
| | Month 6 | <20 | 954 | |
| 8 | Start cART | 11,655 | 369 | 22 |
| | Month 3 | <75 | 377 | |
| | Month 6 | <20 | 418 | |
| 9 | Start cART | 95,304 | 270 | 25 |
| | Month 3 | <75 | – | |
| | Month 6 | <20 | 485 | |
| 10 | Start cART | 1360 | 815 | 28 |
| | Month 3 | <20 | 668 | |
| | Month 6 | <20 | 969 | |

**Note:**— –indicates not obtained.

[a] Viral load decreased ($P < .001$), CD4 cell count increased ($P < .001$), and CD4/CD8 ratio was unchanged ($P = .48$). While compliance with therapy was assessed at each site visit, our data suggest that 2 participants did not adhere to their medication regimen. One had a viral load of <75 at 3 months and a viral load of 3423 at 6 months. For the other, a viral load of 1439 was seen at 2 weeks, indicating therapeutic response. However, at 3 months, the viral load had increased to 22,149.

**On-line Table 5: Scores on various tests[a]**

| Test | Subject 2 | Subject 3 | Subject 4 | Subject 5 | Subject 6 | Subject 7 | Subject 8 | Subject 9 |
|---|---|---|---|---|---|---|---|---|
| IHDS | 11 | 11 | 11 | 12 | 12 | 10.5 | 12 | 11 |
| Motor Speed | 4 | 4 | 3 | 4 | 4 | 4 | 4 | 4 |
| Psychomotor Speed | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Memory Recall | 3 | 3 | 4 | 4 | 4 | 2.5 | 4 | 3 |
| HVLT | | | | | | | | |
| Total Recall | 24 (36) | 20 (25) | 24 (37) | 26 (43) | 26 (43) | 27 (44) | 26 (41) | 24 (35) |
| Retention (% retained) | 83 | 92 | 100 | 100 | 100 | 100 | 100 | 100 |
| Recognition Discrimination Index | 10 | 9 | 12 | 12 | 12 | 12 | 12 | 9 |
| HIV Dementia Motor Scale | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| Strength | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Tone | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Reflexes | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Coordination | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Gait | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| UPDRS Motor Scale | 3 | 1 | 1 | 0 | 1 | 0 | 0 | 4 |
| Grooved Pegboard Test | | | | | | | | |
| Dominant hand (sec) | 63 (55) | 57 (62) | 84 (42) | 55 (61) | 67 (53) | 49 (66) | 73 (44) | 72 (45) |
| Nondominant hand (sec) | 63 (61) | 59 (64) | 83 (47) | 55 (66) | 72 (52) | 54 (62) | 85 (40) | 71 (53) |

**Note:**—IHDS indicates International HIV Dementia Screen; HVLT, Hopkins Verbal Learning Test; UPDRS, Unified Parkinson's Disease Rating Scale.

[a] T-scores are in parentheses next to raw scores for the HVLT and Grooved Pegboard.