Supplemental Table 1. List of non-antiretroviral medications reported by WIHS participants with known adverse cognitive effects and frequency of reported use during the study analysis period.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Opioids** | Frequency | **Antianxiety** | Frequency | **Antidepressants** | Frequency |
| Codeine | 16 | Alprazolam | 19 | Amitriptyline\* | 24 |
| Fentanyl | 4 | Clonazepam | 37 | Imipramine\* | 2 |
| Hydrocodone | 77 | Diazepam | 11 | Mirtazapine\* | 32 |
| Hydromorphone | 5 | Lorazepam | 37 | Nortriptyline\* | 4 |
| Meperidine | 1 | Temazepam | 8 | Paroxetine\* | 26 |
| Morphine | 26 | Triazolam | 1 | Trazodone\* | 58 |
| Oxycodone | 61 | Zolpidem | 83 |  |  |
|  |  |  |  |  |  |
| **Anticonvulsants** | Frequency | **Antihistamine** | Frequency | **Antipsychotics** | Frequency |
| Carbamazepine | 5 | Cetirizine\* | 14 | Chlorpromazine\* | 1 |
| Lamotrigine | 19 | Cyproheptadine\* | 2 | Haloperidol\* | 1 |
| Oxcarbazepine | 1 | Diphenhydramine\* | 27 | Olanzapine\* | 12 |
| Phenytoin | 5 | Hydroxyzine\* | 20 | Perphenazine\* | 1 |
| Pregabalin | 19 | Loratadine\* | 43 | Pramipexole\* | 2 |
| Topiramate | 12 | Meclizine\* | 1 | Prochlorperazine\* | 6 |
| Valproate | 19 | Promethazine\* | 3 | Quetiapine\* | 72 |
|  |  |  |  | Risperidone\* | 23 |
|  |  |  |  | Ziprasidone\* | 5 |
| **Anticholinergic** | Frequency | **Gastrointestinal agents** | Frequency | **Muscle Relaxant** | Frequency |
| Benztropine\* | 8 | Cimetidine\* | 2 | Baclofen\* | 14 |
| Dicyclomine\* | 2 | Loperamide\* | 6 | Carisoprodol\* | 5 |
|  |  | Metoclopramide\* | 7 | Cyclobenzaprine\* | 16 |
|  |  | Oxybutynin\* | 5 | Methocarbamol\* | 6 |
|  |  | Ranitidine\* | 19 | Tizanidine \* | 3 |
|  |  |  |  |  |  |
|  |  | **Beta-Blockers** | Frequency |  |  |
|  |  | Atenolol | 48 |  |  |
|  |  | Propranolol | 7 |  |  |

\*= anticholinergic properties per Rudolph, J.L., et al., *The anticholinergic risk scale and anticholinergic adverse effects in older persons.* Arch Intern Med, 2008. **168**(5): p. 508-13.

**Note:** NC-AE medications identified in literature but not reported by these WIHS women during this study period: amantadine, atropine products, bromazepam, carbidopa-levodopa, chlordiazepoxide, chlorpheniramine, clobazam, clomipramine, clozapine, clorpromazine, cyclizine, clorazepate, desipramine, entacapone, flunitrazepam, fluvoxamine, flurazepam, fluphenazine, halazepam, hysocyamine, loxapine, meperidine, mianserin, moclobemide, nefozodone, nitrazepam, olanzapine-fluoxetine, oxazepam, perphenazine, phyostigmine, scopolamine, tolterodine, trifluoperazine

Supplemental Table 2. HIV-related characteristics as a function of anticholinergic burden.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Total Anticholinergic Medications** | | |  |
| **Variable** | **0**  (n=792)  n (%) | **1**  (n=171)  n (%) | **>1**  (n=74)  n (%) | **p-value** |
| HIV RNA  Undetectable  Detectable, median (IQR)  > 10,000cp/ml | 419 (53)  1282 (15308)  111 (14) | 83 (49)  697 (23915)  26 (15) | 40 (55)  561 (3416)  4 (5) | 0.57  0.42  0.23 |
| CD4 count, median (IQR)  Current  Nadir | 48 (1037)  506 (416)  189 (200) | 53 (679)  490 (384)  179 (217) | 48 (312)  518 (344)  207 (197) | 0.44  0.21 |
| Prior AIDS diagnosis | 323 (41) | 98 (57) | 38 (51) | <0.001 |
| cART and >95% adherence | 498 (82) | 119 (86) | 50 (86) | 0.43 |
| ART duration (years), median (IQR) | 13.1 (5.4) | 13.4 (6.3) | 12.5 (4.4) | 0.53 |
| CPE Exposure  Low (<8)  Medium (8-9)  High (>9) | 337 (55)  154 (25)  119 (20) | 71 (51)  44 (32)  24 (17) | 35 (61)  17 (29)  6 (10) | 0.27 |
| Nuceloside RTI use | 587 (74) | 137 (80) | 57 (77) | 0.24 |
| Zidovudine | 95 (12) | 18 (11) | 8 (11) | 0.84 |
| Emtricitabine | 355 (45) | 82 (48) | 35 (47) | 0.69 |
| Lamivudine | 183 (23) | 43 (25) | 20 (27) | 0.67 |
| Abacavir | 123 (16) | 36 (21) | 14 (19) | 0.19 |
| Tenofovir | 428 (54) | 101 (59) | 39 (53) | 0.46 |
| Non-nucleoside RTI use | 238 (30) | 53 (31) | 20 (27) | 0.82 |
| Nevirapine | 44 (6) | 12 (7) | 6 (8) | 0.56 |
| Efavirenz | 162 (20) | 38 (22) | 13 (18) | 0.70 |
| Protease inhibitor use | 384 (46) | 84 (49) | 33 (45) | 0.72 |
| Ritonavir | 224 (28) | 53 (31) | 19 (26) | 0.66 |
| Lopinavir | 92 (12) | 12 (7) | 8 (11) | 0.21 |
| Atazanavir | 166 (21) | 45 (26) | 17 (23) | 0.30 |
| Darunavir | 59 (7) | 11 (6) | 3 (4) | 0.52 |
| Integrase inhibitor use | 80 (10) | 15 (9) | 6 (8) | 0.77 |
| Raltegravir | 80 (10) | 15 (9) | 6 (8) | 0.77 |

Note. cART=combination antiretroviral therapy; ART = antiretroviral therapy; CPE=CNS Penetration Effectiveness; RTI= reverse-transcriptase inhibitors; IQR=interquartile range. Variables reported as n (%) were analyzed with Chi-square tests. Variables reported as median/IQR were analyzed with Kruskal-Wallis test.

Supplemental Table 3. Cognitive performance by opioids and anxiolytics/anticonvulsants in the overall sample.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Total opioid burden** | | | |  | **Total Anxiolytic/anticonvulsant burden** | | | |
| **Outcome** | **Obs** | **0** | **>1** |  | **Generalized linear model†** |  | **0** | **>1** |  | **Generalized linear model†** | |
| **(n=1388)** | **(n=170)** |  |  | **(n=1333)** | **(n=225)** |  |
| M (SE) | M (SE) |  | p-value |  | M (SE) | M (SE) |  | p-value | |
| Global NP | 1556 | 3.3 (0.10) | 3.2 (0.15) |  | 0.53 |  | 3.3 (0.10) | 3.4 (0.14) |  | 0.50 | |
| Memory | 1553 | 2.5 (0.08) | 2.3 (0.13) |  | 0.30 |  | 2.4 (0.08) | 2.6 (0.13) |  | 0.23 | |
| Learning | 1553 | 2.6 (0.08) | 2.3 (0.12) |  | 0.03 |  | 2.5 (0.08) | 2.5 (0.12) |  | 0.94 | |
| Attention/WM | 1398 | 2.4 (0.08) | 2.2 (0.13) |  | 0.36 |  | 2.3 (0.08) | 2.3 (0.12) |  | 0.47 | |
| Executive Function | 1540 | 2.8 (0.09) | 2.9 (0.15) |  | 0.30 |  | 2.8 (0.09) | 3.0 (0.14) |  | 0.20 | |
| Speed | 1555 | 2.7 (0.09) | 2.7 (0.14) |  | 0.88 |  | 2.7 (0.09) | 2.7 (0.13) |  | 0.74 | |
| Fluency | 1550 | 2.6 (0.08) | 2.6 (0.13) |  | 0.57 |  | 2.6 (0.08) | 2.6 (0.12) |  | 0.95 | |
| Motor | 1531 | 2.5 (0.09) | 2.4 (0.14) |  | 0.82 |  | 2.4 (0.09) | 2.6 (0.14) |  | 0.22 | |

Note. Bold=significant at p<0.05. WM=working memory; NP=neuropsychological. M = estimated mean T-score; SE = standard error; OR=odds ratio. **†** controlling for HIV- and HCV status, site, current employment status, depressive symptoms, heavy drinking, smoking, marijuana, crack, cocaine and/or heroin use. After controlling the false discovery rate using the Benjamini-Hochberg procedure, none of the associations remained significant.