**Supplementary Table 1.** Demographic and antifungal susceptibility data of the 233 *C. neoformans/gattii* species complexes strains from the pre-HIV-pandemic era used in this study.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **NIH No.** | **Isolates No.** | **Country** | **Source** | ***URA5*-RFLP** | **MIC AMB** | **MIC 5FC** | **MIC ITC** | **MIC FLC** | **Patient code*a*** | **Prior AMB Treatment** |
| 4 | 1 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 1 |   | Yes |
| 7 | 2 | USA | Clinical | VNII | 0.5 | 0.12 | ≤0.06 | 0.5 |   | No |
| 8 | 3 | USA | Clinical | VNI | 0.25 | 0.12 | ≤0.06 | 2 |   | No |
| 9 | 4 | USA | Clinical | VNI | 0.5 | 0.5 | ≤0.06 | 2 |   | No |
| 12 | 5 | USA | Clinical | VNIV | 1 | 0.5 | ≤0.06 | 0.5 |   | No |
| 13 | 6 | USA | Clinical | VNI | 1 | 0.25 | ≤0.06 | 1 |   | No |
| 14 | 7 | USA | Clinical | VNI | ≤0.06 | 0.12 | ≤0.06 | 0.5 |   | No |
| 15 | 8 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 2 |   | No |
| 16 | 9 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 2 |   | Unknown |
| 17 | 10 | USA | Clinical | VGI | 0.25 | 0.12 | 0.06 | 2 | C | Unknown |
| 18 | 11 | USA | Clinical | VGIII | 1 | 0.25 | ≤0.06 | 1 |   | Unknown |
| 19 | 12 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 1 | J | Yes |
| 20 | 13 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 1 | J | Yes |
| 22 | 14 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 1 |   | No |
| 23 | 15 | USA | Clinical | VNI | 0.5 | 0.25 | ≤0.06 | 2 |   | Yes |
| 25 | 16 | USA | Clinical | VNI | 2 | 0.12 | ≤0.06 | 1 |   | No |
| 26 | 17 | USA | Clinical | VNI | 0.06 | 0.12 | ≤0.06 | 1 | M | No |
| 27 | 18 | USA | Clinical | VNI | 0.5 | 1 | ≤0.06 | 0.12 | M | Yes |
| 28 | 19 | USA | Clinical | VNI | 0.25 | 0.12 | ≤0.06 | 1 |   | No |
| 29 | 20 | USA | Clinical | VNI | 0.06 | 0.25 | ≤0.06 | 2 |   | No |
| 30 | 21 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 1 |   | No |
| 31 | 22 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 1 |   | No |
| 32 | 23 | USA | Clinical | VNI | 0.12 | 0.12 | ≤0.06 | 1 | F | No |
| 33 | 24 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 1 | F | No |
| 34 | 25 | USA | Clinical | VGIII | 0.5 | 0.12 | ≤0.06 | 8 |   | Unknown |
| 37 | 26 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 2 |   | Yes |
| 39 | 27 | USA | Clinical | VNII | 2 | 0.12 | ≤0.06 | 1 |   | Unknown |
| 40 | 28 | USA | Clinical | VNI | 0.5 | 0.12 | ≤0.06 | 1 |   | No |
| 41 | 29 | USA | Clinical | VNI | 0.5 | 0.12 | ≤0.06 | 1 | B | No |
| 42 | 30 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 1 | B | No |
| 46 | 31 | USA | Clinical | VNI | 2 | 0.12 | ≤0.06 | 1 |   | No |
| 48 | 32 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 1 |   | No |
| 49 | 33 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 1 |   | No |
| 50 | 34 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 2 |   | No |
| 53 | 35 | USA | Clinical | VNII | 1 | 0.12 | ≤0.06 | 0.5 |   | No |
| 55 | 36 | USA | Clinical | VNIII | 0.06 | 0.12 | ≤0.06 | 0.5 |   | Yes |
| 58 | 37 | USA | Clinical | VNI | 0.25 | 0.12 | ≤0.06 | 4 |   | No |
| 59 | 38 | USA | Clinical | VNI | 0.5 | 0.12 | ≤0.06 | 2 |   | Yes |
| 60 | 39 | USA | Clinical | VNI | 0.25 | 0.12 | ≤0.06 | 2 |   | Unknown |
| 61 | 40 | USA | Clinical | VNII | 1 | 0.12 | ≤0.06 | 0.12 |   | Unknown |
| 62 | 41 | USA | Clinical | VNI | 0.5 | ≥128 | ≤0.06 | 1 |   | No |
| 63 | 42 | USA | Clinical | VNI | 2 | 0.25 | ≤0.06 | 2 |   | No |
| 65 | 43 | USA | Clinical | VNI | 0.5 | 0.12 | ≤0.06 | 0.25 | K | No |
| 67 | 44 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 0.25 | K | Yes |
| 70 | 45 | USA | Clinical | VNI | 0.5 | 0.12 | ≤0.06 | 2 |   | Unknown |
| 71 | 46 | USA | Clinical | VNII | 0.5 | 0.12 | ≤0.06 | 0.12 |   | Unknown |
| 72 | 47 | USA | Clinical | VNI | 0.25 | 0.12 | ≤0.06 | 2 |   | No |
| 76 | 48 | USA | Clinical | VGI | 0.5 | 0.12 | 0.06 | 2 |   | Unknown |
| 77 | 49 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 2 |   | No |
| 80 | 50 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 1 |   | No |
| 88 | 51 | USA | Clinical | VGI | 1 | 0.12 | ≤0.06 | 2 | C | Unknown |
| 93 | 52 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 1 | L | No |
| 95 | 53 | USA | Clinical | VNI | 0.25 | 0.12 | ≤0.06 | 1 | L | Yes |
| 96 | 54 | USA | Clinical | VNI | 0.5 | 0.12 | ≤0.06 | 0.5 | L | Yes |
| 97 | 55 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 1 | L | Yes |
| 114 | 56 | USA | Clinical | VNI | ≤0.06 | 0.12 | ≤0.06 | 1 |   | No |
| 115 | 57 | USA | Environmental | VNI | 1 | 0.12 | ≤0.06 | 1 |   | N/A |
| 116 | 58 | USA | Environmental | VNIV | 0.06 | 0.12 | ≤0.06 | 0.25 |   | N/A |
| 117 | 59 | USA | Environmental | VNI | 1 | 0.12 | ≤0.06 | 1 |   | N/A |
| 118 | 60 | USA | Environmental | VNI | 1 | 0.12 | ≤0.06 | 1 |   | N/A |
| 119 | 61 | USA | Environmental | VNI | 1 | 0.12 | ≤0.06 | 2 |   | N/A |
| 120 | 62 | USA | Environmental | VNI | 1 | 0.12 | ≤0.06 | 2 |   | N/A |
| 121 | 63 | USA | Clinical | VNII | 2 | 0.12 | ≤0.06 | 1 |   | Unknown |
| 126*b* | 64 | USA | Environmental | VNI | 2 | 0.12 | ≤0.06 | 1 |   | N/A |
| 129 | 65 | USA | Clinical | VNII | 2 | 0.12 | 8 | 0.5 |   | No |
| 130 | 66 | USA | Clinical | VNIV | ≤0.06 | 0.12 | ≤0.06 | 1 | D | Unknown |
| 131 | 67 | USA | Clinical | VNIV | 1 | 0.12 | ≤0.06 | 1 | D | Unknown |
| 132 | 68 | USA | Clinical | VNII | 1 | 0.12 | ≤0.06 | 1 |   | No |
| 133 | 69 | USA | Clinical | VNIV | 0.06 | 0.12 | ≤0.06 | 1 |   | Yes |
| 134 | 70 | USA | Clinical | VNI | 2 | 0.12 | ≤0.06 | 1 |   | No |
| 135 | 71 | USA | Clinical | VNI | 2 | 0.12 | 0.06 | 2 |   | No |
| 136 | 72 | USA | Clinical | VNIV | 0.06 | 0.12 | ≤0.06 | 0.5 | D | Unknown |
| 138 | 73 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 1 |   | No |
| 141*b* | 74 | USA | Environmental | VNI | 2 | 0.12 | ≤0.06 | 1 |   | N/A |
| 144 | 75 | USA | Clinical | VNII | 1 | 0.12 | ≤0.06 | 0.25 | N | Yes |
| 146 | 76 | USA | Clinical | VNII | 0.5 | 0.12 | ≤0.06 | 0.25 | N | Yes |
| 149 | 77 | USA | Clinical | VNII | 1 | 0.12 | ≤0.06 | 0.25 | N | Yes |
| 151 | 78 | USA | Clinical | VNII | 1 | 0.12 | ≤0.06 | 0.25 | N | Yes |
| 152 | 79 | USA | Clinical | VNII | 1 | 0.12 | ≤0.06 | 0.5 | N | Yes |
| 156 | 80 | USA | Clinical | VNII | 1 | 0.12 | ≤0.06 | 0.5 | N | Yes |
| 157 | 81 | USA | Clinical | VNI | 0.5 | 0.12 | 0.06 | 2 |   | No |
| 158 | 82 | USA | Clinical | VNII | 1 | 0.12 | ≤0.06 | 0.5 | N | Yes |
| 160 | 83 | USA | Clinical | VNII | 1 | 0.12 | ≤0.06 | 1 | N | Yes |
| 161 | 84 | USA | Clinical | VNIV | 0.5 | 0.12 | ≤0.06 | 0.5 |   | No |
| 167 | 85 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 0.5 | R | No |
| 168 | 86 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 0.5 |  R | Unknown |
| 169 | 87 | USA | Clinical | VNI | 2 | 0.12 | 0.25 | 2 |   | No |
| 171 | 88 | USA | Clinical | VNI | 2 | 0.25 | ≤0.06 | 0.25 |   | Yes |
| 172 | 89 | USA | Clinical | VNI | 1 | 0.12 | 0.06 | 2 |   | No |
| 175 | 90 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 1 |   | Yes |
| 177 | 91 | USA | Clinical | VNI | 0.5 | 0.12 | ≤0.06 | 0.25 |   | Unknown |
| 178 | 92 | USA | Clinical | VGIII | 1 | 0.12 | ≤0.06 | 2 |   | Unknown |
| 179 | 93 | USA | Clinical | VGIII | 0.5 | 0.12 | ≤0.06 | 1 |   | Unknown |
| 181 | 94 | USA | Clinical | VNI | 0.5 | 0.12 | ≤0.06 | 2 |   | Unknown |
| 182 | 95 | USA | Clinical | VGIII | 1 | 0.12 | ≤0.06 | 1 |   | Unknown |
| 183 | 96 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 1 |   | Unknown |
| 184 | 97 | USA | Clinical | VGIII | 2 | 0.12 | ≤0.06 | 0.5 |   | Unknown |
| 185 | 98 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 1 |  | Unknown |
| 186 | 99 | USA | Clinical | VNI | 0.5 | 0.12 | ≤0.06 | 2 |  | Unknown |
| 187 | 100 | USA | Clinical | VGIII | 1 | 0.12 | ≤0.06 | 4 |   | Unknown |
| 188 | 101 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 2 |   | Unknown |
| 189 | 102 | USA | Clinical | VGIII | 4 | 0.12 | ≤0.06 | 8 |   | Unknown |
| 190 | 103 | USA | Clinical | VGIII | 1 | 0.12 | ≤0.06 | 1 |   | Unknown |
| 191 | 104 | Canada | Clinical | VGIII | 2 | 0.25 | 0.12 | 4 |   | Unknown |
| 192 | 105 | USA | Environmental | VNI | 1 | 0.12 | ≤0.06 | 1 |   | N/A |
| 193 | 106 | USA | Environmental | VNI | 1 | 0.25 | 0.06 | 0.5 |   | N/A |
| 194 | 107 | USA | Veterinary | VNI | 0.5 | 0.12 | ≤0.06 | 1 |   | N/A |
| 195 | 108 | USA | Veterinary | VNI | 0.5 | 0.12 | ≤0.06 | 1 |   | N/A |
| 196 | 109 | USA | Environmental | VNI | 1 | 0.12 | ≤0.06 | 2 |   | N/A |
| 197 | 110 | USA | Clinical | VNII | 1 | 0.12 | ≤0.06 | 0.12 |   | Unknown |
| 198 | 111 | USA | Clinical | VGIII | 1 | 0.12 | ≤0.06 | 1 |   | Unknown |
| 200 | 112 | USA | Clinical | VGIII | 1 | 0.12 | ≤0.06 | 4 |   | Unknown |
| 201 | 113 | USA | Environmental | VNI | 1 | 0.12 | ≤0.06 | 1 |   | N/A |
| 203 | 114 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 1 | O | No |
| 204 | 115 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 0.5 | O | Yes |
| 221 | 116 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 1 | G | No |
| 222 | 117 | USA | Clinical | VNI | 0.5 | 0.12 | ≤0.06 | 0.5 | G | No |
| 224 | 118 | USA | Clinical | VNI | 2 | 0.12 | ≤0.06 | 0.5 | O | Yes |
| 226 | 119 | USA | Clinical | VNI | 4 | 0.12 | ≤0.06 | 1 |   | No |
| 227 | 120 | USA | Clinical | VNII | 1 | 0.12 | ≤0.06 | 0.5 | P | No |
| 228 | 121 | USA | Clinical | VNII | 1 | 0.12 | ≤0.06 | 0.5 | P | Yes |
| 233 | 122 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 1 |   | Unknown |
| 234 | 123 | USA | Clinical | VNI | 0.12 | 0.12 | ≤0.06 | 0.25 |   | Unknown |
| 235 | 124 | USA | Clinical | VNI | ≤0.06 | 0.12 | ≤0.06 | 0.5 |   | Unknown |
| 236 | 125 | USA | Clinical | VNI | 0.5 | 0.12 | ≤0.06 | 1 |   | Unknown |
| 237 | 126 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 0.25 |   | Unknown |
| 238 | 127 | USA | Clinical | VNII | 0.5 | 0.12 | ≤0.06 | 2 |   | Unknown |
| 261 | 128 | USA | Clinical | VNII | 0.5 | ≥128 | ≤0.06 | 0.5 | N | Yes |
| 266 | 129 | USA | Clinical | VNI | 0.5 | 0.12 | ≤0.06 | 1 | R | Yes |
| 267 | 130 | USA | Clinical | VNI | 2 | 0.12 | ≤0.06 | 1 |  | Yes |
| 268 | 131 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 1 |   | No |
| 271 | 132 | USA | Clinical | VNII | 1 | 0.12 | ≤0.06 | 0.5 |   | No |
| 272 | 133 | USA | Clinical | VNII | 1 | 0.12 | ≤0.06 | 0.5 |   | No |
| 275 | 134 | USA | Clinical | VNI | 0.5 | 0.12 | ≤0.06 | 1 |   | No |
| 276 | 135 | USA | Clinical | VNIV | 1 | ≥128 | ≤0.06 | 1 |   | No |
| 277 | 136 | USA | Clinical | VNII | 1 | 0.12 | ≤0.06 | 0.12 |   | Yes |
| 278 | 137 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 0.5 |   | No |
| 279 | 138 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 0.5 |   | Yes |
| 280 | 139 | USA | Clinical | VNI | 0.5 | ≥128 | ≤0.06 | 0.5 | O | Yes |
| 284 | 140 | USA | Clinical | VNI | 0.5 | 0.12 | ≤0.06 | 1 | R | Yes |
| 286 | 141 | USA | Clinical | VNII | 1 | 0.12 | ≤0.06 | 1 | H | No |
| 287 | 142 | USA | Clinical | VNII | 0.5 | 0.12 | ≤0.06 | 1 | H | No |
| 288 | 143 | USA | Clinical | VNI | 1 | 0.12 | 0.06 | 2 |   | No |
| 289 | 144 | USA | Clinical | VNI | 2 | 0.12 | 0.06 | 2 |   | No |
| 291 | 145 | USA | Clinical | VNII | 2 | 2 | ≤0.06 | 0.5 | N | Yes |
| 292 | 146 | USA | Clinical | VNII | 2 | 0.12 | ≤0.06 | 1 | N | Yes |
| 293 | 147 | USA | Clinical | VNI | 0.5 | 0.12 | ≤0.06 | 1 |   | No |
| 294 | 148 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 1 |   | No |
| 295 | 149 | USA | Clinical | VNI | 2 | 0.12 | ≤0.06 | 1 |   | No |
| 296 | 150 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 2 |   | Unknown |
| 297 | 151 | USA | Clinical | VNI | 1 | 0.12 | 0.12 | 4 |   | Unknown |
| 298 | 152 | USA | Clinical | VGIII | 2 | 0.12 | ≤0.06 | 1 |   | Unknown |
| 300 | 153 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 1 |   | Unknown |
| 302 | 154 | USA | Clinical | VNII | 1 | 0.12 | ≤0.06 | 0.5 |   | Unknown |
| 304 | 155 | USA | Clinical | VNIII | 1 | 0.12 | ≤0.06 | 2 |   | Unknown |
| 306 | 156 | USA | Clinical | VNI | ≤0.06 | 0.12 | ≤0.06 | 1 |   | Unknown |
| 307 | 157 | USA | Clinical | VNI | 0.5 | 0.12 | ≤0.06 | 0.5 |   | Unknown |
| 310 | 158 | USA | Clinical | VNIII | 1 | 0.12 | ≤0.06 | 1 |   | Unknown |
| 311 | 159 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 2 |   | Unknown |
| 312 | 160 | USA | Clinical | VGIII | 1 | 0.12 | ≤0.06 | 2 |   | Unknown |
| 313 | 161 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 1 |   | No |
| 314 | 162 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 1 |   | No |
| 315 | 163 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 1 |   | No |
| 316 | 164 | USA | Environmental | VNI | 1 | 0.12 | ≤0.06 | 1 |   | N/A |
| 318 | 165 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 1 |   | No |
| 319 | 166 | USA | Clinical | VNIV | 1 | 0.12 | ≤0.06 | 1 |   | Unknown |
| 321 | 167 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 1 | I | No |
| 324 | 168 | USA | Clinical | VNI | 0.5 | 0.12 | ≤0.06 | 1 | I | No |
| 358 | 169 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 1 |   | Unknown |
| 359 | 170 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 0.5 |   | No |
| 362 | 171 | USA | Clinical | VNI | 0.5 | 0.12 | ≤0.06 | 1 |   | No |
| 363 | 172 | Thailand | Clinical | VGI | 0.25 | 0.12 | ≤0.06 | 0.25 |   | Unknown |
| 364 | 173 | Thailand | Clinical | VNI | 1 | 0.12 | ≤0.06 | 1 |   | Unknown |
| 368 | 174 | Thailand | Clinical | VNI | 1 | 0.12 | ≤0.06 | 2 |   | Unknown |
| 369 | 175 | Thailand | Environmental | VNI | 2 | 0.12 | ≤0.06 | 0.5 |   | N/A |
| 370 | 176 | Thailand | Environmental | VNI | 4 | 0.12 | ≤0.06 | 1 |   | N/A |
| 371 | 177 | Thailand | Environmental | VNI | 1 | 32 | 0.06 | 2 |   | N/A |
| 372 | 178 | Thailand | Environmental | VNI | 0.25 | 0.12 | ≤0.06 | 1 |   | N/A |
| 373 | 179 | Thailand | Environmental | VNI | 2 | 0.12 | ≤0.06 | 1 |   | N/A |
| 374 | 180 | Thailand | Environmental | VNI | 1 | 0.12 | ≤0.06 | 1 |   | N/A |
| 375 | 181 | Thailand | Environmental | VNI | 1 | 0.12 | ≤0.06 | 0.5 |   | N/A |
| 376 | 182 | Thailand | Environmental | VNI | 1 | 0.12 | ≤0.06 | 2 |   | N/A |
| 377 | 183 | Thailand | Environmental | VNI | 1 | 0.12 | 0.06 | 2 |   | N/A |
| 378 | 184 | Thailand | Environmental | VNI | 1 | 0.12 | ≤0.06 | 1 |   | N/A |
| 379 | 185 | Thailand | Environmental | VNI | 1 | 0.12 | ≤0.06 | 1 |   | N/A |
| 380 | 186 | USA | Clinical | VNII | 1 | 0.12 | ≤0.06 | 0.5 |   | Unknown |
| 381 | 187 | USA | Clinical | VNII | 2 | 0.12 | ≤0.06 | 0.5 |   | Unknown |
| 390 | 188 | USA | Clinical | VNI | 2 | 0.12 | 0.06 | 2 |   | No |
| 391 | 189 | USA | Clinical | VNII | 0.5 | 0.12 | ≤0.06 | 0.12 |   | Unknown |
| 392 | 190 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 0.5 |   | Unknown |
| 393 | 191 | USA | Clinical | VNI | 2 | 0.12 | ≤0.06 | 1 |   | No |
| 395 | 192 | USA | Clinical | VNI | 2 | 0.12 | ≤0.06 | 0.5 |   | No |
| 399 | 193 | USA | Clinical | VNI | 4 | 0.12 | ≤0.06 | 1 |   | Unknown |
| 408 | 194 | USA | Veterinary | VGI | 1 | 0.12 | ≤0.06 | 1 |   | N/A |
| 409 | 195 | USA | Veterinary | VGIII | 1 | 0.25 | ≤0.06 | 2 |   | N/A |
| 411 | 196 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 1 |   | Unknown |
| 412 | 197 | USA | Clinical | VGIII | 2 | 0.12 | ≤0.06 | 0.25 |   | Unknown |
| 418 | 198 | USA | Veterinary | VNIV | 2 | 2 | ≤0.06 | 1 |   | N/A |
| 424 | 199 | Denmark | Environmental | VNIV | 2 | 0.25 | ≤0.06 | 1 |   | N/A |
| 425 | 200 | Denmark | Environmental | VNI | 1 | 0.12 | ≤0.06 | 2 |   | N/A |
| 430 | 201 | Denmark | Environmental | VNIV | ≤0.06 | 0.12 | ≤0.06 | 1 |   | N/A |
| 431 | 202 | Denmark | Environmental | VNIV | ≤0.06 | 0.5 | ≤0.06 | 1 |   | N/A |
| 432 | 203 | Denmark | Environmental | VNIV | 1 | 0.12 | ≤0.06 | 0.5 |   | N/A |
| 433 | 204 | Denmark | Environmental | VNIV | 2 | 0.12 | ≤0.06 | 2 |   | N/A |
| 434 | 205 | Denmark | Environmental | VNIV | 1 | 0.12 | ≤0.06 | 2 |   | N/A |
| 438 | 206 | USA | Clinical | VNI | 4 | 0.25 | ≤0.06 | 1 |   | Unknown |
| 439 | 207 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 1 |   | Unknown |
| 440 | 208 | Denmark | Environmental | VNIV | 2 | 0.25 | ≤0.06 | 1 |   | N/A |
| 441 | 209 | Denmark | Environmental | VNI | 1 | 0.12 | ≤0.06 | 2 |   | N/A |
| 442 | 210 | Denmark | Environmental | VNIV | 0.06 | 0.12 | ≤0.06 | 0.5 |   | N/A |
| 444 | 211 | USA | Clinical | VGII | 1 | 2 | 0.06 | 4 |   | Unknown |
| 449 | 212 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 4 |   | Unknown |
| 487 | 213 | USA | Clinical | VGI | 2 | 0.12 | ≤0.06 | 2 |   | Unknown |
| 488 | 214 | USA | Veterinary | VNI | 1 | 0.12 | 0.06 | 2 |   | N/A |
| 511 | 215 | USA | Clinical | VNI | 2 | 0.12 | ≤0.06 | 2 |   | No |
| 512 | 216 | USA | Clinical | VNI | 0.25 | 0.12 | ≤0.06 | 1 | A | No |
| 514 | 217 | USA | Clinical | VNI | 1 | ≥128 | ≤0.06 | 1 | A | No |
| 515 | 218 | USA | Clinical | VNI | 1 | ≥128 | ≤0.06 | 1 | A | No |
| 516 | 219 | USA | Clinical | VNI | 2 | ≥128 | ≤0.06 | 1 | A | No |
| 517 | 220 | USA | Clinical | VNI | 2 | ≥128 | ≤0.06 | 1 | A | No |
| 527 | 221 | Italy | Clinical | VNIV | ≤0.06 | 0.12 | ≤0.06 | 0.5 |   | Unknown |
| 528 | 222 | Italy | Clinical | VNIV | 0.2 | 0.12 | ≤0.06 | 1 |   | Unknown |
| 529 | 223 | Italy | Clinical | VNIV | 0.06 | 0.12 | ≤0.06 | 1 |   | Unknown |
| 530 | 224 | Italy | Veterinary | VNIV | 0.5 | 0.12 | ≤0.06 | 1 |   | N/A |
| 571 | 225 | USA | Clinical | VNII | 1 | 0.12 | ≤0.06 | 2 |   | Unknown |
| 642 | 226 | USA | Clinical | VGIII | 2 | 0.12 | ≤0.06 | 4 |   | Unknown |
| 700 | 227 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 1 |   | Unknown |
| 702 | 228 | USA | Clinical | VNI | 1 | 0.12 | ≤0.06 | 1 |   | Unknown |
| 709 | 229 | Italy | Clinical | VNIV | 0.5 | 0.12 | ≤0.06 | 0.25 |   | Unknown |
| 710 | 230 | Italy | Clinical | VNIV | 2 | 0.5 | 0.25 | 0.5 |   | Unknown |
| 711 | 231 | Italy | Environmental | VNIII | 1 | 0.12 | ≤0.06 | 1 |   | N/A |
| 712 | 232 | Italy | Environmental | VNII | 1 | 0.12 | ≤0.06 | 2 |   | N/A |
| 713 | 233 | Italy | Environmental | VNIII | 1 | 8 | ≤0.06 | 2 |   | N/A |

Abbreviations: MIC = minimum inhibitory concentration (µg/ml), AMB = amphotericin B, 5FC = 5-fluorocytosine, ITC = itraconazole, FLC = fluconazole, Note: *a*Sequential strains from 18 patients, *b*Duplicate strains from bark of the same mesquite tree

**Supplementary Table 2.** The data of sequential isolates from 16 patients in our study

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Patient code** | **Country** | ***URA5*-RFLP** | **MIC AMB** | **MIC 5FC** | **MIC ITC** | **MIC FLC** | **Prior AMB Therapy** | **Note** |
| A | USA | VNI | 2 | 0.12 | ≤0.06 | 1 | No | Failed 5FCtherapy |
| USA | VNI | 0.25 | ≥128 | ≤0.06 | 1 | No |
| USA | VNI | 2 | ≥128 | ≤0.06 | 1 | No |
| USA | VNI | 1 | ≥128 | ≤0.06 | 1 | No |
| USA | VNI | 1 | ≥128 | ≤0.06 | 1 | No |
| B | USA | VNI | 0.5 | 0.12 | ≤0.06 | 1 | No |  |
| USA | VNI | 1 | 0.12 | ≤0.06 | 1 | No |
| C | USA | VGI | 0.25 | 0.12 | 0.06 | 2 | Unknown |
| USA | VGI | 1 | 0.12 | ≤0.06 | 2 | Unknown |
| D | USA | VNIV | ≤0.06 | 0.12 | ≤0.06 | 1 | Unknown |
| USA | VNIV | 1 | 0.12 | ≤0.06 | 1 | Unknown |
| USA | VNIV | 0.06 | 0.12 | ≤0.06 | 0.5 | Unknown |
| F | USA | VNI | 0.12 | 0.12 | ≤0.06 | 1 | No |
| USA | VNI | 1 | 0.12 | ≤0.06 | 1 | No |
| G | USA | VNI | 1 | 0.12 | ≤0.06 | 1 | No |
| USA | VNI | 0.5 | 0.12 | ≤0.06 | 0.5 | No |
| H | USA | VNII | 1 | 0.12 | ≤0.06 | 1 | No |
| USA | VNII | 0.5 | 0.12 | ≤0.06 | 1 | No |
| I | USA | VNI | 1 | 0.12 | ≤0.06 | 1 | No |
| USA | VNI | 0.5 | 0.12 | ≤0.06 | 1 | No |
| J | USA | VNI | 1 | 0.12 | ≤0.06 | 1 | Yes |
| USA | VNI | 1 | 0.12 | ≤0.06 | 1 | Yes |
| K | USA | VNI | 0.5 | 0.12 | ≤0.06 | 0.25 | No |
| USA | VNI | 1 | 0.12 | ≤0.06 | 0.25 | Yes |
| L | USA | VNI | 1 | 0.12 | ≤0.06 | 1 | No |
| USA | VNI | 0.25 | 0.12 | ≤0.06 | 1 | Yes |
| USA | VNI | 0.5 | 0.12 | ≤0.06 | 0.5 | Yes |
| USA | VNI | 1 | 0.12 | ≤0.06 | 1 | Yes |
| M | USA | VNI | 0.06 | 0.12 | ≤0.06 | 1 | No |
| USA | VNI | 0.5 | 1 | ≤0.06 | 0.12 | Yes |
| N | USA | VNII | 1 | 0.12 | ≤0.06 | 1 | Yes | Failed 5FCtherapy |
| USA | VNII | 1 | 0.12 | ≤0.06 | 0.25 | Yes |
| USA | VNII | 1 | 0.12 | ≤0.06 | 0.25 | Yes |
| USA | VNII | 1 | 0.12 | ≤0.06 | 0.25 | Yes |
| USA | VNII | 1 | 0.12 | ≤0.06 | 0.25 | Yes |
| USA | VNII | 1 | 0.12 | ≤0.06 | 0.5 | Yes |
| USA | VNII | 1 | 0.12 | ≤0.06 | 0.5 | Yes |
| USA | VNII | 1 | 0.12 | ≤0.06 | 0.5 | Yes |
| USA | VNII | 0.5 | ≥128 | ≤0.06 | 0.5 | Yes |
| USA | VNII | 2 | 2 | ≤0.06 | 0.5 | Yes |
| USA | VNII | 0.5 | 0.12 | ≤0.06 | 1 | Yes |
| O | USA | VNI | 1 | 0.12 | ≤0.06 | 1 | No | Failed 5FCtherapy |
| USA | VNI | 1 | 0.12 | ≤0.06 | 0.5 | Yes |
| USA | VNI | 2 | 0.12 | ≤0.06 | 0.5 | Yes |
| USA | VNI | 0.5 | ≥128 | ≤0.06 | 0.5 | Yes |
| P | USA | VNII | 1 | 0.12 | ≤0.06 | 0.5 | No |  |
| USA | VNII | 1 | 0.12 | ≤0.06 | 0.5 | Yes |
| R | USA | VNI | 1 | 0.12 | ≤0.06 | 0.5 | No |
| USA | VNI | 1 | 0.12 | ≤0.06 | 0.5 | Unknown |
| USA | VNI | 0.5 | 0.12 | ≤0.06 | 1 | Yes |
| USA | VNI | 0.5 | 0.12 | ≤0.06 | 1 | Yes |

Abbreviations: MIC = minimum inhibitory concentration (µg/ml), AMB = amphotericin B, 5FC = 5-fluorocytosine, ITC = itraconazole, FLC = fluconazole

**Supplementary Table 3.** Antifungal susceptibility patterns of *C. neoformans/gattii* species complexes in pre-HIV pandemic

|  |  |  |
| --- | --- | --- |
| **Species (No. of isolates)** | **Antifungal agents** | **MIC (µg/ml)** |
| **Range** | **Geometric mean** | **MIC50** | **MIC90** |
| **Total *C. neoformans/gattii* species complex** **(n = 233)** | **Amphotericin B** | ≤ 0.06 – 4 | 0.85 | 1 | 2 |
| **5 – fluorocytosine**  | 0.12 - ≥ 128 | 0.14 | 0.12 | 0.12 |
| **Itraconazole** | ≤ 0.06 – 8 | 0.10 | 0.06 | 0.25 |
| **Fluconazole** | 0.12 – 8  | 0.96 | 1 | 2 |
| ***C. neoformans* species complex****(n = 209)** | **Amphotericin B** | ≤ 0.06 – 4 | 0.83 | 1 | 2 |
| **5 – fluorocytosine**  | 0.12 - ≥ 128 | 0.14 | 0.12 | 0.12 |
| **Itraconazole** | ≤ 0.06 – 8 | 0.11 | 0.06 | 0.25 |
| **Fluconazole** | 0.12 – 4 | 0.90 | 1 | 2 |
| ***C. gattii* species complex****(n = 24)** | **Amphotericin B** | 0.25 – 4 | 1.03 | 1 | 2 |
| **5 – fluorocytosine**  | 0.12 - 2 | 0.15 | 0.12 | 0.25 |
| **Itraconazole** | ≤ 0.06 – 0.12 | 0.07 | 0.06 | 0.10 |
| **Fluconazole** | 0.25 – 8  | 1.68 | 2 | 4 |
| **Clinical isolates molecular type *C. neoformans*/VNI** **(n = 118)*a*** | **Amphotericin B** | ≤ 0.06 – 4 | 0.84 | 1 | 2 |
| **5 – fluorocytosine**  | 0.12 - ≥ 128 | 0.13 | 0.12 | 0.12 |
| **Itraconazole** | ≤ 0.06 – 0.25 | 0.08 | 0.06 | 0.16 |
| **Fluconazole** | 0.12 – 4  | 1.02 | 1 | 2 |
| **Clinical isolates molecular type *C. neoformans*/VNII****(n = 33)*b*** | **Amphotericin B** | 0.5 – 2 | 0.96 | 1 | 2 |
| **5 – fluorocytosine**  | 0.12 - ≥ 128 | 0.13 | 0.12 | 0.12 |
| **Itraconazole** | ≤ 0.06 – 8 | ND | ≤ 0.06 | ND |
| **Fluconazole** | 0.12 – 2  | 0.47 | 0.50 | 1 |
| **Clinical isolates molecular type *C. neoformans × deneoformans hybrid*/VNIII****(n = 3)** | **Amphotericin B** | 0.06 – 1 | 0.39 | 1 | 1 |
| **5 – fluorocytosine**  | 0.12  | 0.12 | 0.12 | 0.12 |
| **Itraconazole** | ≤ 0.06 | ND | ≤ 0.06 | ND |
| **Fluconazole** | 0.5 – 2  | 1.00 | 1 | 1 |
| **Clinical isolates molecular type *C. deneoformans*/VNIV****(n = 13)*c*** | **Amphotericin B** | ≤ 0.06 – 2 | 0.38 | 0.50 | 1 |
| **5 – fluorocytosine**  | 0.12 - ≥ 128 | 0.15 | 0.12 | 0.46 |
| **Itraconazole** | ≤ 0.06 – 0.25 | ND | ≤ 0.06 | ND |
| **Fluconazole** | 0.25 – 1  | 0.69 | 1 | 1 |
| **Clinical isolates molecular type *C. gattii*/VGI** **(n = 5)*d*** | **Amphotericin B** | 0.25 – 2  | 0.57 | 0.50 | 1.60 |
| **5 – fluorocytosine**  | 0.12 | 0.12 | 0.12 | 0.12 |
| **Itraconazole** | ≤ 0.06 – 0.06 | 0.06 | ≤ 0.06 | 0.06 |
| **Fluconazole** | 0.25 – 2  | 1.26 | 2 | 2 |
| **Clinical isolates molecular type *C. deuterogattii*/VGII****(n = 1)** | **Amphotericin B** | 1 | ND | ND | ND |
| **5 – fluorocytosine**  | 2 | ND | ND | ND |
| **Itraconazole** | 0.06 | ND | ND | ND |
| **Fluconazole** | 4 | ND | ND | ND |
| **Clinical isolates molecular type *C. bacillisporus*/VGIII****(n = 16)** | **Amphotericin B** | 0.5 – 4  | 1.24 | 1 | 2 |
| **5 – fluorocytosine**  | 0.12 – 0.25  | 0.13 | 0.12 | 0.19 |
| **Itraconazole** | ≤ 0.06 – 0.12 | ND | ≤ 0.06 | ND |
| **Fluconazole** | 0.25 – 8  | 1.76 | 1.50 | 6 |
| **Environmental isolates molecular type *C. neoformans*/VNI** **(n = 25)*e*** | **Amphotericin B** | 0.25 – 4  | 1.12 | 1 | 2 |
| **5 – fluorocytosine**  | 0.12 – 32  | 0.15 | 0.12 | 0.12 |
| **Itraconazole** | ≤ 0.06 – 0.06  | 0.06 | ≤ 0.06 | 0.06 |
| **Fluconazole** | 0.5 – 2  | 1.15 | 1 | 2 |
| **Environmental isolates molecular type *C. neoformans*/VNII****(n = 1)** | **Amphotericin B** | 1 | ND | ND | ND |
| **5 – fluorocytosine**  | 0.12 | ND | ND | ND |
| **Itraconazole** | ≤ 0.06 | ND | ND | ND |
| **Fluconazole** | 2 | ND | ND | ND |
| **Environmental isolates molecular type *C. neoformans × deneoformans hybrid*/VNIII****(n = 2)** | **Amphotericin B** | 1 | 1.00 | 1 | 1 |
| **5 – fluorocytosine**  | 0.12 – 8  | 0.98 | 4.06 | 7.21 |
| **Itraconazole** | ≤ 0.06 | ND | ≤ 0.06 | ND |
| **Fluconazole** | 1 – 2  | 1.41 | 1.50 | 1.90 |
| **Environmental isolates molecular type *C. deneoformans*/VNIV****(n = 9)** | **Amphotericin B** | ≤ 0.06 – 2 | 0.60 | 1 | 2 |
| **5 – fluorocytosine**  | 0.12 – 0.5  | 0.17 | 0.12 | 0.30 |
| **Itraconazole** | ≤ 0.06 | ND | ≤ 0.06 | ND |
| **Fluconazole** | 0.25 – 2  | 0.86 | 1 | 2 |
| **Veterinary isolates molecular type *C. neoformans*/VNI****(n = 3)** | **Amphotericin B** | 0.5 – 1 | 0.63 | 0.50 | 0.90 |
| **5 – fluorocytosine**  | 0.12 | 0.12 | 0.12 | 0.12 |
| **Itraconazole** | ≤ 0.06 – 0.06  | 0.06 | ≤ 0.06 | 0.06 |
| **Fluconazole** | 1 – 2 | 1.26 | 1 | 1.80 |
| **Veterinary isolates molecular type *C. deneoformans*/VNIV****(n = 2)** | **Amphotericin B** | 0.5 – 2  | 1.00 | 1.25 | 1.85 |
| **5 – fluorocytosine**  | 0.12 – 2  | 0.49 | 1.06 | 1.81 |
| **Itraconazole** | ≤ 0.06 | ND | ≤ 0.06 | ND |
| **Fluconazole** | 1 | 1.00 | 1 | 1 |
| **Veterinary isolates molecular type *C. gattii*/VGI****(n = 1)** | **Amphotericin B** | 1 | ND | ND | ND |
| **5 – fluorocytosine**  | 0.12 | ND | ND | ND |
| **Itraconazole** | ≤ 0.06 | ND | ND | ND |
| **Fluconazole** | 1 | ND | ND | ND |
| **Veterinary isolates molecular type *C. bacillisporus*/VGIII****(n = 1)** | **Amphotericin B** | 1 | ND | ND | ND |
| **5 – fluorocytosine**  | 0.25 | ND | ND | ND |
| **Itraconazole** | ≤ 0.06 | ND | ND | ND |
| **Fluconazole** | 2 | ND | ND | ND |

Abbreviations: ND = not determine, MIC = minimum inhibitory concentration, Note: *a*Isolated from 98 different patients, *b*Isolated from 21 different patients, *c*Isolated from 11 different patients, *d*Isolated from 4 different patients, *e*Isolated from 24 different sources