Brazilian Journal of Microbiology (2022) 53:2003–2008
https://doi.org/10.1007/s42770-022-00817-y

CLINICAL MICROBIOLOGY - SHORT COMMUNICATION

Evaluation of the synergistic antifungal activity of micafungin and voriconazole plus sertraline against *Candida auris*

Sergio A. Alanís-Ríos[1] · Gloria M. González[1] · Angel Andrade[1] · Miguel A. Becerril-García[1] · Alexandro Bonifaz[2] · Efrén R. Robledo-Leal[3] · Alexandra M. Montoya[1] · Rogelio de J. Treviño-Rangel[1]

Received: 30 May 2022 / Accepted: 22 August 2022 / Published online: 29 August 2022

Abstract

Candida auris is an emerging global public health threat. It is an opportunistic yeast that usually affects critically ill patients in healthcare settings and is characterized by reduced susceptibility to multiple antifungal classes. Combination therapy with antifungals and repurposed drugs is a feasible alternative to overcome this problem. The aim of this study was to examine the in vitro interactions and potential synergy of micafungin (MFG) and voriconazole (VRC) plus the antidepressant sertraline (SRT) against clinical isolates of *C. auris*. Conventional antifungal testing was first performed with the three drugs according to the CLSI methodology. Drug interactions were determined by the checkerboard microdilution assay using the fractional inhibitory concentration (FIC) index. Synergistic interactions were noted with the combination of MFG and SRT plus VRC with FIC values of 0.37 to 0.49 for some strains. Indifferent interactions were observed when MFG was combined with SRT with just one exception (FIC 0.53). No antagonism was observed for any combination. The combination of VRC with MCF or SRT may be relevant for treating *C. auris* infections.

Keywords *Candida auris* · Micafungin · Voriconazole · Sertraline · Synergy

Introduction

Initially isolated in 2009 from otic drainage of a Japanese patient, *Candida auris* is an opportunistic nosocomial yeast pathogen that emerged simultaneously on five continents, spreading to over 30 countries since its first description [1–3]. Major risk factors for developing *C. auris* infections are longer hospital stays, particularly in intensive care units (ICU) [4, 5], current exposure to indwelling medical devices, and having undergone invasive procedures [6, 7]. Candidemia is the most common fungal infection, especially in low-immunity patients in the ICU; it is associated with a poor outcome and overall mortality approaching 68% [6].

As a result of its easy transmission, provoking global outbreaks, and exceptional multidrug resistance, *C. auris* was recently classified as an "urgent health threat" by the US Centers for Disease Control and Prevention (CDC) [8]. This fungus is characterized by reduced susceptibility to azoles, polyenes, and echinocandins [9]. Even if the latter are considered first-line therapy for *C. auris* infections [10], resistance to these agents and therapeutic failures have been reported [11], severely limiting available treatment options. Thus, alternative strategies are urgently needed to overcome this alarming crisis.

Combination therapy is a convenient approach defined as the co-application of two or more drugs with distinct biological targets to achieve a synergistic interaction, increasing the probability of therapeutic success and limiting the emergence of drug resistance [12, 13]. Few antifungal combinations have

Responsible Editor: Luiz Henrique Rosa

Sergio A. Alanís-Ríos and Gloria M. González contributed equally to this work as first authors.

✉ Rogelio de J. Treviño-Rangel
roghe24@gmail.com

[1] Departamento de Microbiología, Facultad de Medicina, Universidad Autónoma de Nuevo León, Ave. Francisco I. Madero & Dr. Eduardo A. Pequeño. Mitras Centro, 64460 Monterrey, Mexico

[2] Servicio de Dermatología and Departamento de Micología, Hospital General de México "Dr. Eduardo Liceaga", Mexico City, Mexico

[3] Departamento de Microbiología e Inmunología, Facultad de Ciencias Biológicas, Universidad Autónoma de Nuevo León, San Nicolas de los Garza, Mexico

been evaluated against multidrug-resistant *C. auris* strains. A good example is the recently reported in vitro synergistic interaction between micafungin and voriconazole [14]. Alternatively, the combination of antifungals with "off-patent" non-antifungal drugs has also been investigated in the context of drug repurposing for treating invasive infections [15]. In this sense, sertraline, the most frequently prescribed antidepressant, exhibited in vitro antifungal activity against *C. auris* [16], but this effect has not been evaluated in combination with antifungals. This study examined the in vitro interactions and potential synergy between sertraline and two antifungals with different modes of action (micafungin and voriconazole) against clinical isolates of *C. auris*. Therefore, the tested hypothesis of the work was the following: the in vitro combinations of micafungin and voriconazole plus sertraline exert synergistic antifungal activity against *C. auris*.

Material and methods

Ethics statement

This study was evaluated and approved by the local Ethics Committee of the Universidad Autónoma de Nuevo León (registration number: MB22-00001), and was conducted in agreement with Good Laboratory Practices.

Clinical isolates

Twelve strains previously identified by DNA multilocus sequence typing as *C. auris* from an outbreak of COVID-19-associated *C. auris* infections in a tertiary care hospital in Monterrey, Mexico [5] were included in this study. Isolates were recovered from blood (6/12), urine (8/12), and both (2/12). All belong to the clade IV (South American). Fungal strains were retrieved from frozen stocks on 15% glycerol suspensions maintained at −70 °C and cultivated in Sabouraud dextrose agar (SDA) at 37 °C for 24 h before each experiment.

Agents

The drugs tested included micafungin (MFG) (Mycamine®; Astellas Pharma, Deerfield, IL, USA), voriconazole (VRC) (Pfizer, New York, NY, USA), and sertraline (SRT) (TCI Chemicals Inc., New York, NY, USA). The drugs were dissolved in 100% dimethyl sulfoxide (DMSO) (Bio Basic, USA) [17, 18] to obtain stock solutions of 3200 µg/mL and kept at −80 °C until use.

Conventional antifungal testing

Broth microdilution testing was performed according to the Clinical and Laboratory Standards Institute (CLSI) M27-A3 [17]. In brief, serial two-fold dilutions were prepared for each agent. Further dilutions were made in RPMI-1640 with L-glutamine and buffered with 165 mM MOPS (Hardy Diagnostics, USA), reaching final concentrations ranging from 0.03 to 16 µg/mL for VRC and from 0.015 to 8 µg/mL for MFG. Finally, the inoculated plates were incubated at 35 °C and read after 24 h. The minimum inhibitory concentration (MIC) endpoint was visually determined as the lowest drug concentration that produced a significant decrease (≥ 50%) in growth compared to the growth of the drug-free control. *Candida parapsilosis* ATCC 22019 and *Candida krusei* ATCC 6258 were quality-control strains. MIC breakpoints for interpreting results were those recommended by the CDC (http://www.cdc.gov/fungal/candida-auris/c-auris-antifungal.html). Experiments were conducted in duplicate on different days.

To obtain the minimum fungicidal concentration (MFC), 0.1 mL of each serial drug dilution was taken from each well with no visible growth and poured onto SDA [19]. Plates were incubated at 37 °C for 24–48 h. The MFC was the lowest drug concentration yielding less than five yeast colonies.

Antifungal combination testing

Interactions between MFG and VRC, and these with SRT, were investigated using the checkerboard microdilution assay based on the CLSI reference method with 96-well microtiter plates (Corning, USA) [20, 21]. Broadly, drug dilutions were prepared at four times the final concentration ranging from 0.25 to 32 µg/mL for SRT, 0.03 to 4 µg/mL for VRC, and 0.06 to 4 µg/mL for MFG. These ranges depended on MIC results previously obtained for each strain. For two-dimensional microplate preparation, 50 µL of each concentration of SRT was added into the wells of columns 2 through 9; then, 50 µL of the partner drug (MFG or VRC) was added into the wells of rows A through G, respectively. For the combination MFG-VRC, the echinocandin was collocated from rows A to G and the triazole from columns 2 to 9. The wells of column 1 and row H contained the respective drugs alone. Column 10 was the drug-free well and the growth control, while column 11 was the uninoculated well corresponding to the sterile control. Trays were kept at −80 °C until use.

Once trays were defrosted, the inoculum was adjusted spectrophotometrically and further diluted with RPMI 1640; 100 µL of the suspension was added to each plate well,

except for the sterile control. Trays were incubated at 37 °C for 24 h, and a 100% inhibition reading was recorded with a convex mirror [22, 23]. Experiments were performed in duplicate on different days. Drug combination interactions were evaluated based on the fractional inhibitory concentration (FIC) index: FIC A (MIC drug A in combination/MIC drug A alone) + FIC B (MIC drug B in combination/MIC drug B alone). The summation of the FIC (∑FIC) index was calculated for each drug combination and strain and its interpretation was synergy, ≤ 0.5; partial synergy, > 0.5 to < 1.0; additivity, 1.0; indifference, > 1.0 to < 4.0; antagonism, ≥ 4.0 [17].

Results

All *C. auris* strains tested in this study were susceptible to MFG (range: 0.125–0.5 µg/mL, MIC_{50}: 0.25 µg/mL, MIC_{90}: 0.5 µg/mL) and VRC (range: 0.03–1 µg/mL, MIC_{50}: 0.25 µg/mL, MIC_{90}: 1 µg/mL), with a median of 2 µg/mL and 1 µg/mL for MFG and VRC, respectively. Regarding SRT, MICs ranged from 4 to 8 µg/mL, with an MIC_{50} and MIC_{90} of 8 µg/mL and a median MFC of 16 µg/mL.

The results of the drug combinations evaluated in this study are summarized in Table 1. When SRT was combined with MFG, the ∑FIC ranged from 0.53 to 1.03, indicative of no-interaction (or indifferent activity) except for strain #3, for which a partial synergy was observed ($\sum FIC_{min}$ 0.53). When this drug was combined with VRC, a synergistic interaction was noted in three strains (∑FIC 0.37 to 0.49) in addition to a partial synergy evidenced in strain #12 ($\sum FIC_{min}$ 0.54); moreover, the MIC ranges of SRT and VRC were reduced to 0.5 to 4 µg/mL and 0.03 to 0.06 µg/mL, respectively. On the other hand, synergistic effects of VRC plus MFG were shown against four *C. auris* isolates (∑FIC 0.37 to 0.49) with a reduction in MIC ranges of VRC and MFG to 0.03 to 0.125 µg/mL and 0.25 to 0.5 µg/mL, correspondingly. No antagonistic activity was observed for any combination tested.

Discussion

C. auris is an emerging global multidrug-resistant nosocomial pathogen considered a major threat to healthcare settings. It exhibits a clade-specific resistance to fluconazole (FLC) but varying susceptibility to other triazoles, amphotericin B (AMB), and echinocandins [6, 24]. Resistance rates for FLC, VRC and AMB were nearly 90%, 3–73%, and 13–35%, respectively [6, 24, 25]. Roughly 4% of *C. auris* isolates resistant to echinocandins have been reported in the USA [26]. In this context, combination drug therapy is an attractive strategy to fight and overcome antifungal resistance in *C. auris* and presents known benefits over the single use of drugs [27].

Limited antifungal combinations have been evaluated against *C. auris*. One of the most promising combinations is triazoles plus echinocandins [14, 28, 29]. Pfaller et al. [28] evaluated the interaction of VRC or isavuconazole (ISA) in combination with anidulafungin (AFG) against isolates of *C. auris* using the FIC index analysis. They reported synergism or partial synergism against most isolates, mainly for the combination of ISA with AFG. Later, Fakhim et al. [14] communicated that the combination of MFG plus VRC exhibited synergistic activity against all ten multidrug-resistant strains of *C. auris* belonging to the South Asian clade, determined by the FIC index. More recently, Caballero et al. [29] observed the synergism of ISA and echinocandins against six *C. auris* bloodstream isolates from an outbreak in a Spanish hospital. Their findings were consistent with the two previous reports. In our study, we found a synergistic interaction of VRC plus MFG in four *C. auris* strains in accordance with Fakhim et al. [14]. The proportion of synergic isolates they reported is higher than what we encountered, this finding may be because the strains tested belonged to different clades and had strain-specific behaviors.

Drug repurposing is another increasingly interesting alternative approach to search for new potential antifungal candidates. Several reports have described good in vitro antifungal activity of the antidepressant SRT for *Cryptococcus* spp. [30] Moreover, in vivo studies have revealed that this repurposed drug has a role alone or in combination for treating invasive fungal infections [31, 32]. Recently, Gowri et al. [16] reported that SRT inhibited the yeast to hyphae conversion of *C. auris* and biofilm formation upon treatment. In our study, SRT exhibited antifungal activity against all the *C. auris* isolates tested with MICs ranging from 4 to 8 µg/mL. These levels are considerably lower than those previously communicated by Gowri et al. [16] Additionally, while the combination of SRT plus MFG overall redounded in indifference except for strain #3, the combination of SRT plus VRC resulted in synergism for three strains and partial synergy for strain #12.

Even though our study shares some limitations with the reports mentioned above, such as the reduced number of isolates tested, all belonging to the clade IV (South American), and the absence of strains resistant to the antifungals used, this work fills a gap as there is no report on the efficacy of antifungal combinations against *C. auris* from the Monterrey, Mexico outbreak. Furthermore, to our knowledge, this is the first attempt to use SRT in combination against *C. auris* with encouraging results.

Table 1 Synergy results for the antifungal combinations tested in this study against 12 strains of *C. auris*

		SRT + MFG					SRT + VRC					VRC + MFG				
		MIC (µg/mL)					MIC (µg/mL)					MIC (µg/mL)				
Strain	Source[a]	SRT	MFG	SRT/MFG	$\sum FIC_{min}$[b]	INT[c]	SRT	VRC	SRT/VRC	$\sum FIC_{min}$[b]	INT[c]	VRC	MFG	VRC/MFG	$\sum FIC_{min}$[b]	INT[c]
1	B	8	0.5	0.25/0.5	1.03	IND	8	0.25	4/0.03	0.62	IND	0.25	0.5	0.125/0.25	1	IND
2	U	8	0.5	0.25/0.5	1.03	IND	8	0.25	4/0.03	0.62	IND	0.25	0.5	0.125/0.25	1	IND
3	B/U	8	2	0.25/1	0.53	PSYN	8	0.25	2/0.06	0.49	SYN	0.25	2	0.06/0.25	0.37	SYN
4	U	4	1	4/0.06	1.06	IND	4	0.25	2/0.03	0.62	IND	0.25	1	0.03/0.5	0.62	IND
5	B	8	1	0.25/1	1.03	IND	8	0.25	2/0.06	0.49	SYN	0.25	1	0.03/0.5	0.62	IND
6	B	8	1	0.25/1	1.03	IND	8	0.25	4/0.06	0.74	IND	0.25	1	0.06/0.25	0.49	SYN
7	B/U	8	1	0.25/1	1.03	IND	8	0.25	2/0.03	0.37	SYN	0.25	1	0.06/0.25	0.49	SYN
8	U	8	1	0.25/1	1.03	IND	8	0.125	2/0.06	0.74	IND	0.125	1	0.03/0.5	0.74	IND
9	U	8	1	0.25/1	1.03	IND	8	0.125	2/0.06	0.71	IND	0.125	1	0.06/0.25	0.71	IND
10	U	8	1	0.25/1	1.03	IND	8	0.125	2/0.06	0.71	IND	0.125	0.5	0.06/0.25	0.71	IND
11	B	8	1	2/0.5	0.75	IND	8	0.125	1/0.06	0.61	IND	0.125	0.5	0.03/0.25	0.49	SYN
12	U	8	1	0.25/1	1.03	IND	8	0.125	0.5/0.06	0.54	PSYN	0.125	1	0.03/0.5	0.74	IND

MIC minimum inhibitory concentration, *SRT* sertraline, *MFG* micafungin, *VRC* voriconazole

[a]Source: *B* blood, *U* urine

[b]Lowest fractional inhibitory concentration

[c]*INT* interaction, *IND* indifference, *PSYN* partial synergy, *SYN* synergy

Conclusions

The tested hypothesis of the work was corroborated. We have shown that interaction between SRT or MFG plus VCZ exhibited synergistic antifungal activity against some strains of *C. auris*.

Acknowledgements The authors want to thank the medical writer certified, Sergio Lozano-Rodríguez, M.D., for his review of the manuscript before submission.

Funding This work was supported by a grant of the Consejo Nacional de Ciencia y Tecnología (CONACyT — Ciencia Básica y/o Ciencia de Frontera 2022) No. 319414.

Declarations

Conflict of interest The authors declare no competing interests.

References

1. Satoh K, Makimura K, Hasumi Y, Nishiyama Y, Uchida K, Yamaguchi H (2009) *Candida auris* sp. nov., a novel ascomycetous yeast isolated from the external ear canal of an inpatient in a Japanese hospital. Microbiol Immunol 53:41–44. https://doi.org/10.1111/j.1348-0421.2008.00083.x
2. Rhodes J, Fisher MC (2019) Global epidemiology of emerging *Candida auris*. Curr Opin Microbiol 52:84–89. https://doi.org/10.1016/j.mib.2019.05.008
3. Lockhart SR (2019) *Candida auris* and multidrug resistance: defining the new normal. Fungal Genet Biol 131:103243. https://doi.org/10.1016/j.fgb.2019.103243
4. Rudramurthy SM, Chakrabarti A, Paul RA, Sood P, Kaur H, Capoor MR et al (2017) *Candida auris* candidaemia in Indian ICUs: analysis of risk factors. J Antimicrob Chemother 72:1794–1801. https://doi.org/10.1093/jac/dkx034
5. Villanueva-Lozano H, Treviño-Rangel RJ, González GM, Ramírez-Elizondo MT, Lara-Medrano R, Alemán-Bocanegra MC et al (2021) Outbreak of *Candida auris* infection in a COVID-19 hospital in Mexico. Clin Microbiol Infect 27:813–816. https://doi.org/10.1016/j.cmi.2020.12.030
6. Lockhart SR, Etienne KA, Vallabhaneni S, Farooqi J, Chowdhary A, Govender NP et al (2017) Simultaneous emergence of multidrug-resistant *Candida auris* on 3 continents confirmed by whole-genome sequencing and epidemiological analyses. Clin Infect Dis 64:134–140. https://doi.org/10.1016/j.cmi.2020.12.030
7. Ademe M, Girma F (2020) *Candida auris*: from multidrug resistance to pan-resistant strains. Infect Drug Resist 13:1287–1294. https://doi.org/10.2147/idr.s249864
8. CDC (2019) Antibiotic resistance threats in the United States. Atlanta, GA, USA. https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf. Accessed 30 May 2022
9. Navalkele BD, Revankar S, Chandrasekar P (2017) *Candida auris*: a worrisome, globally emerging pathogen. Expert Rev Anti Infect Ther 15:819–827. https://doi.org/10.1080/14787210.2017.1364992
10. Kenters N, Kiernan M, Chowdhary A, Denning DW, Peman J, Saris K et al (2019) Control of *Candida auris* in healthcare institutions: outcome of an International Society for Antimicrobial Chemotherapy expert meeting. Int J Antimicrob Agents 54:400–406. https://doi.org/10.1080/14787210.2017.1364992
11. Biagi MJ, Wiederhold NP, Gibas C, Wickes BL, Lozano V, Bleasdale SC et al (2019) Development of high-level Echinocandin resistance in a patient with recurrent *Candida auris* Candidemia secondary to chronic Candiduria. Open Forum Infect Dis 6:ofz262. https://doi.org/10.1093/ofid/ofz262
12. Fohrer C, Fornecker L, Nivoix Y, Cornila C, Marinescu C, Herbrecht R (2006) Antifungal combination treatment: a future perspective. Int J Antimicrob Agents 27(Suppl 1):25–30. https://doi.org/10.1016/j.ijantimicag.2006.03.016
13 Mukherjee PK, Sheehan DJ, Hitchcock CA, Ghannoum MA (2005) Combination treatment of invasive fungal infections. Clin Microbiol Rev 18:163–94. https://doi.org/10.1128/CMR.18.1.163-194.2005
14. Fakhim H, Chowdhary A, Prakash A, Vaezi A, Dannaoui E, Meis JF et al (2017) In vitro interactions of Echinocandins with Triazoles against multidrug-resistant *Candida auris*. Antimicrob Agents Chemother 61:e01056-e1117. https://doi.org/10.1128/aac.01056-17
15. Wall G, Chaturvedi AK, Wormley FL Jr, Wiederhold NP, Patterson HP, Patterson TF et al (2018) Screening a repurposing library for inhibitors of multidrug-resistant *Candida auris* identifies Ebselen as a repositionable candidate for antifungal drug development. Antimicrob Agents Chemother 62:e01084-e1118. https://doi.org/10.1128/aac.01084-18
16. Gowri M, Jayashree B, Jeyakanthan J, Girija EK (2020) Sertraline as a promising antifungal agent: inhibition of growth and biofilm of *Candida auris* with special focus on the mechanism of action in vitro. J Appl Microbiol 128:426–437. https://doi.org/10.1111/jam.14490
17 CLSI (2017) Reference method for broth dilution antifungal susceptibility testing of yeasts, 4th edn. Pennsylvania, Wayne
18. Villanueva-Lozano H, González GM, Espinosa-Mora JE, Bodden-Mendoza BA, Andrade A, Martínez-Reséndez MF et al (2020) Evaluation of the expanding spectrum of sertraline against uncommon fungal pathogens. J Infect Chemother 26:309–311. https://doi.org/10.1016/j.jiac.2019.10.001
19. Espinel-Ingroff A, Fothergill A, Peter J, Rinaldi MG, Walsh TJ (2002) Testing conditions for determination of minimum fungicidal concentrations of new and established antifungal agents for *Aspergillus* spp.: NCCLS collaborative study. J Clin Microbiol 40:3204–8. https://doi.org/10.1128/JCM.40.9.3204-3208.2002
20. Odds FC (2003) Synergy, antagonism, and what the chequerboard puts between them. J Antimicrob Chemother 52:1. https://doi.org/10.1093/jac/dkg301
21 CLSI (2018) Development of *in vitro* susceptibility testing criteria and quality control parameters, 5th edn. Pennsylvania, Wayne
22. Ren P, Luo M, Lin S, Ghannoum MA, Isham N, Diekema DJ et al (2015) Multilaboratory testing of antifungal drug combinations against *Candida* species and *Aspergillus fumigatus*: utility of 100 percent inhibition as the endpoint. Antimicrob Agents Chemother 59:1759–66. https://doi.org/10.1128/AAC.04545-14
23. O'Brien B, Chaturvedi S, Chaturvedi V (2020) In vitro evaluation of antifungal drug combinations against multidrug-resistant *Candida auris* isolates from New York outbreak. Antimicrob Agents Chemother 64:e02195-e2219. https://doi.org/10.1128/aac.02195-19
24. Chaabane F, Graf A, Jequier L, Coste AT (2019) Review on antifungal resistance mechanisms in the emerging pathogen *Candida auris*. Front Microbiol 10:2788. https://doi.org/10.3389/fmicb.2019.02788
25. Chowdhary A, Anil Kumar V, Sharma C, Prakash A, Agarwal K, Babu R et al (2014) Multidrug-resistant endemic clonal strain of *Candida auris* in India. Eur J Clin Microbiol Infect Dis 33:919–926. https://doi.org/10.1007/s10096-013-2027-1

26. Ostrowsky B, Greenko J, Adams E, Quinn M, O'Brien B, Chaturvedi V, et al (2020) *Candida auris* isolates resistant to three classes of antifungal medications — New York, 2019. MMWR Morb Mortal Wkly Rep 69:6–9. https://doi.org/10.15585/mmwr.mm6901a2
27. Mahmoudi S, Rezaie S, Daie Ghazvini R, Hashemi SJ, Badali H, Foroumadi A et al (2019) *In vitro* interaction of geldanamycin with triazoles and Echinocandins against common and emerging *Candida* Species. Mycopathologia 184:607–613. https://doi.org/10.1007/s11046-019-00370-7
28. Pfaller MA, Messer SA, Deshpande LM, Rhomberg PR, Utt EA, Castanheira M (2021) Evaluation of synergistic activity of Isavuconazole or Voriconazole plus Anidulafungin and the occurrence and genetic characterization of *Candida auris* detected in a surveillance program. Antimicrob Agents Chemother 65:e02031-e2120. https://doi.org/10.1128/aac.02031-20
29. Caballero U, Kim S, Eraso E, Quindos G, Vozmediano V, Schmidt S et al (2021) In vitro synergistic interactions of Isavuconazole and Echinocandins against *Candida auris*. Antibiotics (Basel) 10:355. https://doi.org/10.3390/antibiotics10040355
30. Zhai B, Wu C, Wang L, Sachs MS, Lin X (2012) The antidepressant sertraline provides a promising therapeutic option for neurotropic cryptococcal infections. Antimicrob Agents Chemother 56:3758–3766. https://doi.org/10.1128/aac.00212-12
31 Rhein J, Morawski BM, Hullsiek KH, Nabeta HW, Kiggundu R, Tugume L et al (2016) Efficacy of adjunctive sertraline for the treatment of HIV-associated cryptococcal meningitis: an open-label dose-ranging study. Lancet Infect Dis 16:809–18. https://doi.org/10.1016/S1473-3099(16)00074-8
32. Treviño-Rangel RJ, Villanueva-Lozano H, Méndez-Galomo KS, Solís-Villegas EM, Becerril-García MA, Montoya AM et al (2019) *In vivo* evaluation of the antifungal activity of sertraline against *Aspergillus fumigatus*. J Antimicrob Chemother 74:663–666. https://doi.org/10.1093/jac/dky455