

Best of infections fongiques en 2022

SPILF

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Intro

Introduction

IFI

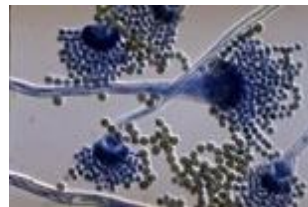
Levures

- *Candida*
- *Cryptococcus*



Filamenteux

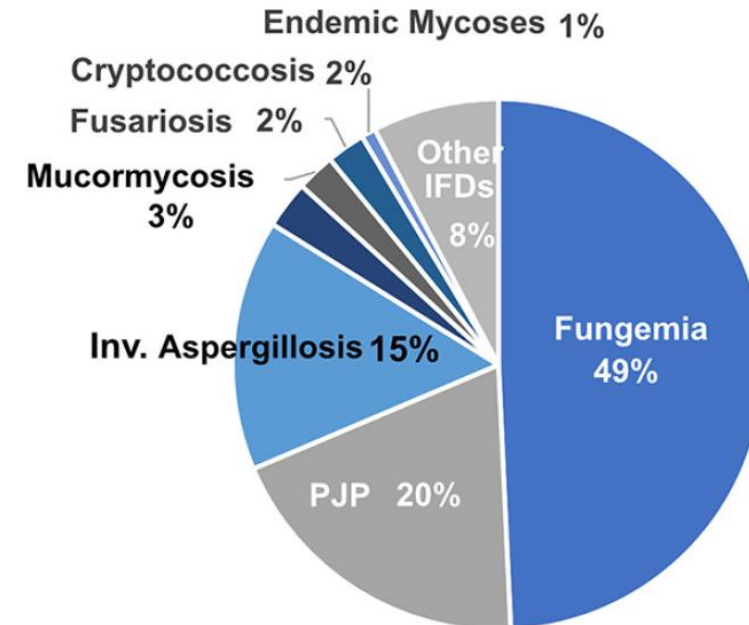
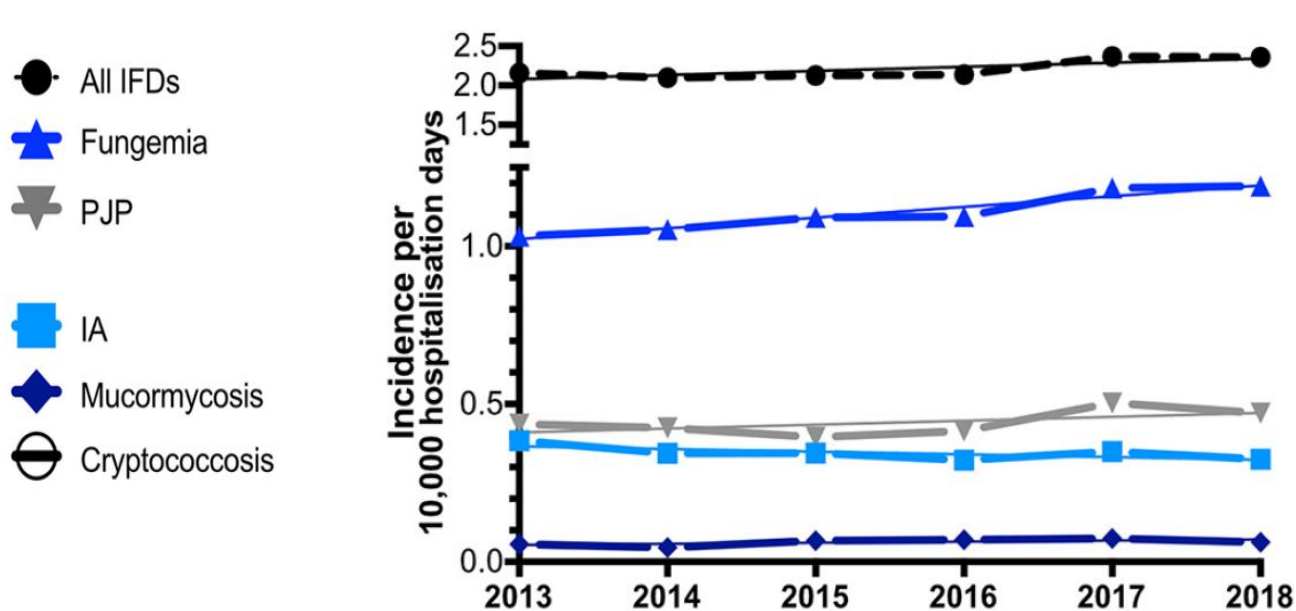
- *Aspergillus*
- *Mucorales*

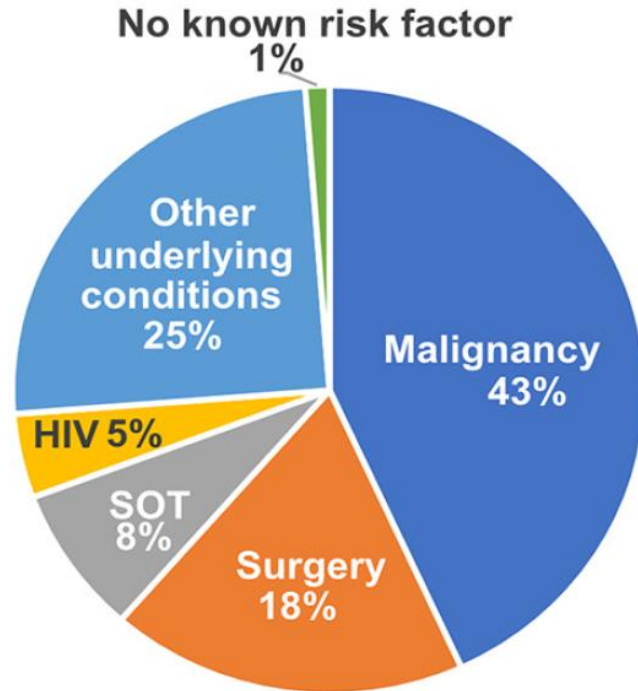


Dimorphiques

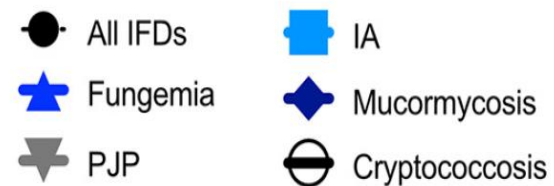
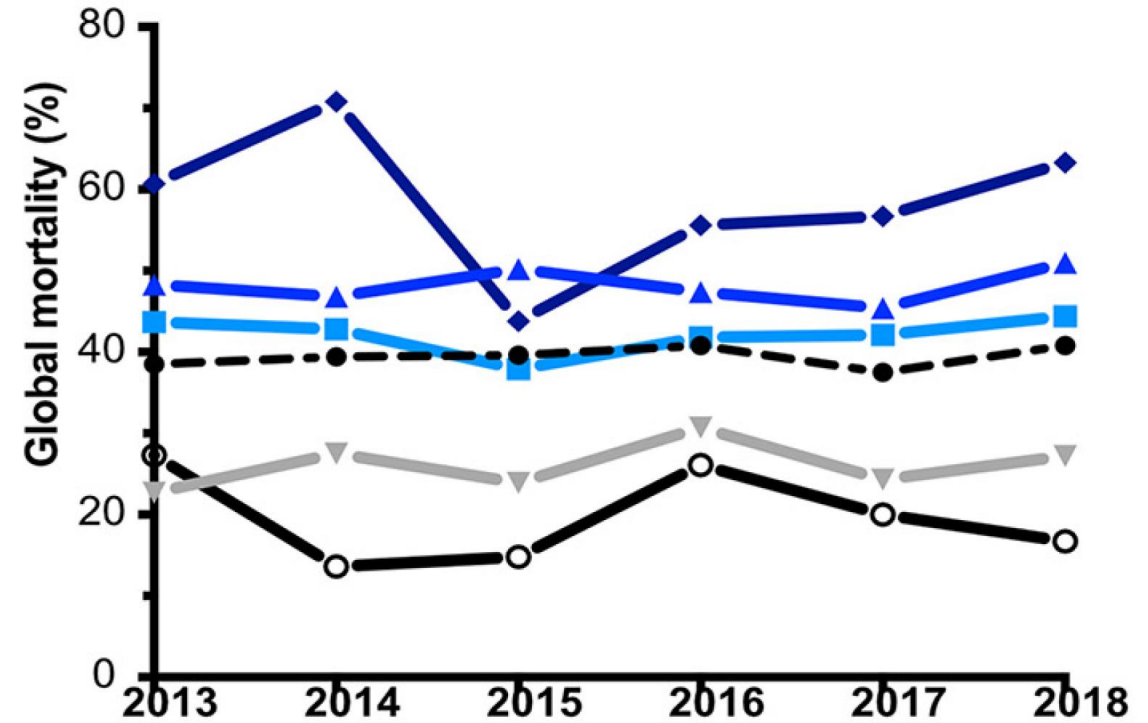
- *Histoplasma*

10 886 IFIs entre 2012 et 2018, en augmentation 2,16 à 2,36/10 000 hospitalisations
 Augmentation de l'incidence des fongémies 1.03 à 1.19/10 000 hospitalisations



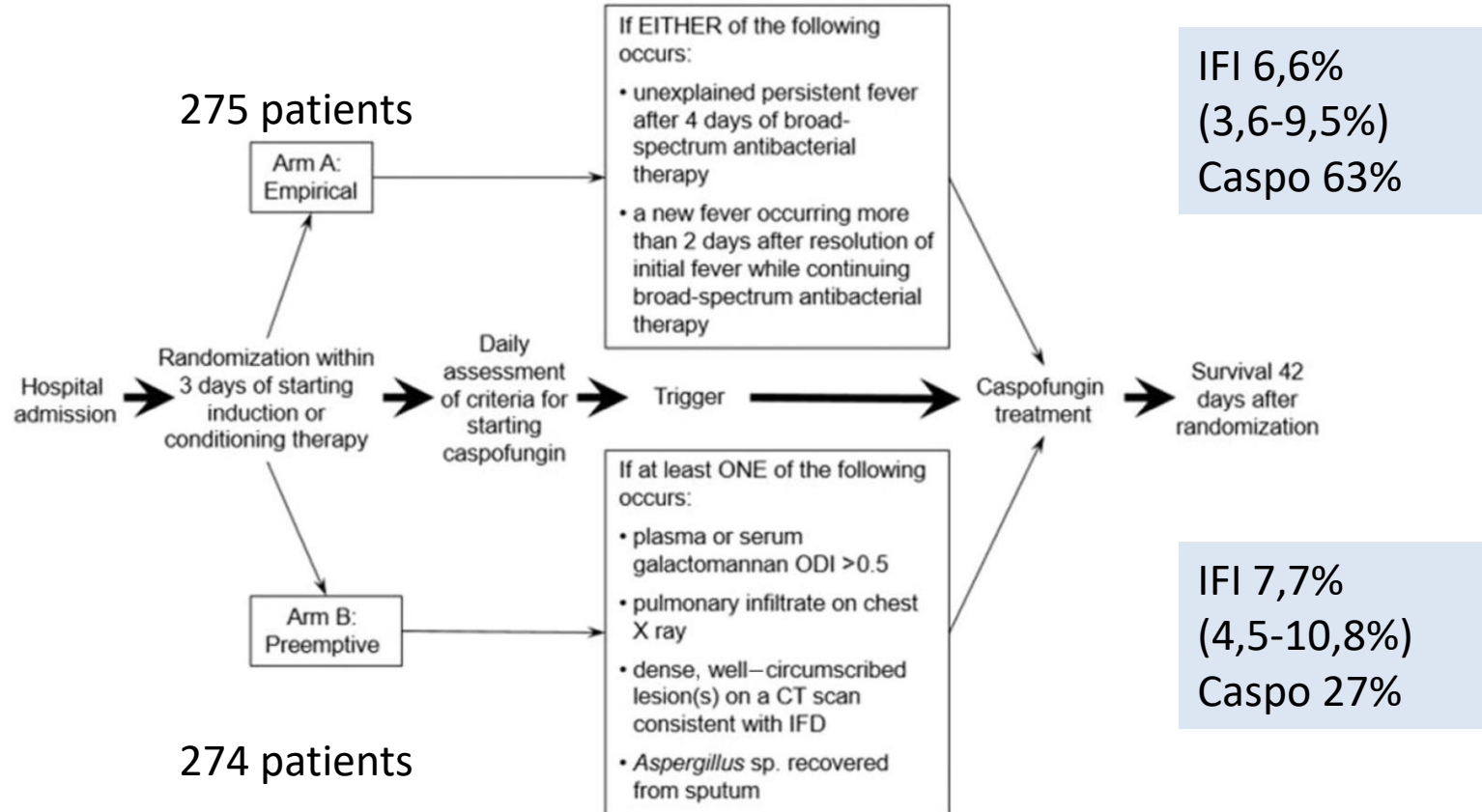


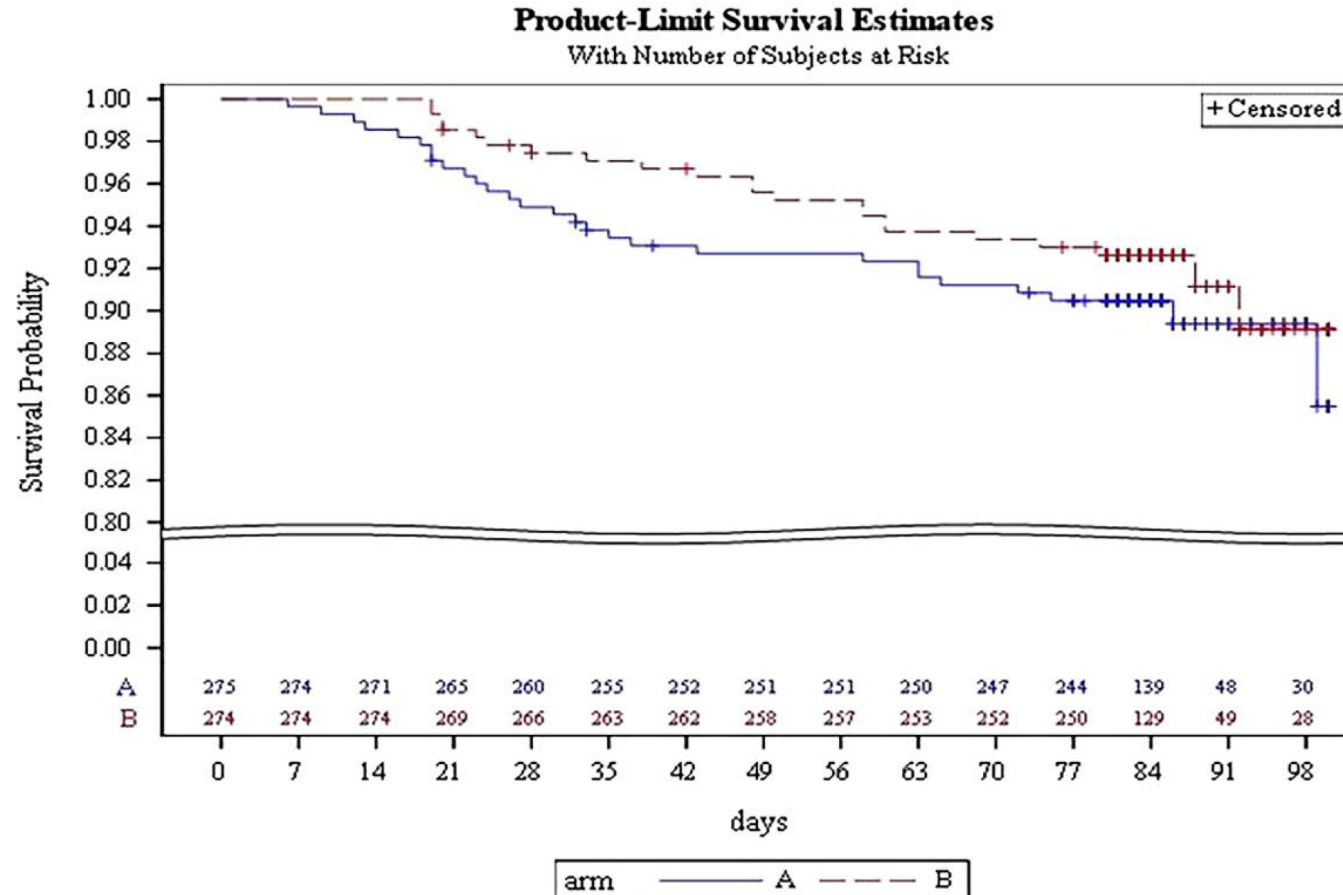
Réseau RESSIF



Phase III, randomisé

Caspofungine en traitement empirique versus pré-emptif chez les patients neutropéniques à haut risque sous fluconazole





Overall survival at day 42: Arm A: 93.1% (95% CI, 89.3-95.5%) and Arm B: 96.7% (95% CI, 93.8-98.3%)

Candidémie

Candida

Rezafungin

**Echinocandine de nouvelle génération à longue demi-vie,
injection 1x/semaine (400 mg J1 – 200 mg J8 -200 mg J15 si nécessaire)**

Etude ReSTORE 2018 – 2022: candidémie et candidose invasive

Etude de non-infériorité (marge 20%) rezafungine versus caspofungine +/- FCZ
CdJ: -guérison globale (guérison clinique, radiologique et mycologique) à J14
-mortalité toute cause à J30

	Rezafungin group (n=100)	Caspofungin group (n=99)
Age	59.5 (15.8)	62.0 (14.6)
<65 years	60 (60%)	58 (59%)
≥65 years	40 (40%)	41 (41%)
Sex		
Male	67 (67%)	56 (57%)
Diagnosis		
Candidaemia only	70 (70%)	68 (69%)
Invasive candidiasis*	30 (30%)	31 (31%)

	Rezafungin group (n=98)	Caspofungin group (n=98)
Patients with ≥1 treatment-emergent adverse event	89 (91%)	83 (85%)
Treatment-emergent adverse events with incidence ≥5% in either treatment group		
Pyrexia	14 (14%)	5 (5%)
Hypokalaemia	13 (13%)	9 (9%)
Pneumonia	10 (10%)	3 (3%)
Septic shock	10 (10%)	9 (9%)

Candida

Rezafungin

	Rezafungin group (n=93)	Caspofungin group (n=94)	Treatment difference (95% CI)
All-cause mortality at day 30 (US FDA primary outcome)			
Died	22 (24%)	20 (21%)	2.4 (-9.7 to 14.4)*
Known to have died	19 (20%)	17 (18%)	..
Unknown survival	3 (3%)	3 (3%)	..
All-cause mortality at day 30 by diagnosis			
Candidaemia only	18/64 (28%)	17/67 (25%)	2.8 (-12.5 to 18.0)*
Invasive candidiasis	4/29 (14%)	3/27 (11%)	2.7 (-16.7 to 21.7)*
Global response at day 14 as assessed by DRC (EMA primary outcome)			
Cure	55 (59%)	57 (61%)	-1.1 (-14.9 to 12.7)†
Failure	28 (30%)	29 (31%)	..
Indeterminate	10 (11%)	8 (9%)	..
Global response at day 14 as assessed by DRC by diagnosis			
Candidaemia only			
Cure	39/64 (61%)	43/67 (64%)	-3.2 (-19.6 to 13.3)*
Failure	21/64 (33%)	19/67 (28%)	..
Indeterminate	4/64 (6%)	5/67 (7%)	..
Invasive candidiasis			
Cure	16/29 (55%)	14/27 (52%)	3.3 (-22.4 to 28.6)*
Failure	7/29 (24%)	10/27 (37%)	..
Indeterminate	6/29 (21%)	3/27 (11%)	..

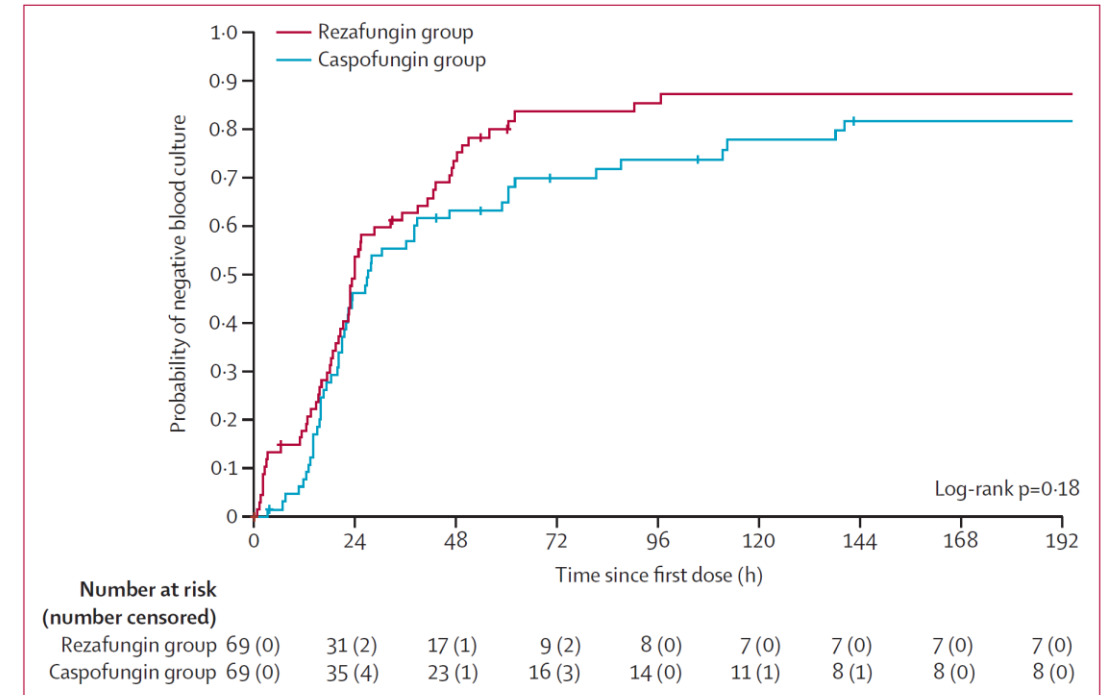


Figure 2: Time to negative blood culture after treatment with rezafungin versus caspofungin in the modified intention-to-treat population

Crypto

Cryptococcose

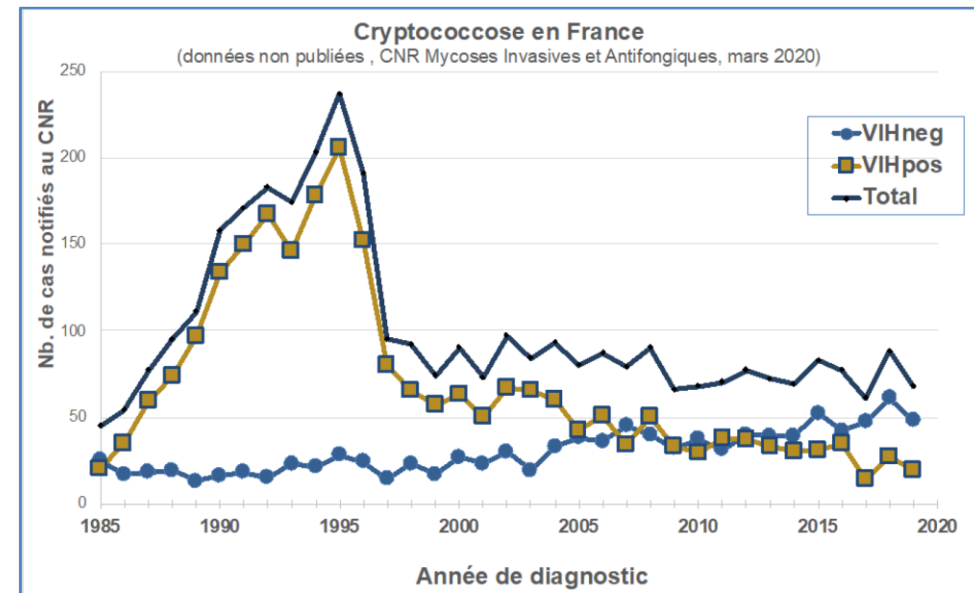
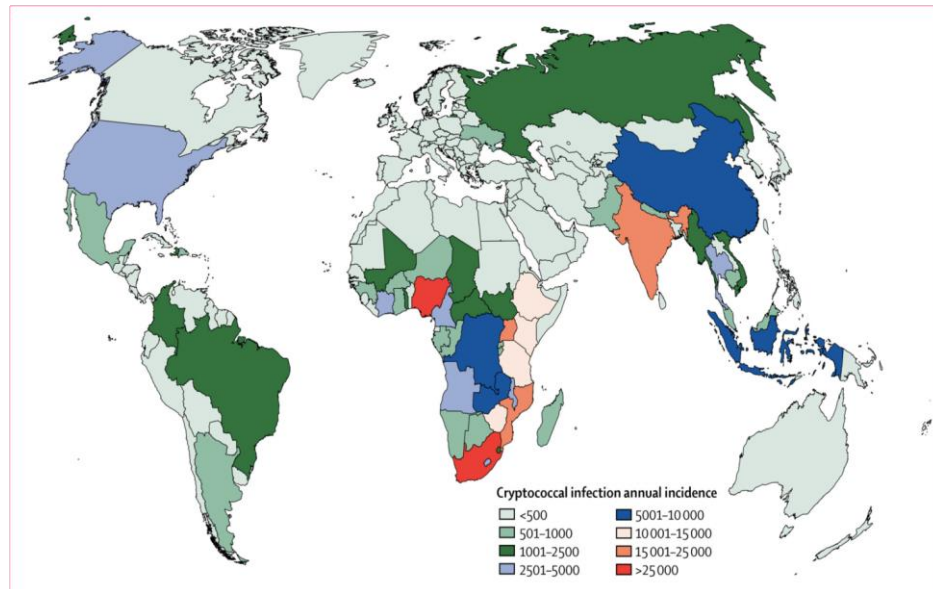


Figure 14 : Évolution des cryptococcoses déclarées en France (1985-2018)

Crypto

Traitement

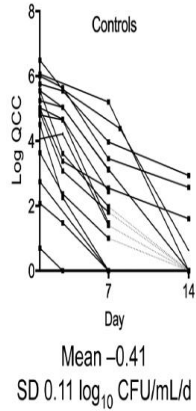
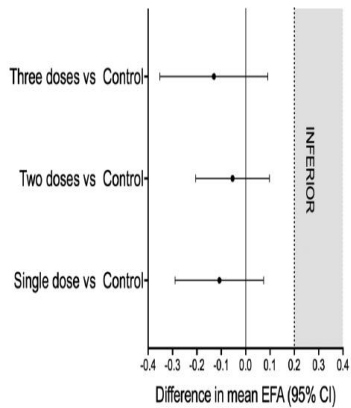


	2-week Induction therapy		Consolidation therapy	Maintenance (or secondary prophylaxis)
	1 st week	2 nd week	Week 3-10	After Week 10
Preferred regimen	Amphotericin B deoxycholate (1.0 mg/kg/day) + Flucytosine (100 mg/kg/day)	Fluconazole (1200 mg daily)	Fluconazole (800 mg daily)	
Alternative regimens: depending on drugs availability	Fluconazole (1200 mg daily) + Flucytosine (100 mg/kg/day)		ART initiation should be deferred by 4–6 weeks	Fluconazole (200 mg daily)
	Amphotericin B deoxycholate (1.0 mg/kg/day) + Fluconazole (1200 mg daily)			

Adapted from: WHO 2018

Crypto

Traitement

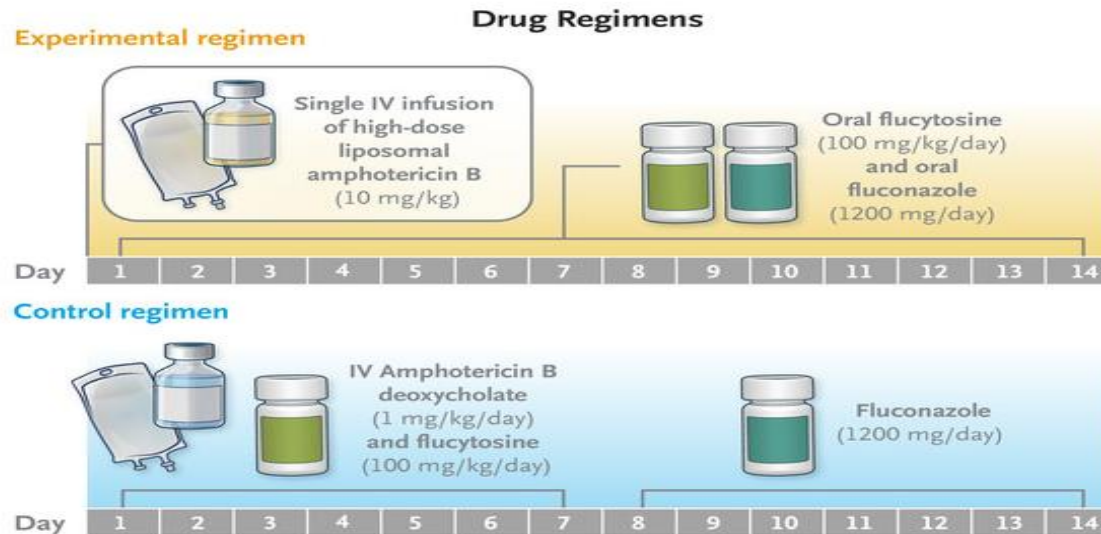


Méningite à *Cryptococcus*, VIH+
AMBITION, **phase III**

Botswana, Malawi, AF du Sud, Ouganda, Zimbabwe

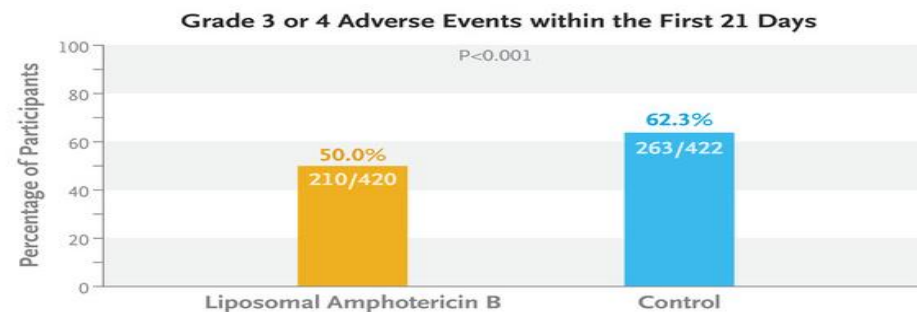
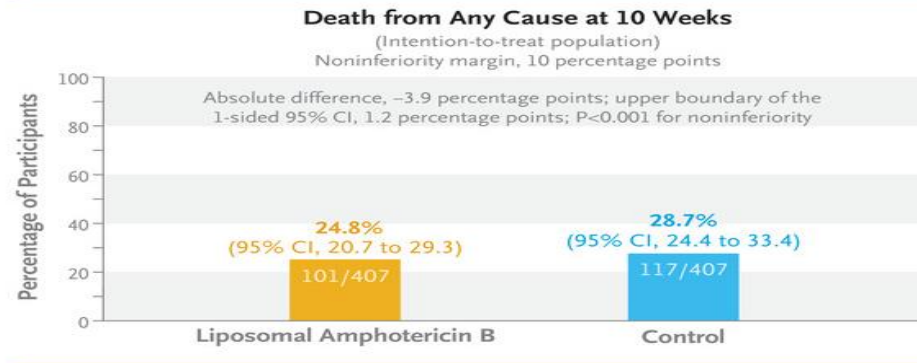
814 patients, 2 bras

- **L-AmB 10 mg/kg 1 dose + 5-FC 100 mg/kg/j + FCZ 1200 mg/j 14j**
- **d-AmB (1 mg/kg/j) + 5-FC 100 mg/kg/j 7j puis 7j 1200 mg FCZ**

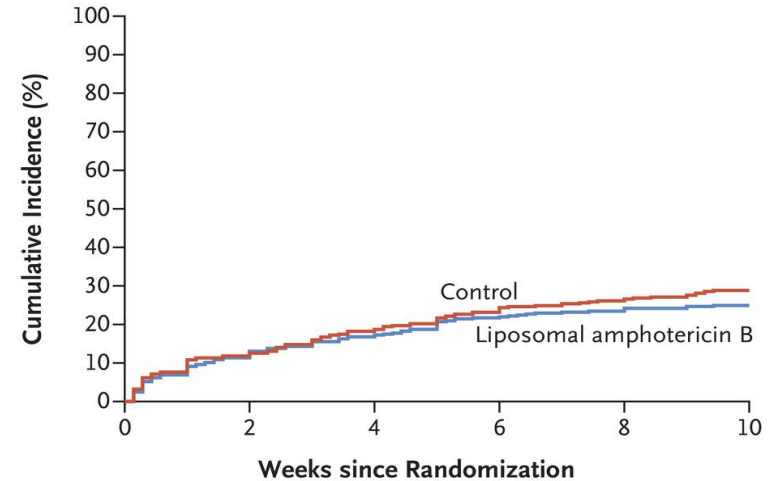


AMBITION, phase III

- L-AmB 10 mg/kg 1 dose + 5-FC 100 mg/kg/j + FCZ 1200 mg/j 14j
- d-AmB (1 mg/kg/j) + 5-FC 100 mg/kg/j 7j puis 7j 1200 mg FCZ



A All-Cause Mortality at Wk 10



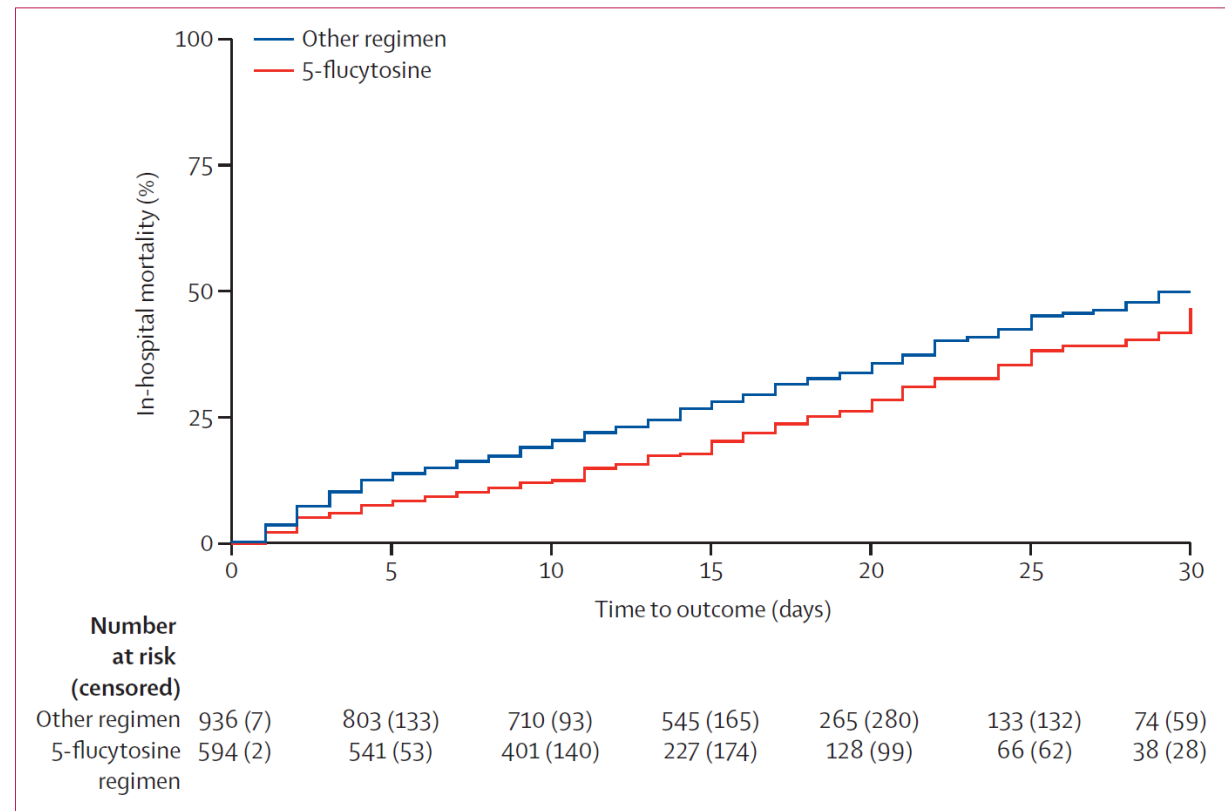
No. at Risk

	0	2	4	6	8	10
Control	407	359	332	311	299	288
Liposomal amphotericin B	407	360	337	317	310	304

Crypto

Traitement

Etude rétrospective en Afrique du Sud des crypto neuro-méningées chez le VIH+
Comparaison bas flucytosine (n=594) versus autres schémas thérapeutiques (n=936)



Crypto

Traitement - recommandations OMS 2022

	2-week Induction therapy		Consolidation therapy	Maintenance (or secondary prophylaxis)
	Week 1	Week 2	Week 3-10	After Week 10
Preferred regimen	Liposomal Amphotericin B 10 mg/kg/day 1 day + Flucytosine (100 mg/kg/day) 14 days + Fluconazole (1200 mg daily) 14 days		Fluconazole (800 mg daily)	Fluconazole (200 mg daily)
Alternative regimens: depending on drugs availability	Fluconazole (1200 mg daily) + Flucytosine (100 mg/kg/day)		ART initiation should be deferred by 4–6 weeks	Fluconazole (200 mg daily)
	Amphotericin B deoxycholate (1.0 mg/kg/day) + Flucytosine (100 mg/kg/day) 7 days	Fluconazole (1200 mg daily)		

Utilisable en Europe chez le patient VIH?

Single-dose AmBisome-based treatment for cryptococcal meningitis in high-income settings

Antifungal activity

Single, high-dose AmBisome-based treatment is at least as fungicidal as 14 days of standard-dose AmBisome

Antifungal activity should not differ between settings



Side effects

The single-dose AmBisome regimen has fewer side effects than 14 days of standard dosing

The improved toxicity profile will be beneficial in all settings



Acceptability

Patient and provider preference for the single-dose AmBisome combination regimen is likely to apply in high-income settings

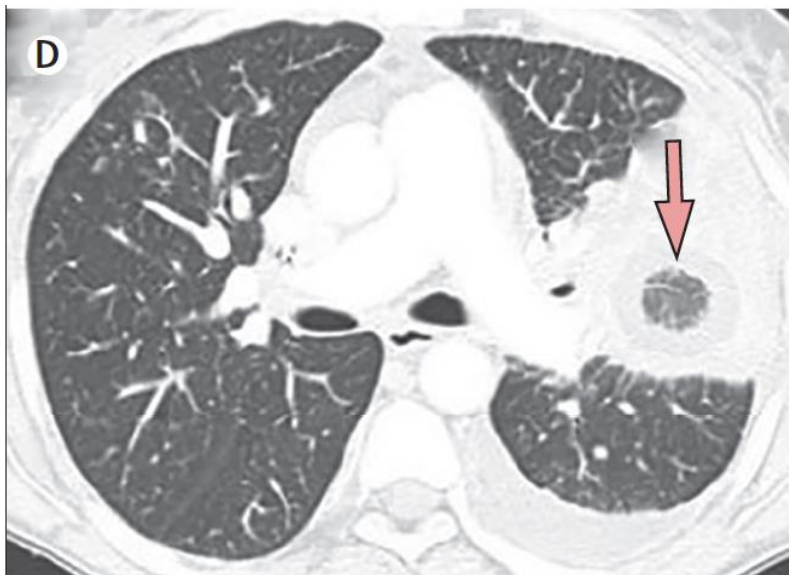


Cost

In settings with high hospitalization and medication costs, the single, high-dose AmBisome regimen will likely be cost-saving



Mucormycoze



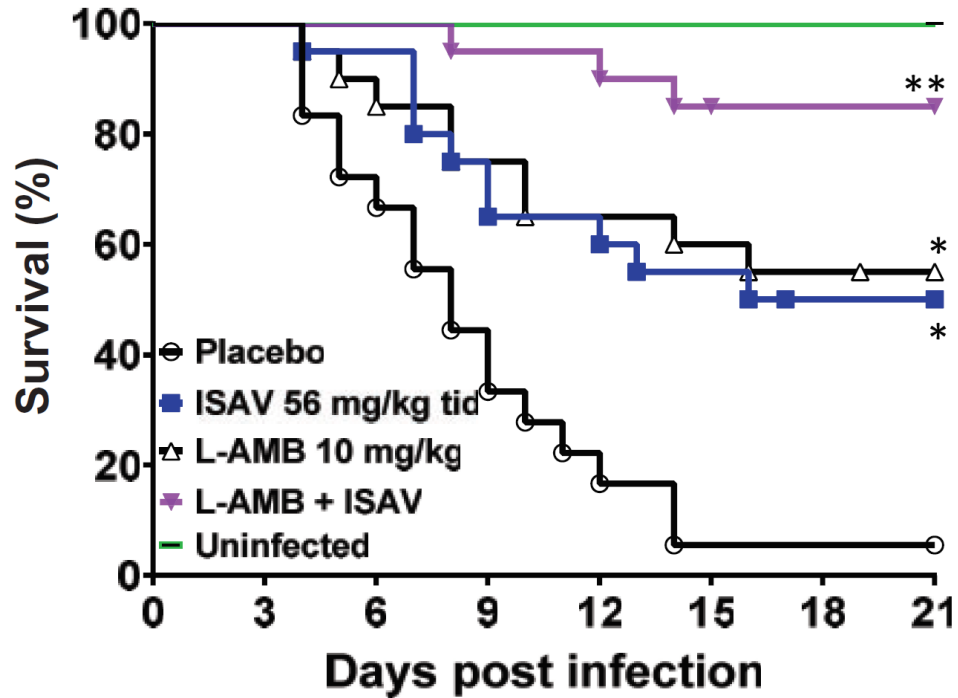
- Etude prospective française, 232 patients suspicion d'IFI
- qPCR ciblant les espèces *Lichtheimia*, *Rhizomucor* et *Mucor/Rhizopus*
- **Sensibilité 85·2%, spécificité 89·8%**
- **Diagnostic précoce:** Positivité 4 jours avant les prélèvements myco/histo and 1 jour avant l'imagerie
- **Marqueur pronostique:** négativité de la PCR Mucorales 7 jours après l'initiation de l'L-AmB associée à une mortalité à J30 inférieure (p= 0·02).

Mucor

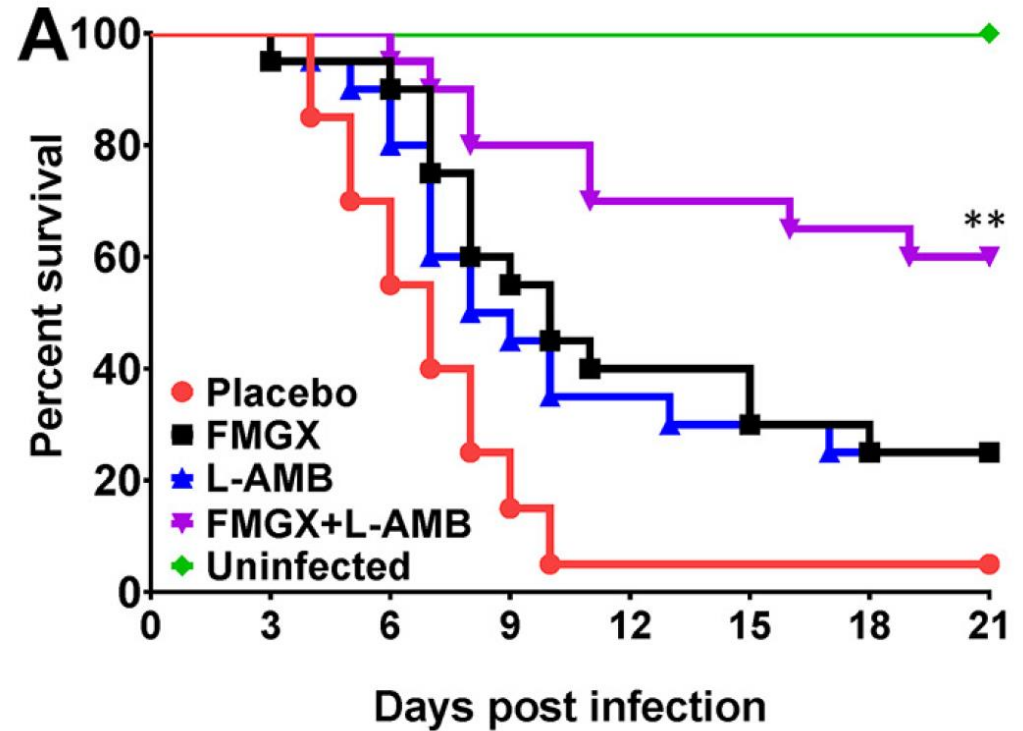
Mucormyose traitement

Modèles murins de mucormyose disséminée

L-AmB + ISA

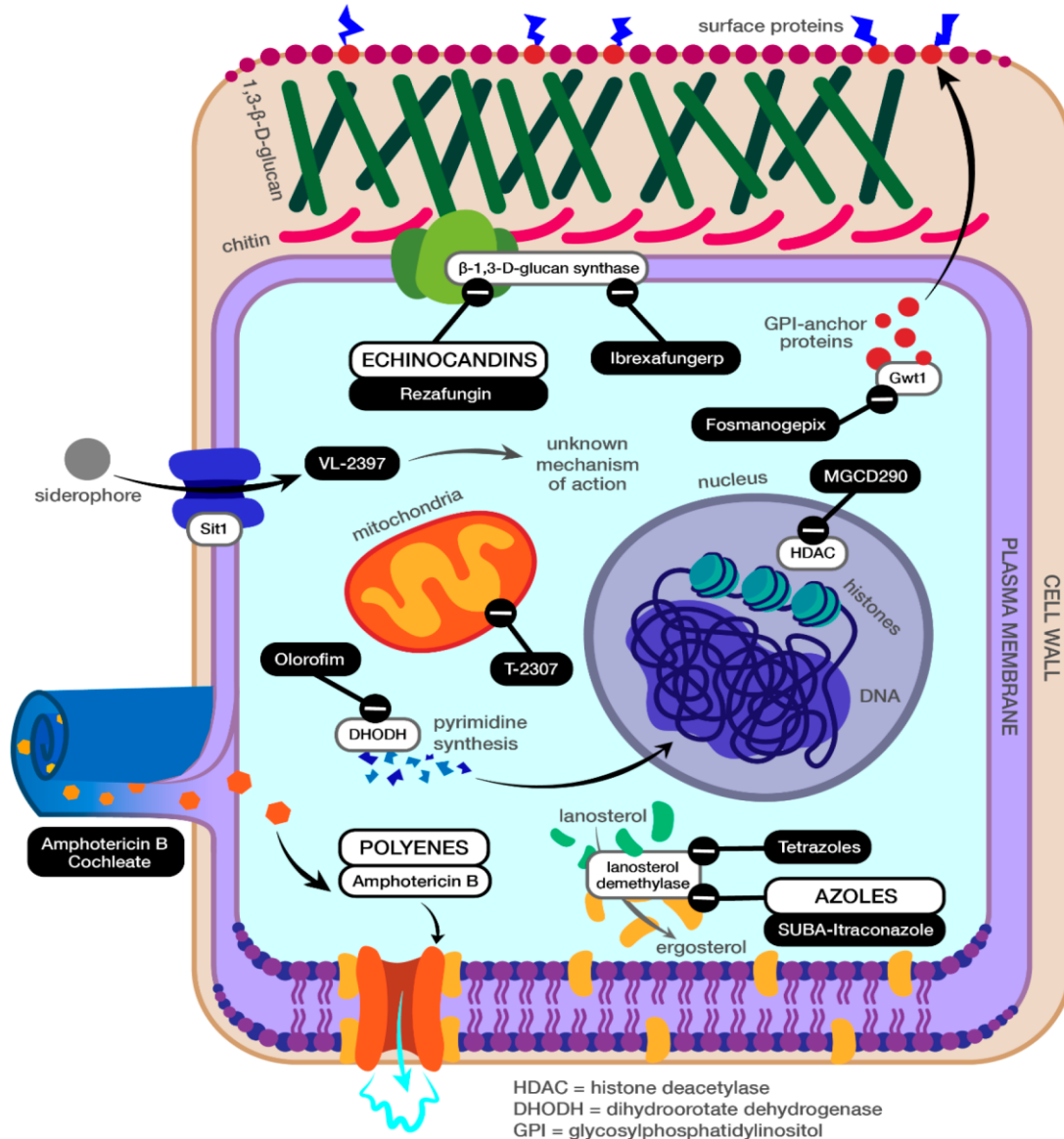


L-AmB + Fosmanogepix



Next
years

Nouvelles Molécules aspergillose invasive



- **Ibrexafungerp**, inhibiteur synthèse BDG
=> Phase 2: VCZ + Ibrexaf. vs VCZ
- **Olorofim** : inhibiteur de dihydro-orotate dehydrogenase
=> Phase 3: olorofim vs L-AmB puis SOC
- **Fosmanogepix** : inhibeur de l'Enzyme fongique Gwt1,
=> phase 2
- **Opelconazole** : azolé inhalé
=> Phase 3: Opelconazole + SOC vs SOC

- IFI
 - Stratégie pré-emptive équivalent à stratégie empirique, cost-effective
- Candidémie
 - Augmentation de l'incidence
 - Rezafungine (Rezzayo): 1 injection par semaine, accord FDA: candidémie avec alternative limitée ou sans alternative
- Cryptococcose+VIH : nouvelles recommandations
 - > monodose L-AmB + flucytosine et fluconazole 1200 mg 14 jours
- Mucormycose: PCR Mucorales, intérêt de la bithérapie dans les modèles murins
- Aspergillose invasive: études en cours avec nouvelles molécules