



Traitement de l'aspergillose invasive chez le transplanté d'organe solide: quel azolé choisir en 2017?

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CNR Mycoses Invasives et Antifongiques

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CNRS URA3012



Déclaration d'intérêts de 2013 à 2016

- Intérêts financiers :Aucun
- Liens durables ou permanents :Aucun
- Interventions ponctuelles :Gilead, MSD, Basilea
- Intérêts indirects :

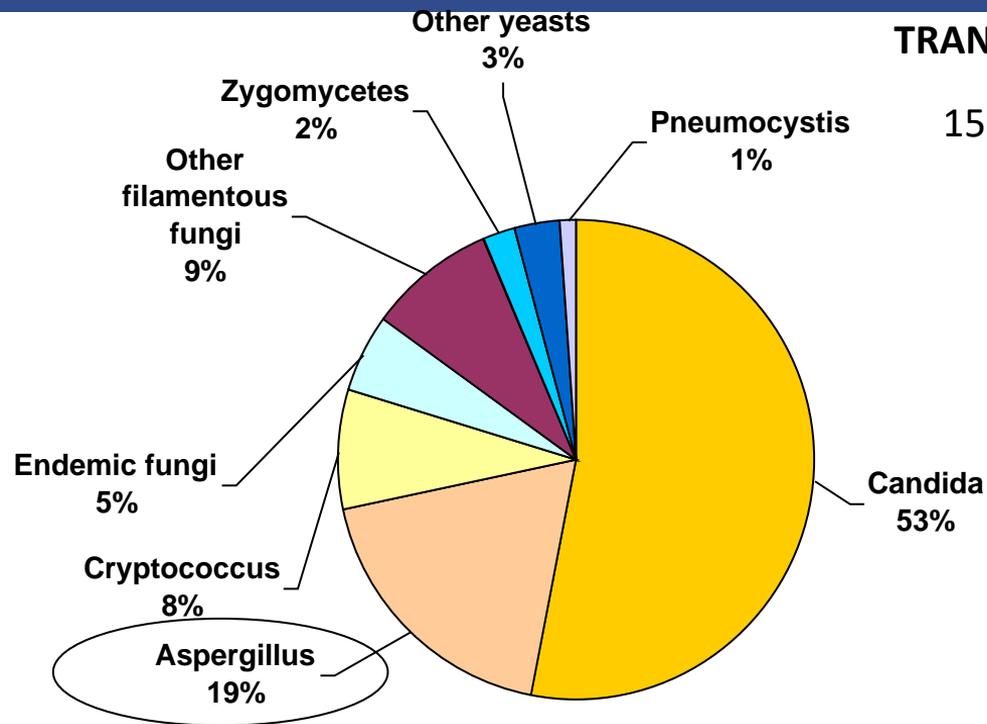
Aspergillose invasive et transplantation d'organe

TRANSNET prospective study

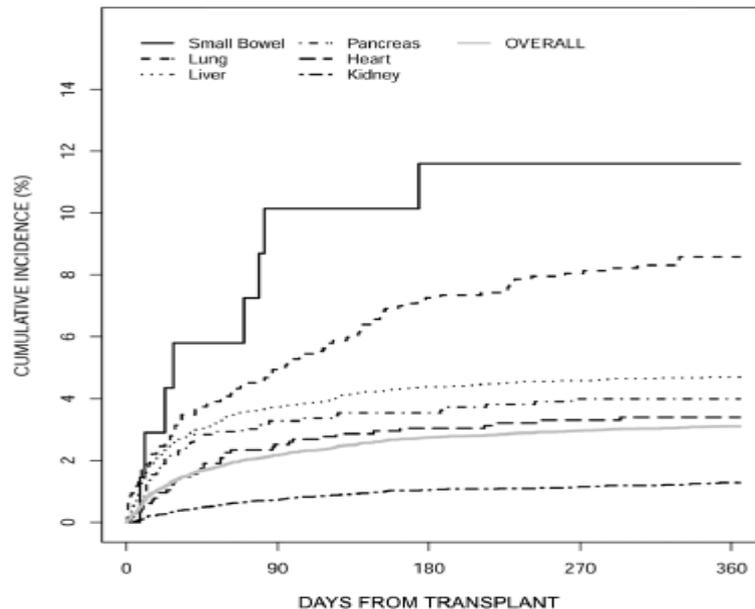
15 centres (2001 – 2006)

□ ≈ 17 000 transplantations

□ 1 208 épisodes IFI

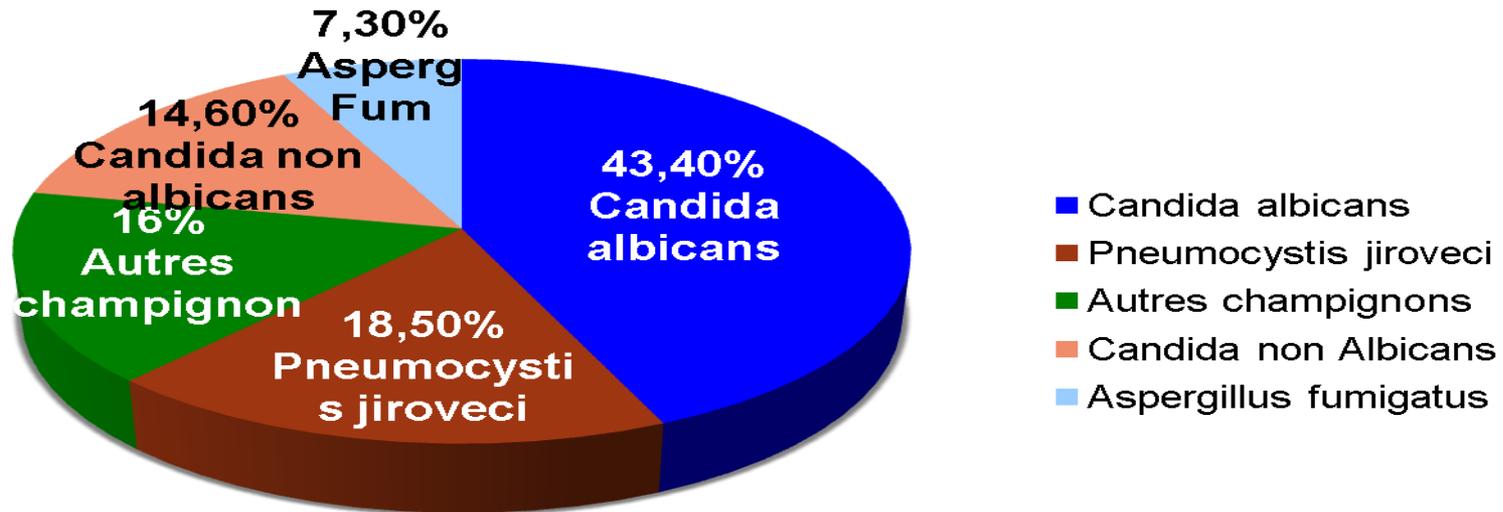


Pappas et al, Clin Infect Dis 2010



Epidémiologie dans un centre Français

- Etude monocentrique Necker Transplantation rénale adulte
- 1420 patients, greffés entre 2000-2012

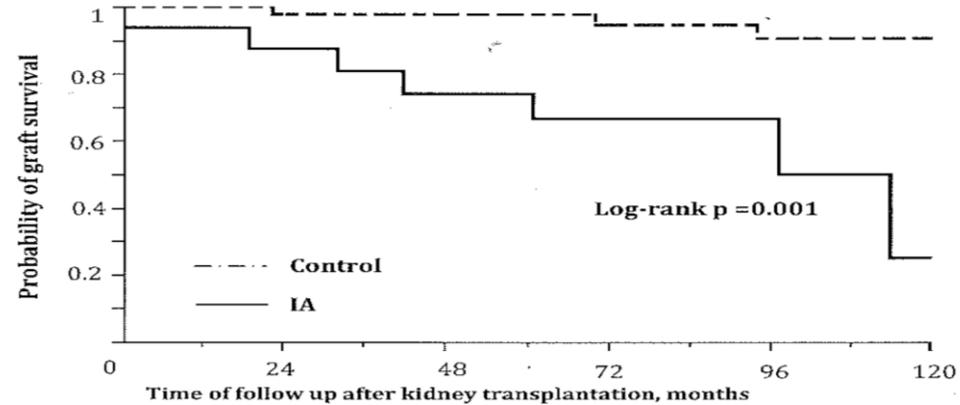
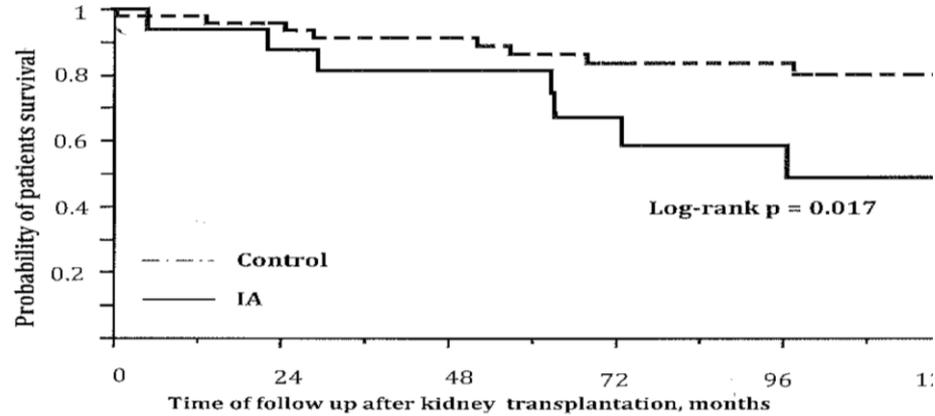


205 Infections fongiques chez 177 patients

Scemla A, données non publiées

Survie patients et greffons après aspergillose invasive

Etude cas-contrôle



Traitement antifongique de l'aspergillose: spectre

	<i>Polyènes</i>	<i>Fluco</i>	<i>Itraco</i>	<i>Vorico</i>	<i>Posaco</i>	<i>Isavu</i>	<i>Candines</i>
<i>Aspergillus fumigatus</i>	+	-	+	+	+	+	+
<i>A. terreus</i>	+/-	-	+	+	+	+	+
<i>A. lentulus</i>	+	-	-	-	-	-	+

Choix de l'antifongique:

- Efficacité
- Site de l'infection
- Hôte
- Interactions
- Dysfonction d'organe

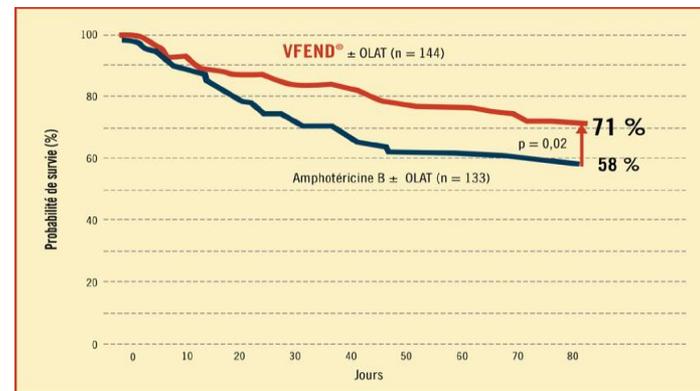
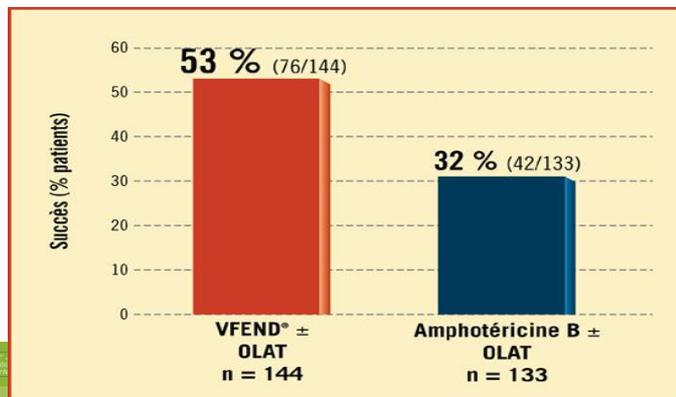
EUCAST clinical breakpoints for Aspergillus

Antifungal agent	MIC breakpoint (mg/L)											
	<i>A. flavus</i>		<i>A. fumigatus</i>		<i>A. nidulans</i>		<i>A. niger</i>		<i>A. terreus</i>		Non-species related breakpoints ¹	
	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >
Amphotericin B	IE ²	IE ²	1	2	Note ³	Note ³	1	2	-	-	IE	IE
Anidulafungin	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE
Caspofungin	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE
Fluconazole	-	-	-	-	-	-	-	-	-	-	-	-
Isavuconazole	IE ²	IE ²	1	1	0.25	0.25	IE ²	IE ²	1	1	IE	IE
Itraconazole⁴	1	2	1	2	1	2	IE ^{2,5}	IE ^{2,5}	1	2	IE ⁵	IE ⁵
Micafungin	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE
Posaconazole⁴	IE ²	IE ²	0.125 ⁶	0.25 ⁶	IE ²	IE ²	IE ²	IE ²	0.125 ⁶	0.25 ⁶	IE	IE
Voriconazole⁴	IE ²	IE ²	1	2	IE	IE	IE ²	IE ²	IE ²	IE ²	IE	IE

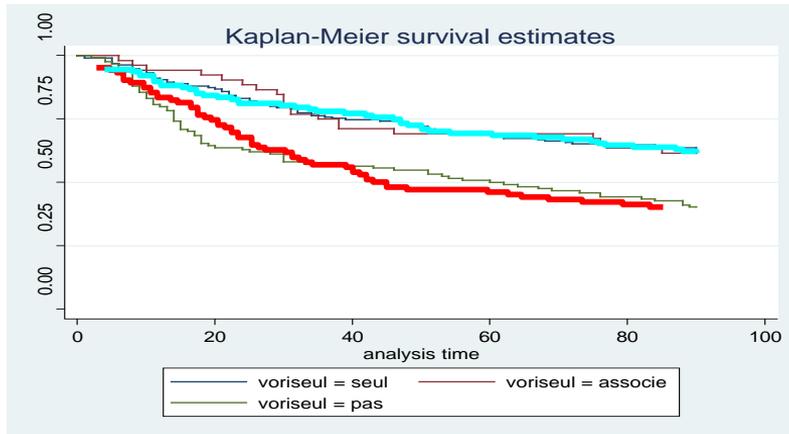
Voriconazole dans le traitement de l'aspergillose invasive

- AI prouvée ou probable, 1997-2000
- Voriconazole IV (n=144)
- Amphotéricine B deoxycholate (n=133) 1-1,5 mg/kg/j
- Réponses à S12

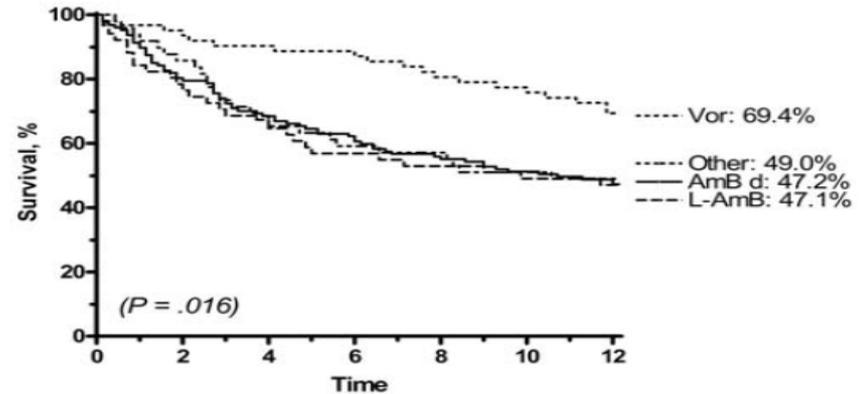
Herbrecht R, NEJM, 2002



Impact du traitement initial des AI

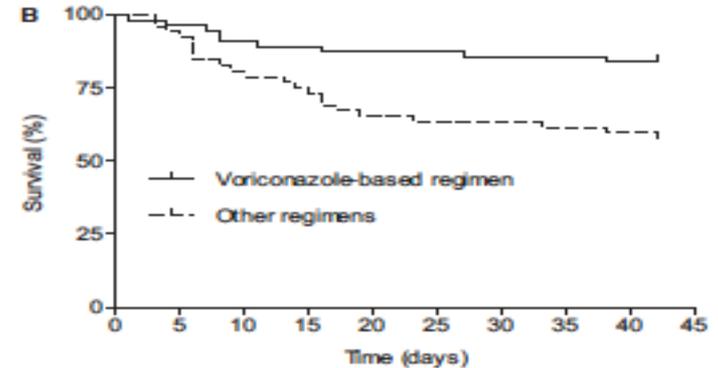


Vori +/- OLAT
Ampho B +/- OLAT



Voriconazole dans le traitement de l'aspergillose en Transplantation: réduction de mortalité

- 112 IA TR, 33 institutions
- 28 AI prouvées, 84 probables
- **Facteurs de mortalité précoce:**
 - Infection précoce
 - Atteinte bilatérale
 - Absence de traitement par voriconazole
- **116 IA T hépatiques**
 - Voriconazole: augmentation de la survie



Lopez-Medrano et al, AJT 2016, Barchiesis F, Liver Tr 2015

Suivi thérapeutique du voriconazole

- **Monitoring taux voriconazole 52 patients avec IFI prouvée, probable ou possible**
- **≤ 1 mg/L:**
 - 13 (25%) des patients
 - 6 (46%): échec, réponse après adaptation des doses chez tous les patients
- **$> 5,5$ mg/L:**
 - 16 (31%)
 - 5 encéphalopathies réversibles

Pascual A, CID 2008

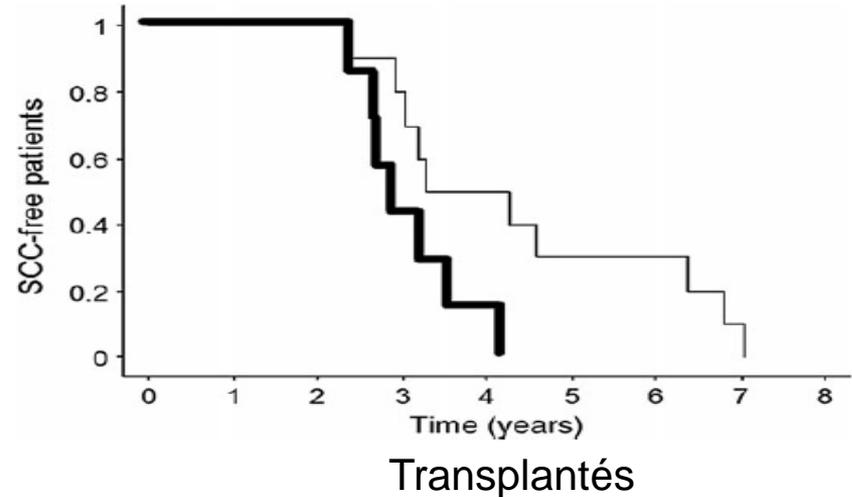
Algorithme pour prédire l'hépatotoxicité du voriconazole chez le transplanté pulmonaire

- Prophylaxie par voriconazole chez le transplanté pulmonaire
- 2006-2010: 361 patients
- Algorithme prédictif de l'hépatotoxicité: 70%

Variable	Hepatotoxicity N = 54 (%)	No hepatotoxicity N = 51 (%)	Univariate analysis	
			Crude OR (95% CI)	p-Value
Perioperative initiation of voriconazole	47 (87)	27 (53)	5.97 (2.27–15.68)	0.0001
Cystic fibrosis	30 (56)	13 (25)	3.65 (1.60–8.36)	0.002
Liver disease	12 (22)	5 (10)	2.63 (0.85–8.09)	0.092
Azathioprine	40 (74)	28 (55)	2.35 (1.03–5.33)	0.042
Age < 40	27 (50)	16 (31)	2.19 (0.99–4.85)	0.054

Complications d'un traitement prolongé par voriconazole

- 2002-2012
- 19 carcinomes epidermoïdes
- 35 mois après le début du ttt
- 1^{ère} année: phototoxicité
- 2^{nde} année: kératose actinique
- 3^{ème} année: carcinome épidermoïde



Surveillance dermatologique

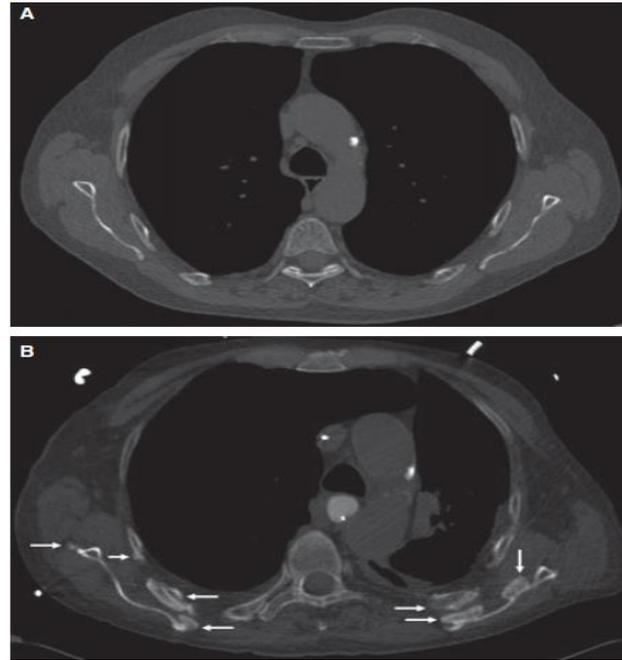
Azolés et neuropathies périphériques

- 220 patients traités par azolés
- 10% de neuropathies
- Survenue à M4
- 9% sous voriconazole
- 3% sous sous posaconazole
- 2 épisodes non réversibles

» Baxter, JAC 2011

Périostite et voriconazole

- **Voriconazole: trifluoré**
- **Exposition prolongée,**
- **Dès 6 semaines**
- **Fortes posologie**
- **Douleurs**
- **PA et fluor élevé**
- **Périostite (scinti)**
- **Enfants**



Prise en charge thérapeutique de l'AI: posaconazole

- **Pas de données disponibles en curatif avec les formulations comprimés et IV**

Isavuconazole

- Nouvel azolé large spectre
- IV et PO
- Pas de cyclodextrine
- Activité in vitro activity Candida, Aspergillus, Mucorales
- 200mg X 3/J J1-J2 puis 200mg/j
- Biodisponibilité 98%

Table 2
Total numbers and MIC distributions for *Aspergillus* species

	n (%)	Isavuconazole MIC (mg/L)				Voriconazole (mg/L)			
		MIC range	MIC ₅₀	ECOFF	MIC > ECOFF (%)	MIC range	MIC ₅₀	ECOFF	MIC > ECOFF (%)
<i>A. fumigatus sensu stricto</i>	211 (69.0)	≤0.125→16	1	2	13.7	≤0.125→16	0.5	1	15.2

Isavuconazole: Cresemba®

- Métabolisé CYP3A4, CYP3A5
- Pas de diffusion dans le LCR ni dans les urines

Type of Interaction, Drug	Recommendation
Increases isavuconazole level	
Lopinavir/ritonavir	Use with caution
Decreases isavuconazole level	
Rifampin	Contraindicated
Carbamazepine	
Long-acting barbiturates	
St John's wort	
Levels increased by isavuconazole	
Sirolimus	Use with caution. Monitor serum levels of these drugs and adjust dose when given with isavuconazole
Tacrolimus	
Cyclosporine	
Mycophenolate mofetil	
Digoxin	
Colchicine	Use with caution. May require dose adjustment
Dagibatran	
Atorvastatin	No dose adjustment recommended when given with isavuconazole; monitor patient
Midazolam	
Levels decreased by isavuconazole	
Bupropion	Use with caution. Dose increase of bupropion may be

Isavuconazole et aspergillose invasive

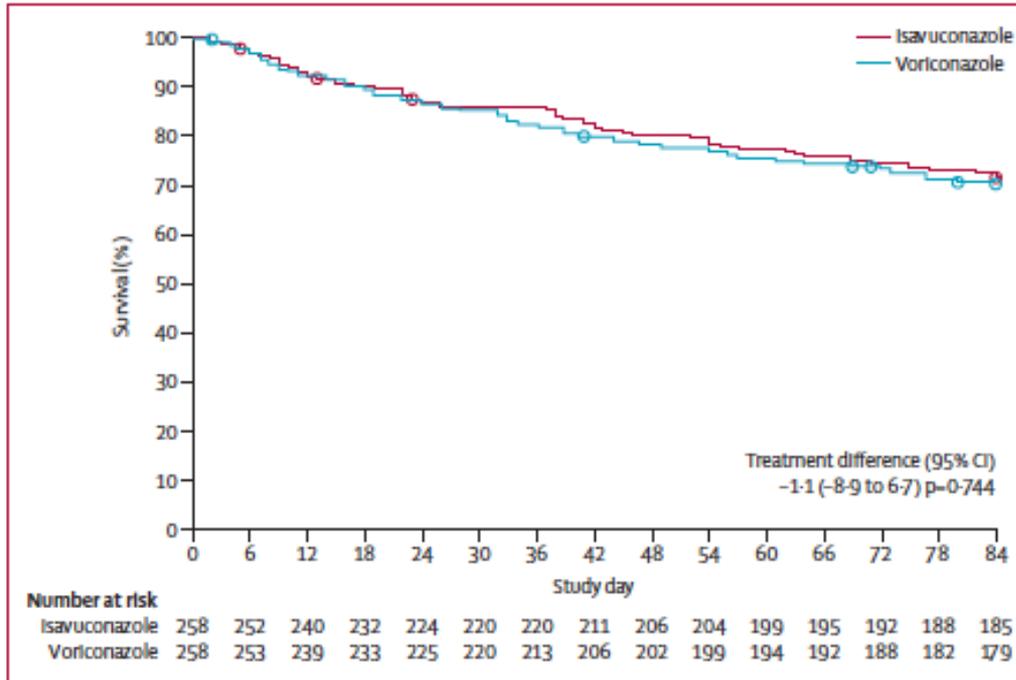


Figure 2: Survival from first dose of study drug to day 84

Patients were censored on the day of their last known survival status, represented by the circles. Figure shows data for ITT population. ITT=intention to treat; all randomised patients who received study drug.

Isavuconazole: tolérance

	Isavuconazole (n=257)	Voriconazole (n=259)	p value
Overall	247 (96%)	255 (98%)	0.122
Gastrointestinal disorders	174 (68%)	180 (69%)	0.705
Infections and infestations	152 (59%)	158 (61%)	0.719
General disorders and administrative site conditions	148 (58%)	144 (56%)	0.658
Respiratory, thoracic, and mediastinal disorders	143 (56%)	147 (57%)	0.859
Metabolism and nutrition disorders	108 (42%)	121 (47%)	0.289
Nervous system disorders	95 (37%)	89 (34%)	0.582
Skin and subcutaneous tissue disorders*	86 (33%)	110 (42%)	0.037¶
Investigations (abnormal laboratory tests)	85 (33%)	96 (37%)	0.357
Blood and lymphatic system disorders	77 (30%)	82 (32%)	0.703
Psychiatric disorders†	70 (27%)	86 (33%)	0.151
Musculoskeletal and connective tissue disorders	69 (27%)	77 (30%)	0.495
Vascular disorders	67 (26%)	77 (30%)	0.378
Renal and urinary disorders	55 (21%)	58 (22%)	0.832
Cardiac disorders	43 (17%)	57 (22%)	0.148
Eye disorders‡	39 (15%)	69 (27%)	0.002¶
Injury, poisoning, and procedural complications	33 (13%)	39 (15%)	0.526
Hepatobiliary disorders§	23 (9%)	42 (16%)	0.016¶
Immune system disorders	20 (8%)	25 (10%)	0.533
Neoplasms benign, malignant and unspecified	19 (7%)	31 (12%)	0.101
Ear and labyrinth disorders	14 (5%)	13 (5%)	0.846
Reproductive system and breast disorders	8 (3%)	13 (5%)	0.373
Endocrine disorders	5 (2%)	3 (1%)	0.503
Congenital, familial, and genetic disorders	3 (1%)	2 (1%)	0.685
Social circumstances	0	1 (<1%)	>0.999

Maertens J, Lancet 2016

Gestion voriconazole et isavuconazole

	Isavuconazole	Voriconazole
Nombre de prise par jour	1/j	2/j
Rapport repas	Indifférent	A jeun
Insuffisance rénale et hémodialyse	Pas d'ajustement de dose	Pas d'ajustement de dose Forme IV Creat >250
Insuffisance hépatique modérée	Pas d'ajustement de dose	Ajustement
Objectif résiduel	2-5 mg/L	1-5 mg/L
QT	Raccourci	Allongé

Townsend RW Eur J Clin Pharmacol 2017, Desai A, AAC, 2016

Interactions

	Voriconazole	Isavuconazole
T1/2	8h	80h
Métabolisme	Hépatique	Hépatique
Inhibe UGT (MMF)	-	+
Tacrolimus	Diminution 50-60%	+ Cmax 42%
Sirolimus	Contre indiqué	+ Cmax 65%

Cout indicatif

Spécialité	Prix unitaire	Statut
Isavuconazole 200mg IV	391€	Hors GHS
Isavuconazole gel 100mg	47 €	Hors GHS
Posaconazole 300mg IV	379 €	In GHS
Posaconazole 100mg cp	30 €	In GHS
Posaconazole suspension 4,2g	584 €	In GHS
Voriconazole 200mg cp	1 €	In GHS
Voriconazole IV 2800mg	475 €	Hors GHS

Cout indicatif APHP

Gestion du traitement IS

- 68 AI transplantés pulmonaires
- Arrêt anticalcineurines: risque IRIS

Singh N, Transplant Immunol 2013

Recommandations IDSA 2016

- **Correction facteur favorisant**
- **1ère ligne**
 - Vfend PO ou IV (formes sévères)
 - LAmB, isavuconazole: Alternative
 - Combinaison vori et echino peut être discutée chez des patients sélectionnés

Recommandations Européennes ESCMID en cours

Recommandations ECIL-6

Première ligne

Table 7. ECIL-6 recommendations for first-line treatment of invasive aspergillosis.

	Grade	Comments
Voriconazole ^a	A I	Daily dose: 2x6 mg/kg on day 1 then 2x4 mg/kg (initiation with oral therapy: C III)
Isavuconazole	A I	As effective as voriconazole and better tolerated
Liposomal amphotericin B	B I	Daily dose: 3 mg/kg
Amphotericin B lipid complex	B II	Daily dose: 5 mg/kg
Amphotericin B colloidal dispersion	C I	Not more effective than d-AmB but less nephrotoxic
Caspofungin	C II	
Itraconazole	C III	
Combination voriconazole ^a + anidulafungin	C I	
Other combinations	C III	
Recommendation against use		
Amphotericin B deoxycholate	A I	Less effective and more toxic

^aMonitoring of serum levels is indicated. In the absence of sufficient data for first-line monotherapy, anidulafungin, micafungin and posaconazole have not been graded.

Recommandations chez le transplanté d'organe

Table 3: Antifungal therapy for invasive aspergillosis in adult organ transplant recipients

Drug	Dosing (Adult)	Comments
Primary therapy		
Voriconazole	6 mg/kg IV every 12 h for 1 day, followed by 4 mg/kg IV every 12 h; oral dosage is 200 mg every 12 h	Monitoring of plasma drug levels of voriconazole, hepatic aminotransferase levels and calcineurin agent levels is recommended
Alternative agents		
Liposomal amphotericin B (AmBisome®)	3–5 mg/kg/day IV	Higher dosages are not more effective
Amphotericin B Lipid Complex (Abelcet®)	5 mg/ kg/day IV	Higher dosages are not more effective
Caspofungin	70 mg day 1 IV and 50 mg/day IV thereafter	Has been evaluated only as salvage therapy. Its role as single agent therapy is controversial
Micafungin ¹	100–150 mg IV qd	May be used as alternative therapy in cases of intolerance or disease refractory to primary therapy
Posaconazole ¹	200mg qid initially and then 400mg po bid	May be used as alternative therapy in cases of intolerance or disease refractory to primary therapy
Itraconazole ²	200–400 mg/day orally	Use should be considered only in mild cases intolerant to other therapies. Itraconazole oral solution and capsule are not bioequivalent and should not be used interchangeably. Therapeutic drug monitoring is recommended intolerance or disease refractory to primary therapy

Duration of therapy for aspergillosis has not been optimally defined. Most experts recommend continuing treatment of infection until resolution or stabilization of all clinical and radiographic manifestations. Generally, treatment is continued for a minimum of 6–12 weeks.

¹Currently micafungin and posaconazole do not have an approved indication for the treatment of invasive aspergillosis.

²IDSA guidelines (2008) recommend 600 mg/day for 3 days, followed by 400 mg/day.

ASPERGILLOSES SNC

- **Mauvaise pénétration des AF: caspo, posa, ampho B**
- **Bonne pénétration voriconazole**
- **Traitement**
 - Voriconazole
 - Chirurgie

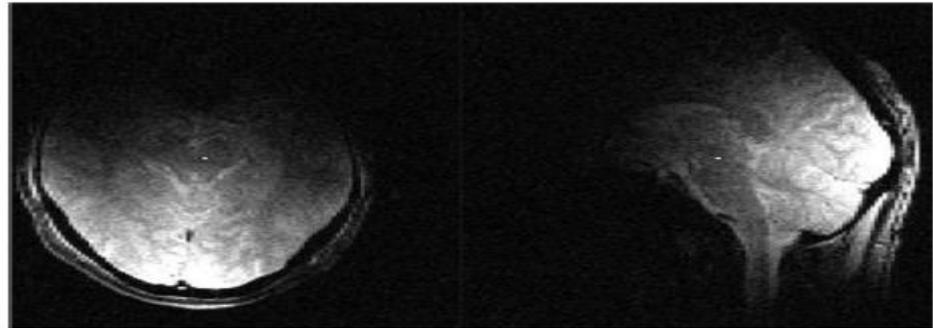


FIG 1 Illustration of the portion of the occipital lobe from which MRS data were collected. The brightest regions correspond to areas of maximum coil sensitivity with the major contribution from brain tissue.

Voriconazole ou Isavuconazole

- **Efficacité:**
 - Non inférieure dans les formes pulmonaires d'aspergillose en hématologie
 - Autres localisation? Autres terrains? Long terme?
- **Interactions:**
 - Moindre pour l'isavuconazole
 - Demi-vie très prolongée
- **Modalités d'administration:**
 - Facilité de prise
 - Peu de variabilité interindividuelle
- **Tolérance**
 - Meilleure sur le court terme pour l'isavuconazole, long terme?
 - Envisager un relais du voriconazole précoce (à 3 mois pour neurotoxicité, à 6 mois pour carcinogénèse cutanée)