IRIS ET TB EN 2024: OÙ EN EST-ON?

4 0ctobre 2024

Pre Anne Bourgarit

Médecine Interne Polyvalente et Immunologie Clinique, CHU Jean Verdier, HUPSSD

Université Sorbonne Paris Nord

CIMI - UMRS SU – Inserm U1135 – CNRS EMR 8255

Immunité, **infection** et **cancer** des cellules **NK & T**

Conflits d’intérêts

- AB ne déclare aucun conflit d’intérêt sur le sujet
- Financements par PHRC, STIC, ANRS

Objectifs pédagogiques et plan

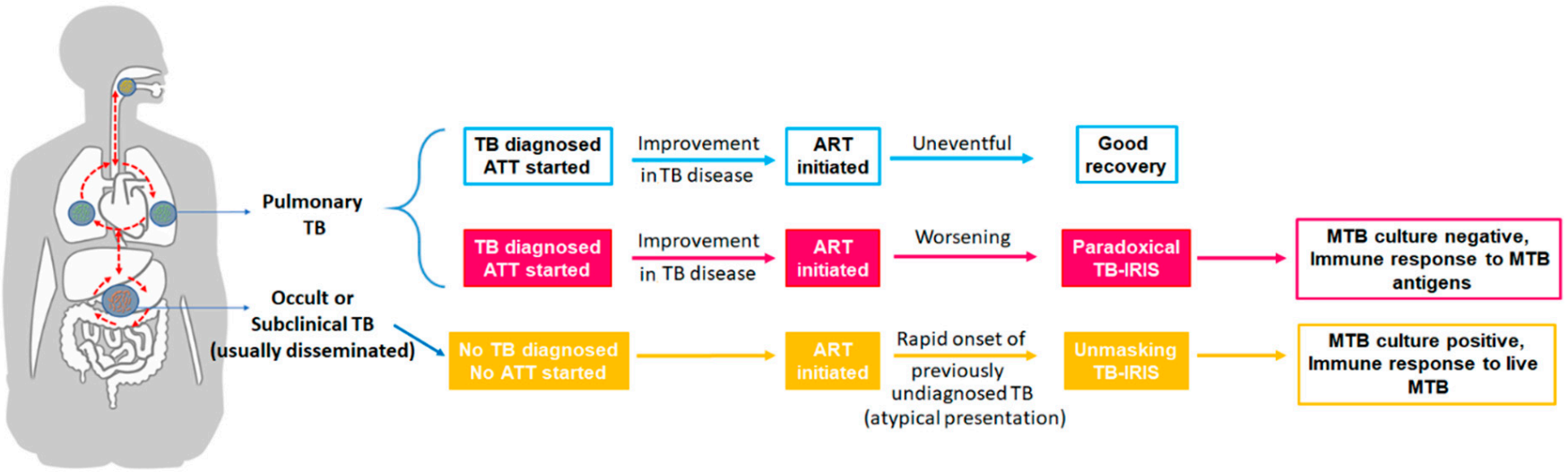
- IRIS ou sd de reconstitution immunitaire/Aggravations paradoxales quoi de neuf en :
  - Définitions
  - Epidémiologie
  - Physiopathologie
  - Diagnostic
  - Traitement

Ce que l'on sait déjà

Knowledge summary	
Incidence	Adults overall: 18% (95% CI 16–21%), with a range of 4–54%; higher rates in patients with lower CD4 counts (up to 57% in patients with CD4 count <200 cells/μl).
	South African children: 6.7% reported in a recent prospective study
Risk factors	Low CD4 count at ART initiation; High HIV viral load at ART initiation
	Shorter time between TB treatment initiation and ART initiation
	Disseminated TB/high mycobacterial load.
Clinical presentation	Systemic, pulmonary and lymph node presentations most common
	In a recent study, median days to symptom onset reported as 6 (range 1–23)
Mortality	All-cause mortality rate of 7% (95% CI 4–11%) and IRIS-attributable deaths of 2% (95% CI 1–3%)
	Higher mortality in CNS TB-IRIS
Pathogenesis	Innate immune cell activation, including neutrophils, monocytes and NK cells; Antigen-specific upregulation of cytotoxic mediators Inflammasome activation; Hypercytokinaemia (including IL-1β, IL-6 and TNF-α) and MMP upregulation/ secretion
Treatment	Prednisone (1.5 mg/kg for 2 weeks followed by 0.75 mg/kg for 2 weeks) for treatment of paradoxical TB-IRIS reduced length of hospital admission and number of therapeutic procedures required, and improved symptoms in paradoxical TB-IRIS
	Consensus is not to stop ART, but to investigate fully for alternative causes, and provide symptomatic treatment
Prevention	Prednisone (40 mg daily for 2 weeks, followed by 20 mg daily for 2 weeks) from ART initiation reduces the risk of future paradoxical TB-IRIS by 30%
	Do not delay ART initiation beyond 2 weeks after TB treatment initiation in patients with CD4 count <50 cells/mm^3, unless CNS TB diagnosed (then delay 4–8 weeks). Early ART improves survival in patients with CD4 < 50 cells/mm^3 even though it increases TB-IRIS risk > two-fold

Walker curr op HIV 2018

Définitions



Vignesh pathogens 2023

Aggravations paradoxales de la tuberculose

- Connue chez l'immunocompétent depuis l'avènement des traitements efficaces (Choremis CB, Am. Rev. Tuberc., 1955)
- Evolution spontanée des tuberculoses ganglionnaires: Ecrouelles et « pouvoir du Roi »
- 1950: premières descriptions avec les traitements antituberculeux actifs *(Choremis CB, Am. Rev. Tuberc., 1955)*
- 1996: redécouvert dans contexte VIH avec l'arrivée des antirétroviraux efficaces (HAART)
  - AZT et *M avium (French, AIDS 1992)*
  - Criteres diagnostiques *(French AIDS 2004)*
  - Definitions roupe d'expert international ISHNIH *(Meintjes ,LID 2008)*
- 2004- descriptions d'IRIS en dehors du VIH

Critères diagnostiques de l'IRIS VIH

- Critères majeurs
  - Présentation atypique d'une maladie opportuniste chez un patient répondeur au TARV
  - Décroissance de la charge virale > 1 log 10copies /ml
- Critères mineurs
  - Augmentation des CD4 après mise sous TARV
  - Augmentation de la réponse immune spécifique au pathogène (ex. IDR)
  - Résolution spontanée sans traitement spécifique et poursuite du TARV.

French M, AIDS 2004

Les principaux acteurs

Une immunodépression réversible

+

Une pathologie intercurrente avec « symptômes immunologiques »

+

Une restauration de l'immunité

=

IRIS

Les principaux acteurs: Une immunodépression réversible

- Physiologique
  - Grossesse
- Iatrogène
  - Neutropénie sous chimiothérapies
  - Immunosuppresseurs:
    - Transplantation
    - Stéroïdes
    - Biothérapies ciblées
- Infectieuse
  - VIH
  - *Mycobacterium tuberculosis, leprae (Sd de reversion?)*
  - *Cryptococcus neoformans*
  - *Tropheryma whipplei…*

Les principaux acteurs: une restauration immunitaire

- Physiologiques
  - Accouchement
- Iatrogènes
  - Arret des immunosuppresseurs
  - ARV
- Infectieuses
  - Traitement des infections
  - ARV

Détermine le délai d'apparition des symptômes d'IRIS:

- Accouchement : 4j post partum
- Arret des anti-TNF: selon molécule 3 à 6 semaines
- HAART 1 à 3 semaines (voire H12)

IRIS en dehors du VIH

- TB disséminée:
  - facteurs de risques:
    - TB disséminée
    - Lymphopénie initiale
  - présentation:
    - J 45
    - IDR phlycténulaire
    - Granulomes
- Grossesse:
  - *Cheng et al*: 29 cas de détérioration clinique de TB au 4e j postpartum (1-30) : méningite, miliaire
  - Méca? Rupture de tolérance à l'accouchement?

- R Réversion lèpre?
  - Gènes de susceptibilités dans la voie d'activation du TNF-α
  - Ac anti-PGL-Tb1 *(Lagrange PH)*
- Sorties d'aplasie, GCSF, TO…
  - Candidoses disséminées chroniques sous GCSF *(Chandesris, JMII 2010)*
  - IRIS post Cryptococose post T rénale *(Singh N, CID 2006)* associé à rejet du greffon
  - Aspergilloses de sortie d'aplasie (*Miceli M, Cancer 2007)*
  - Candidoses disséminées chroniques *(F Legrand, CID 2008*) necessitant corticotherapie systemique
  - Cryptococcose a arret de corticoides (*Narayanan, IJID 2011*)
- Arret des anti TNF

Ce que l'on sait déjà: épidemiologie

Knowledge summary	
Incidence	Adults overall: 18% (95% CI 16–21%), with a range of 4–54%; higher rates in patients with lower CD4 counts (up to 57% in patients with CD4 count <200 cells/μl).
	South African children: 6.7% reported in a recent prospective study
Risk factors	Low CD4 count at ART initiation; High HIV viral load at ART initiation
	Shorter time between TB treatment initiation and ART initiation
	Disseminated TB/high mycobacterial load.
Clinical presentation	Systemic, pulmonary and lymph node presentations most common
	In a recent study, median days to symptom onset reported as 6 (range 1–23)
Mortality	All-cause mortality rate of 7% (95% CI 4–11%) and IRIS-attributable deaths of 2% (95% CI 1–3%)
	Higher mortality in CNS TB-IRIS
Pathogenesis	Innate immune cell activation, including neutrophils, monocytes and NK cells; Antigen-specific upregulation of cytotoxic mediators Inflammasome activation; Hypercytokinaemia (including IL-1β, IL-6 and TNF-α) and MMP upregulation/ secretion
Treatment	Prednisone (1.5 mg/kg for 2 weeks followed by 0.75 mg/kg for 2 weeks) for treatment of paradoxical TB-IRIS reduced length of hospital admission and number of therapeutic procedures required, and improved symptoms in paradoxical TB-IRIS
	Consensus is not to stop ART, but to investigate fully for alternative causes, and provide symptomatic treatment
Prevention	Prednisone (40 mg daily for 2 weeks, followed by 20 mg daily for 2 weeks) from ART initiation reduces the risk of future paradoxical TB-IRIS by 30%
	Do not delay ART initiation beyond 2 weeks after TB treatment initiation in patients with CD4 count <50 cells/mm^3, unless CNS TB diagnosed (then delay 4–8 weeks). Early ART improves survival in patients with CD4 < 50 cells/mm^3 even though it increases TB-IRIS risk > two-fold

Walker curr op HIV 2018

Epidémiologie: rôle des INSTI?
Etude Cas-contrôle retrospective

TABLE 2 Mode of presentation of TB-IRIS between patients receiving INSTIs or non-INSTIs.

Variable	Patients on INSTI-containing regimen	Patients on non-INSTI-containing regimen	All patients	*p* value
Number (%) of patients with TB-IRIS	16/70 (22.9) [95% CI 13.0–32.7]	14/63 (22.2) [95% CI 12.0–32.5]	30/133 (22.6) [95% CI 15.5–29.7]	0.920
Presenting symptoms/signs at the time of TB-IRIS[a]				
Fever	7/16 (43.8)	10/14 (71.4)	17/30 (56.7)	0.127
Abdominal pain	1 /16 (6.3)	3/14 (21.4)	4/30 (13.3)	0.315
New or worsening lymphadenopathy, peripheral	2/16 (12.5)	5/14 (35.7)	7/30 (23.3)	0.204
New or worsening lymphadenopathy, Abdominal/mediastinal	3/16 (18.8)	2/14 (14.3)	5/30 (16.7)	1.000
New or worsening signs on chest radiograph	8/16 (50.0)	3/14 (21.4)	11/30 (36.7)	0.106
CNS symptoms	2/16 (12.5)	1/14 (7.1)	3/30 (10.0)	1.000
Others	3/16 (18.8)	1/14 (7.1)	4/30 (13.3)	0.602
Weeks between ART initiation and TB-IRIS[b]	3 (2–7.8)	4 (2–5.1)	4 (2–6.6)	0.620
CD4 count (/μL) at TB-IRIS[c]	158 (115–288)	128 (101–221.5)	135.5 (105.25–247.75)	0.534
Increase in CD4 count (/μL) at occurrence of TB-IRIS vs. baseline[d,e]	111 (65–235)	98 (65–138.5)	106 (65–166)	0.305
Withholding of ART[f]	2/16 (12.5)	4/13 (30.8)	6/29 (20.7)	0.227
TB-IRIS requiring treatment with corticosteroids	12/16 (75.0)	9/14 (64.3)	21/30 (70.0)	0.523
TB-IRIS requiring hospitalization	12/16 (75.0)	13/14 (92.9)	25/30 (83.3)	0.190
Death from TB-IRIS	0/16 (0)	0/14 (0)	0/30 (0)	-

Chan HIV Med 2024

Epidémiologie: rôle des INSTI?
Reflate TB ANRS

	N[a]	TB-IRIS N = 48	N[a]	No TB-IRIS N = 405	N[a]	Total N = 453	*P*
Antiretroviral treatment, n (%)		…	…	…	…	…	.12
Efavirenz	…	29 (60.4)	…	196 (48.4)	…	225 (49.7)	
Raltegravir	…	19 (39.6)	…	209 (51.6)	…	228 (50.3)	
Country, n (%)	…	…	…	…	…	…	.009
Ivory Coast	…	17 (35.4)	…	153 (37.8)	…	170 (37.5)	
Brazil	…	5 (10.4)	…	38 (9.4)	…	43 (9.5)	
Vietnam	…	20 (41.7)	…	91 (22.5)	…	111 (24.5)	
Mozambique	…	6 (12.5)	…	123 (30.4)	…	129 (28.5)	
Plasma HIV-1 RNA < 50, n (%)							
At week 4	42	2 (4.8)	396	63 (15.9)	438	65 (14.8)	.03
At week 12	43	10 (23.3)	378	206 (54.5)	421	216 (51.3)	<.001
At week 24	…	21 (43.8)	…	247 (61.0)	…	268 (59.2)	.02
At week 48	…	25 (52.1)	…	264 (65.2)	…	289 (63.8)	.07
HIV-1 RNA variation from baseline (log 10), median (IQR)							
At week 4	41	−2.9 (−3.4 - −2.3)	394	−2.8 (−3.3 - −2.3)	435	−2.8 (−3.3 - −2.3)	.99
At week 12	42	−3.6 (−4.1 - −1.9)	376	−3.6 (−4.0 - −3.0)	418	−3.6 (−4.0 - −3.0)	.70
CD4 variation from baseline (/mm³), median (IQR)							
At week 4	41	70.0 (37.0–117.0)	395	84.0 (21.0–152.0)	436	81.0 (24.0–149.5)	.72
At week 12	43	129.0 (40.0–184.0)	378	111.0 (48.0–196.0)	421	113.0 (47.0–193.0)	.79

Coehlo Op For inf dis 2024

Facteurs de risque de RP hors PVVIH

Table 4 Multivariate analysis of factors associated with development of PR: results from conditional logistic regression model

Variable		Odds ratio (95 % CI)	*P* value
Age		0.98 (0.95–1.02) per increasing year	0.409
Sex		0.57 (0.19–1.67) for females	0.302
Site	Chest	1.00	–
	Abdominal	8.11 (0.18–356.01)	–
	Brain	2.22 (0.22–23.30)	–
	Peripheral lymph nodes	64.33 (9.60–431.25)	–
	Other or mixed sites	1.23 (0.41–3.74)	<0.001
HIV Status	Negative	1.00	–
	Positive	5.05 (1.28–19.85)	–
	Not recorded	0.50 (0.02–14.97)	0.028
Immunosuppression	No	1.00	–
	Yes	0.01 (0.00–0.27)	–
	Not recorded	0.13 (0.00–0.90)	0.002
Tobacco use	No	1.00	–
	Yes	0.71 (0.17–2.85)	–
	Not recorded	3.36 (0.39–21.04)	0.462
Alcohol use	No	1.00	–
	Yes	0.21 (0.04–1.01)	–
	Not recorded	0.01 (0.01–0.56)	0.009
ESR[a]	Mean (mm/h)	Could not fit within model	–
TB Diagnosis	% NAAT negative	1.00	–
	% NAAT positive	1.23 (0.11–12.63)	–
	% NAAT not performed	0.10 (0.01–1.11)	0.009
	% culture negative	1.00	–
	% culture positive	6.87 (1.31–36.04)	–
	% culture not performed	3.81 (0.66–22.14)	0.045

Brown BMC ID 2016

Table 2 Site of PR by ethnicity

Site of PR[a]	Number of patients by ethnicity (percentage of total ethnic group with PR)				
	Black	East Asian	Other	South Asian	White
Total	32 (100 %)	6 (100 %)	3 (100 %)	33 (100 %)	8 (100 %)
Chest[b]	15 (47 %)	1 (17 %)	–	6 (18 %)	1 (13 %)
Systemic Symptoms[c]	13 (40 %)	1 (17 %)	–	2 (6 %)	4 (50 %)
Abdominal	6 (19 %)	–	–	–	1 (13 %)
Brain	2 (6 %)	–	–	–	–
Peripheral lymph nodes	8 (25 %)	4 (67 %)	3 (100 %)	25 (76 %)	4 (50 %)
Other	2 (6 %)	1 (17 %)	1 (33 %)	1 (3 %)	3 (38 %)

[a]PR may occur at more than one site for each patient, so percentages do not sum to 100 %
[b]Pulmonary, pleural, and mediastinal lymph nodes
[c]Systemic symptoms are persistent fever and persistent night sweats

Brown BMC ID 2016

Epidémiologie: TB et RP sous anti-TNF

Table 3. Demographic and Clinical Characteristics of 67 Patients Who Developed TB While Undergoing Anti-TNFα Treatment and Whose TB Was Complicated by IRIS

	Median (IQR) or No. (%)
Demographics	
Age, y	41 (28–56)
Male	35 (64.8)
Underlying disease	
Crohn disease	23 (34.3)
Ulcerative colitis	5 (7.5)
Rheumatoid arthritis	12 (17.9)
Spondyloarthropathy	11 (16.4)
Psoriasis	8 (11.9)
SAPHO	3 (4.5)
Behcet disease	2 (3)
Chronic juvenile arthritis	2 (3)
Giant cell arteritis	1 (1.5)
Ongoing treatment	
Anti-TNFα	67 (100)
Infliximab	36 (53.7)
Adalimumab	28 (41.8)
Etanercept	1 (1.5)
Golimumab	1 (1.5)
Certolizumab	1 (1.5)
Anti-TNFα duration, mo	9 (2–36)
Azathioprine	12 (17.9)
Corticosteroids	9 (13.4)
Methotrexate	6 (9)
TB features	
Pulmonary tuberculosis only	4 (6)
Disseminated TB	57 (85)
Miliary	36 (53.7)
Neuromeningeal	8 (11.9)
Hemophagocytic lymphohistiocytosis	5 (7.5)
TB treatment	
Anti-TNFα withdrawal	67 (100)
Anti-TB treatment	67 (100)
Corticosteroids	13 (19.4)
TB-IRIS	
Time between TB diagnosis and IRIS, d	42 (21–90)
Intensive care unit hospitalization	2 (3)
Fever	30 (44.8)
Aggravation of pulmonary lesions	23 (34.3)
Aggravation or onset of lymphadenopathy	29 (43.3)
Aggravation of pleural or pericardial effusion	15 (22.4)
Pancytopenia	2 (3)
Exacerbation of digestive inflammation	4 (6)
Exacerbation of hepatic or splenic lesions	4 (6)
Acute kidney injury	2 (3)
Neurologic IRIS	14 (20.9)
Osteitis	1 (1.5)
Soft tissue abscess	2 (3)
TB-IRIS treatment	
Symptomatic treatment only	20 (29.9)
Corticosteroids	39 (58.2)
Anti-TNFα resumption	11 (16.4)
Thalidomide	1 (1.5)
Cyclosporine	1 (1.5)
Nonsteroidal anti-inflammatory	1 (1.5)
Methotrexate	1 (1.5)
Surgery	7 (10.4)
Outcome	
Missing data	14 (20.9)
Recovery without sequelae	46 (86.8)
Recovery with sequelae	5 (9.4)
Death from TB-IRIS	1 (1.9)
TB relapse	3 (5.7)

Amoura Op For inf Dis 2023

Epidémiologie: RP sous anti-TNF

Table 2. Demographic and Clinical Characteristics of 17 Non-IRIS and 15 IRIS-TB Cases From the Current Cohort and Univariate Analysis for the Risk of IRIS

	Median (IQR) and No. (%)			Univariate Analysis
	Non-IRIS (n = 17)	IRIS (n = 15)	*P* Value	Odds Ratio (95% CI; *P* Value)
Demographics				
Age, y	38 (28–52)	34 (26–40)	.168	0.95 (.88–1.01; .108)
Male	9 (52.9)	13 (86.7)	.060	5.78 (1.13–44.69; .052)
Smoking	8 (53.3)	5 (35.7)	.462	0.49 (.10–2.12; .343)
IBD				
Crohn disease	14 (82.3)	13 (86.7)		…
Ulcerative colitis	3 (17.6)	2 (13.3)		…
Time since diagnosis, mo	108 (78–162)	48 (25–81)	**.013**	**0.98 (.96–1.00; .033)**
Ongoing treatment				
Anti-TNFα	17 (100)	15 (100)		…
Infliximab	11 (64.7)	10 (66.7)	>.99	…
Adalimumab	6 (35.3)	5 (33.3)	>.99	…
Anti-TNFα duration, mo	12 (3–30)	11.50 (3–46)	.913	1 (.97–1.03; .929)
Azathioprine	9 (52.9)	11 (73.3)	.291	0.33 (.02–2.97; .366)
Corticosteroids	3 (17.6)	1 (6.7)	.603	2.44 (.57–11.78; .239)
TB features				
Disseminated TB	14 (82.4)	14 (93.3)	.603	3.00 (.34–64.84; .366)
Miliary	6 (35.3)	12 (80.0)	**.016**	**7.33 (1.60–42.82; .015)**
Neuromeningeal	1 (5.9)	2 (13.3)	.589	2.46 (.21–56.53; .482)
Lymphocyte count/mm^3	1220 (1015–1620)	820 (700–1650)	.411	1.00 (1.00–1.00; .504)
Hemoglobin, g/dL	12.30 (10.5–13.40)	11.40 (10.85–12.95)	.628	0.87 (.57–1.28; .497)
TB treatment				
Anti-TNFα withdrawal	17 (100)	15 (100)		…
Anti-TB treatment	17 (100)	15 (100)		…
Corticosteroids	1 (5.9)	2 (13.3)	.589	2.91 (.25–67.27; .406)
Antibiotic duration, mo	6.00 (6.00–9.00)	9.00 (9.00–12.00)	**.049**	1.34 (1.01–1.90; .068)

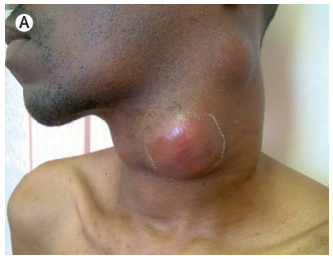
Amoura Op For inf Dis 2023

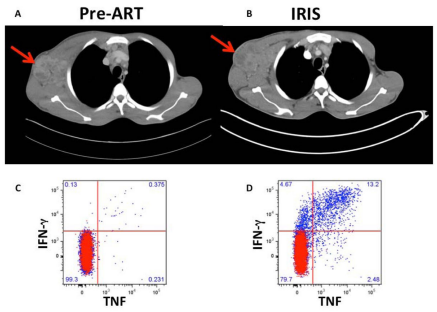
Ce que l'on sait déjà: Physopathologie

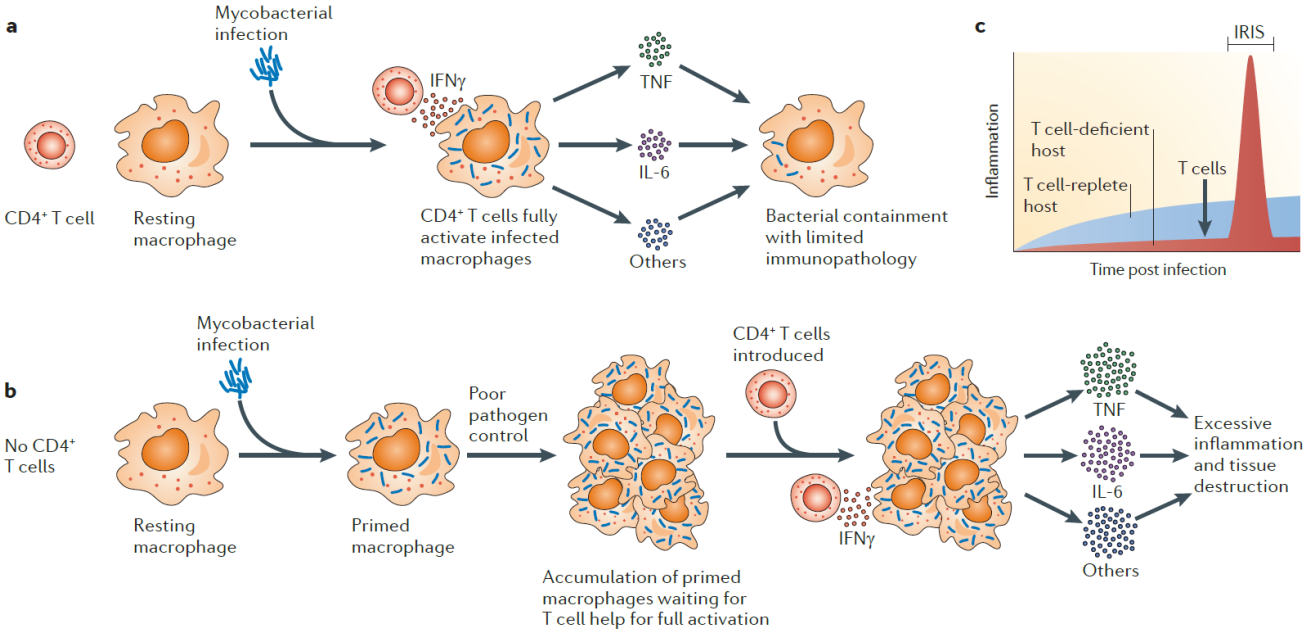
Knowledge summary	
Incidence	Adults overall: 18% (95% CI 16–21%), with a range of 4–54%; higher rates in patients with lower CD4 counts (up to 57% in patients with CD4 count <200 cells/μl).
	South African children: 6.7% reported in a recent prospective study
Risk factors	Low CD4 count at ART initiation; High HIV viral load at ART initiation
	Shorter time between TB treatment initiation and ART initiation
	Disseminated TB/high mycobacterial load.
Clinical presentation	Systemic, pulmonary and lymph node presentations most common
	In a recent study, median days to symptom onset reported as 6 (range 1–23)
Mortality	All-cause mortality rate of 7% (95% CI 4–11%) and IRIS-attributable deaths of 2% (95% CI 1–3%)
	Higher mortality in CNS TB-IRIS
Pathogenesis	Innate immune cell activation, including neutrophils, monocytes and NK cells; Antigen-specific upregulation of cytotoxic mediators Inflammasome activation; Hypercytokinaemia (including IL-1β, IL-6 and TNF-α) and MMP upregulation/ secretion
Treatment	Prednisone (1.5 mg/kg for 2 weeks followed by 0.75 mg/kg for 2 weeks) for treatment of paradoxical TB-IRIS reduced length of hospital admission and number of therapeutic procedures required, and improved symptoms in paradoxical TB-IRIS
	Consensus is not to stop ART, but to investigate fully for alternative causes, and provide symptomatic treatment
Prevention	Prednisone (40 mg daily for 2 weeks, followed by 20 mg daily for 2 weeks) from ART initiation reduces the risk of future paradoxical TB-IRIS by 30%
	Do not delay ART initiation beyond 2 weeks after TB treatment initiation in patients with CD4 count <50 cells/mm^3, unless CNS TB diagnosed (then delay 4–8 weeks). Early ART improves survival in patients with CD4 < 50 cells/mm^3 even though it increases TB-IRIS risk > two-fold

Walker curr op HIV 2018

Physiopathologie : IRIS/RP: Reconstitution d'une réponse spécifique éfficace, non controlée dans un contexte de sur-charge antigénique



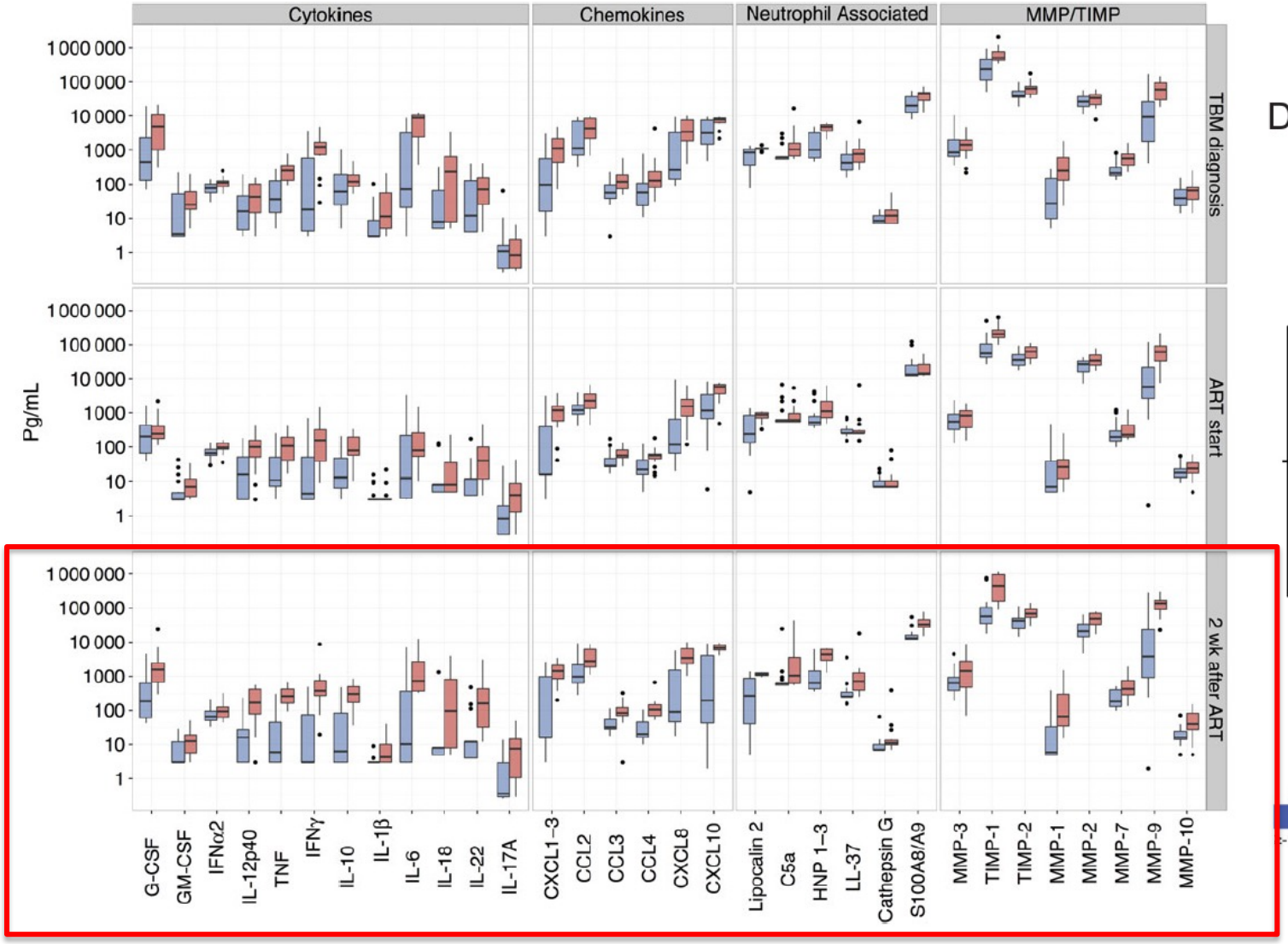


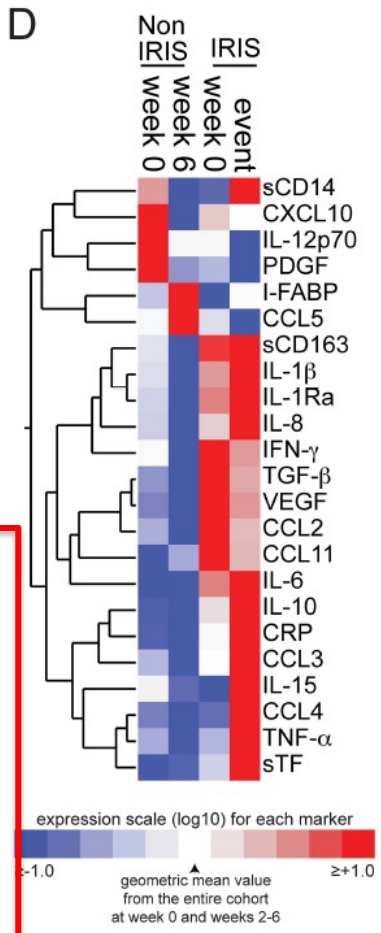


Barber Nat Rev Immunol 2012

Bouloungara Sereti curr op HIV AIDS 2016

IRIS= Reponse inflammatoire non spécifique, intense, immunité innee et acquise

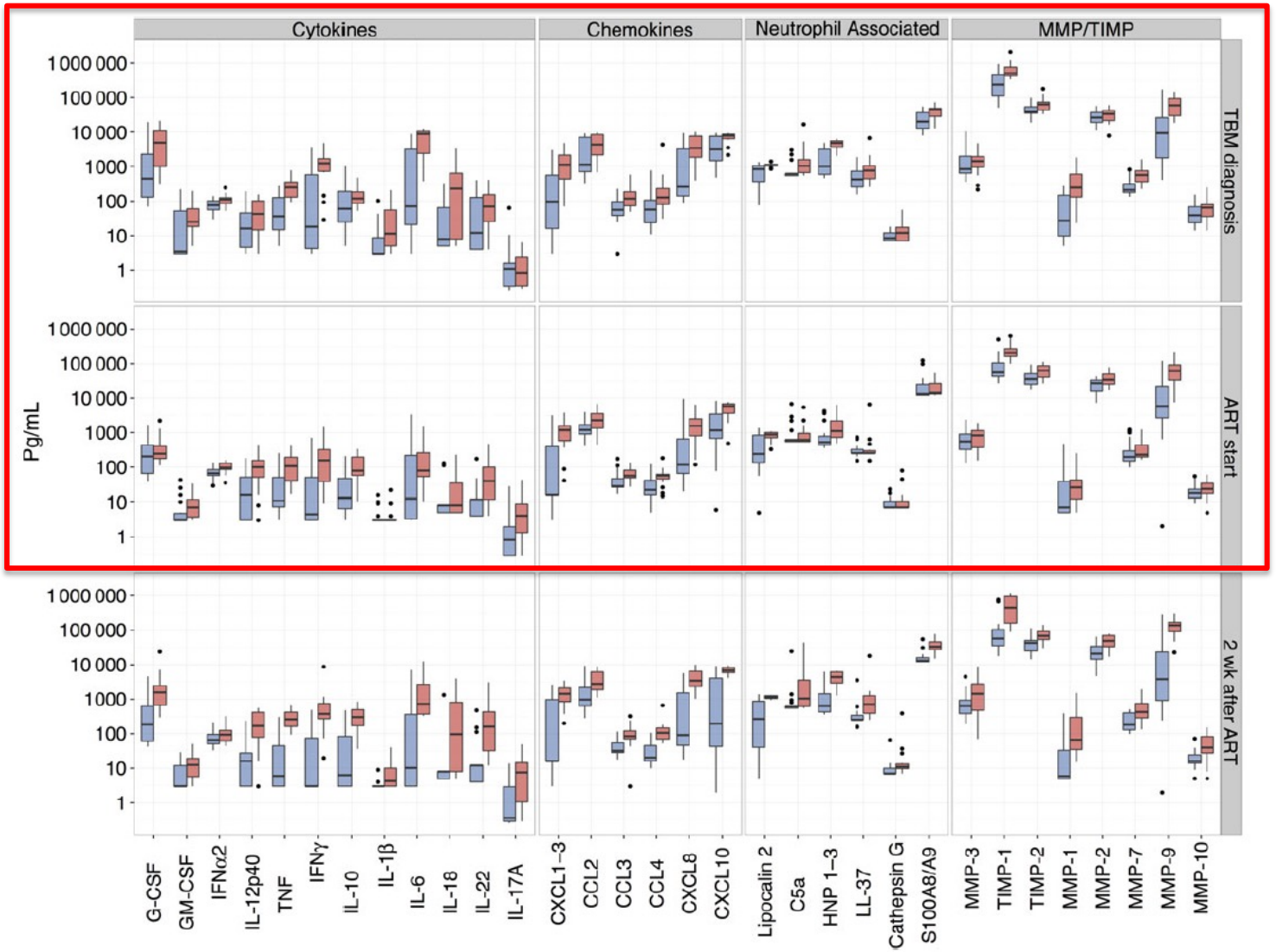


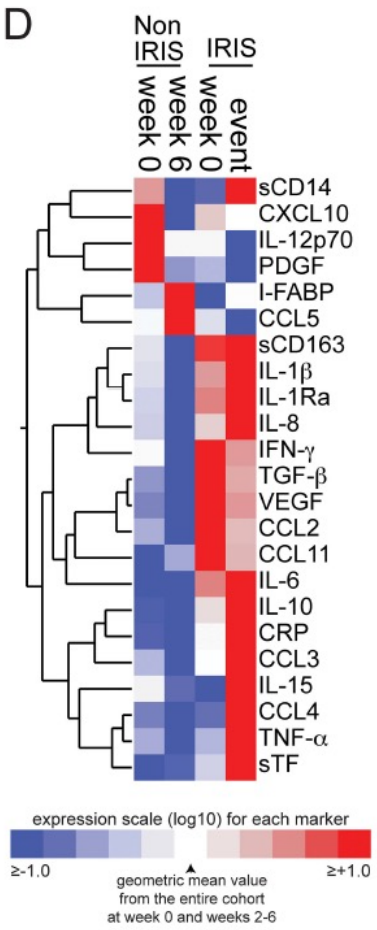


Marais **CID 2014:59 (1 December)** • HIV/AIDS

Tran, Immunobiology 2013

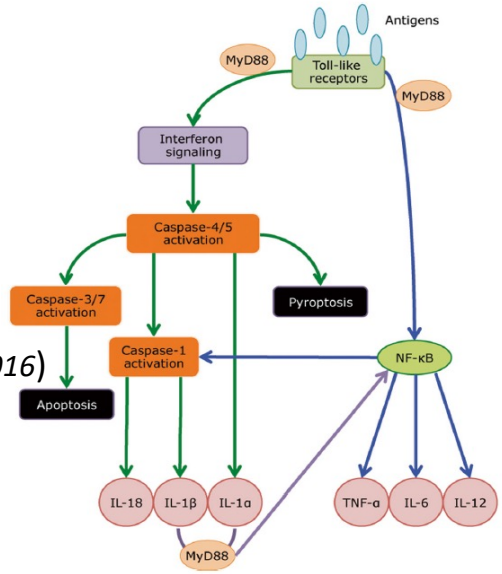
A baseline: syndrome pré-inflammatoire non spécifique





IRIS: Rôle de l'immunité innée

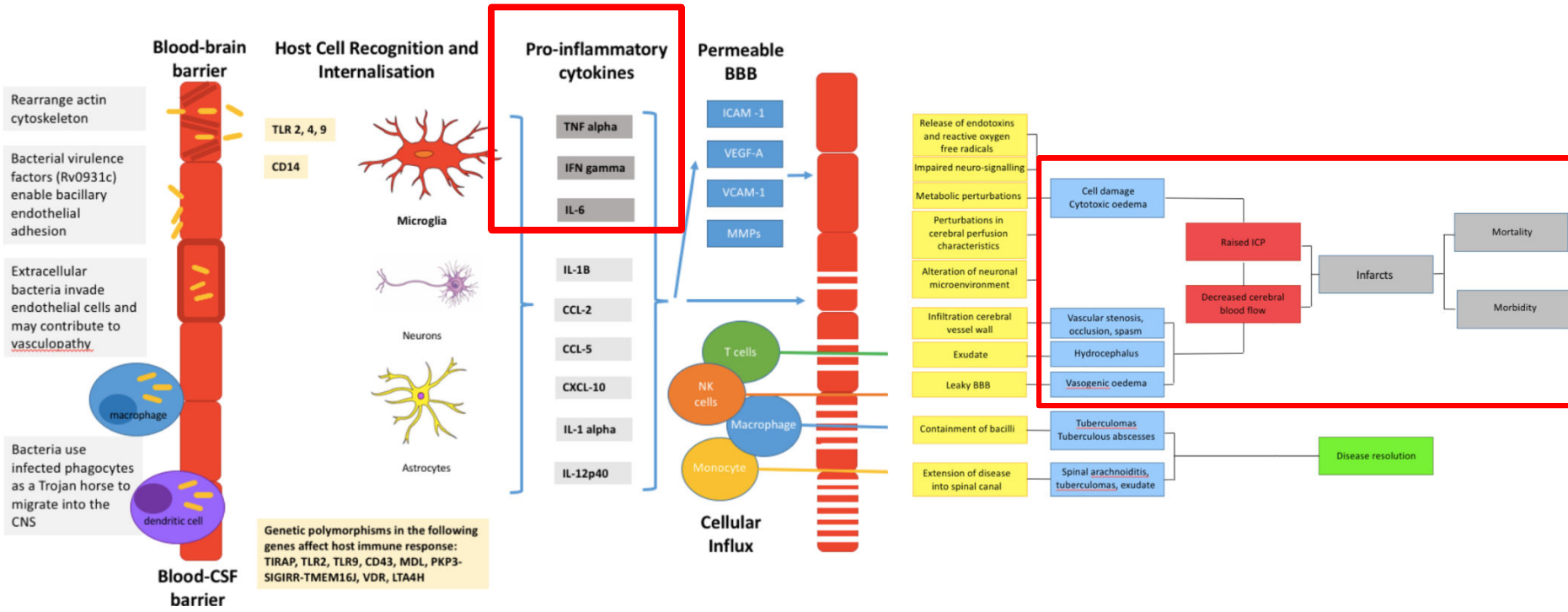
- Défaut de présentation de l'antigène ou anomalies de la réponse à la présentation antigénique (*Barber, Blood 2010*)
- Défaut d'élimination de l'agent pathogène
  - par NK *(Pean, Blood 2012, Camelia),* iNKT
  - par monocytes et PNN: Defaut de phagocytose liee à FcGR et complément (restauré par DXM*) (Bell L, 2017)*
- Anomalies de balance inflammation/regulation
  - inhibiteurs/activateurs sur LT gd *(Bourgarit et al 2009)*
  - Metalloproteases et fibrose/caverne pulmonaire (*Tadokera EJI 2014, Ravimoran 2016*)
  - Augm CD14++CD16- augm sCD14 et 63, IL-6, IFN-g, (*Andrade Plos 2014*),
  - Inflammasome aberrants et caspases Induit par TLR2 (Inhib MyD88)



- Terrain génétique:
  - LT4H genotype muté CT/TT associé à TB-IRIS grave (mais pas apparition de IRIS) *(Narendran Pone 2016)*
- CRP, IL-6 avant HAART prédictifs d'IRIS
  - Lien avec la charge bactérienne?
  - Défaut de contrôle de l'infection?
  - LPS (*Goovaerts, Plos 2014*)

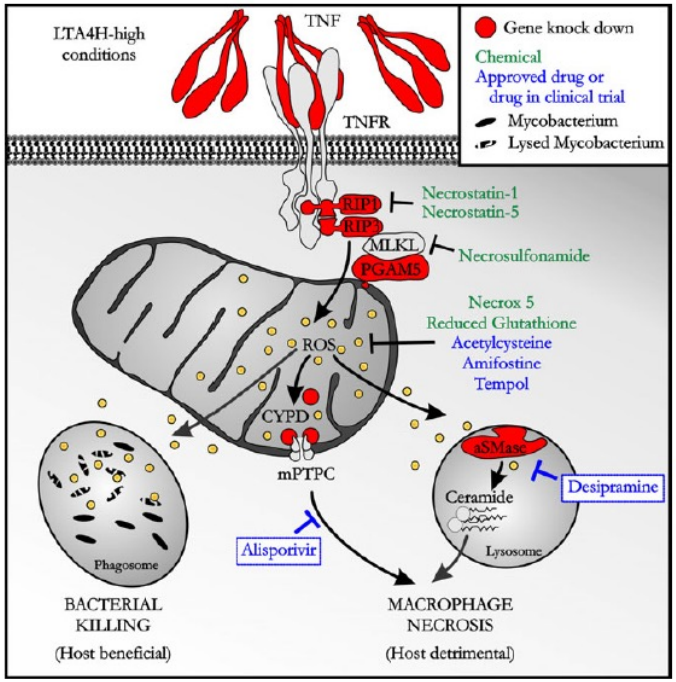
Review: Lai , semin immunopath 2016
Vignesh Pathogens 2023

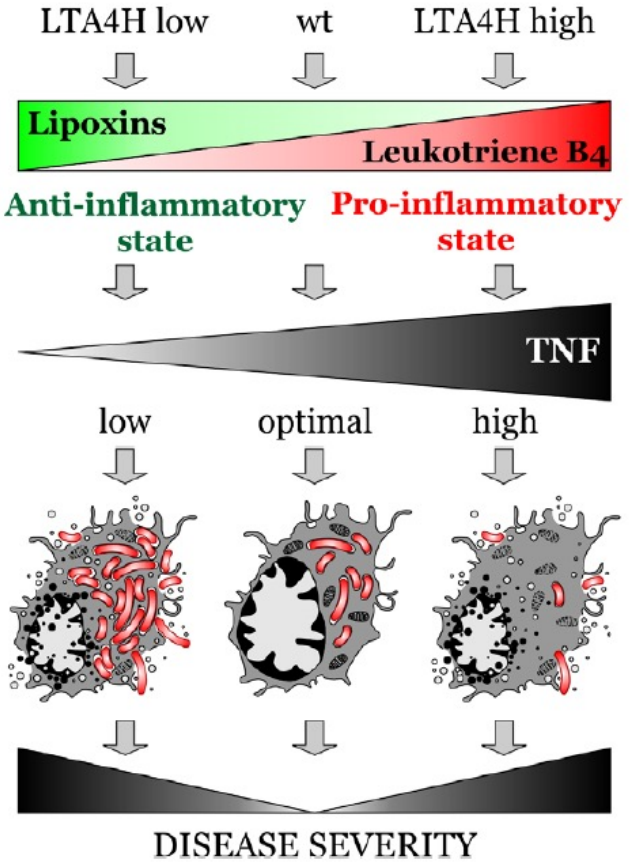
Physiopathologie de la TBM



Davis JLB 2020

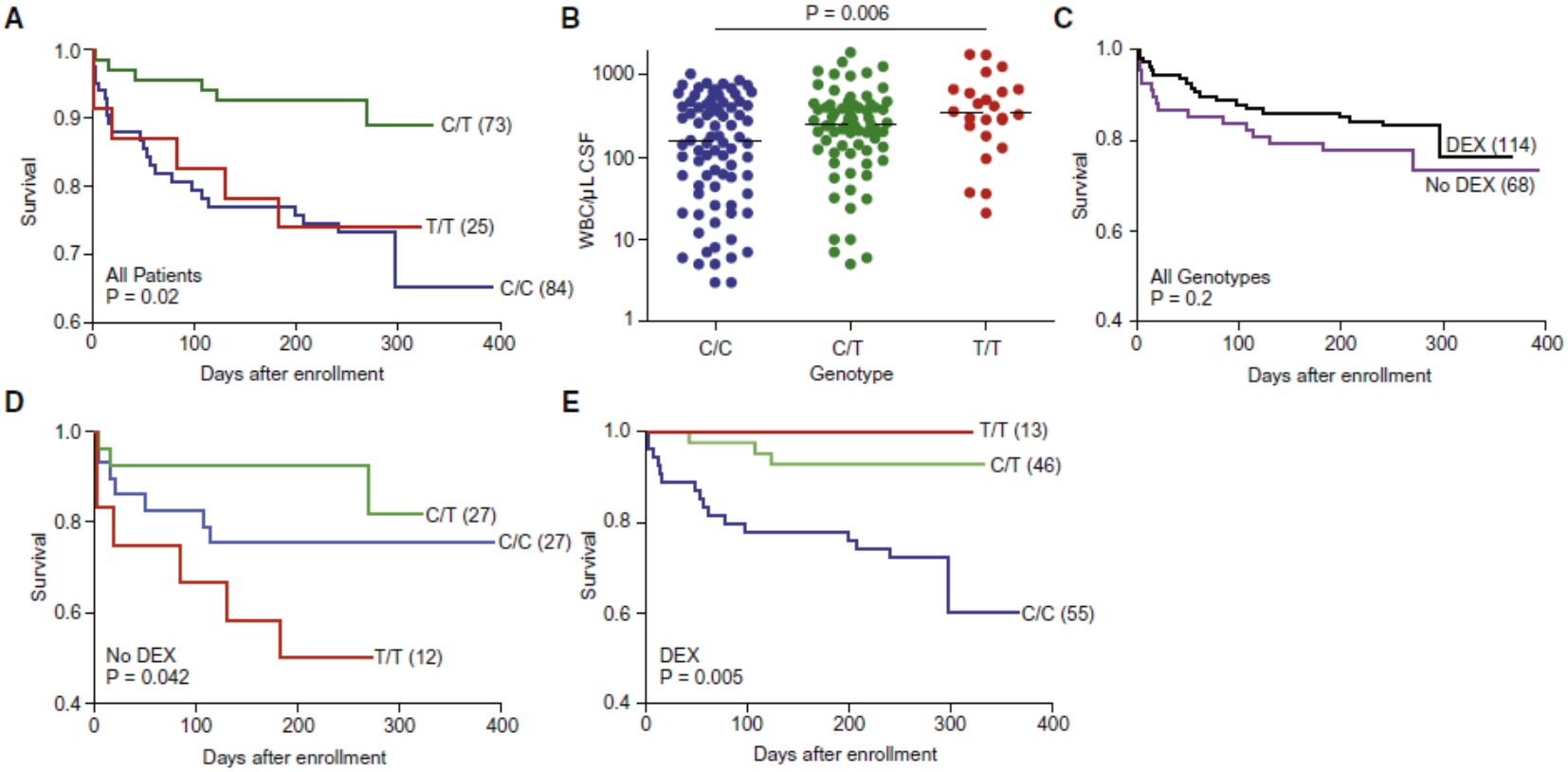
TB et TBM: Equilibre entre absence de réponse et trop d'inflammation





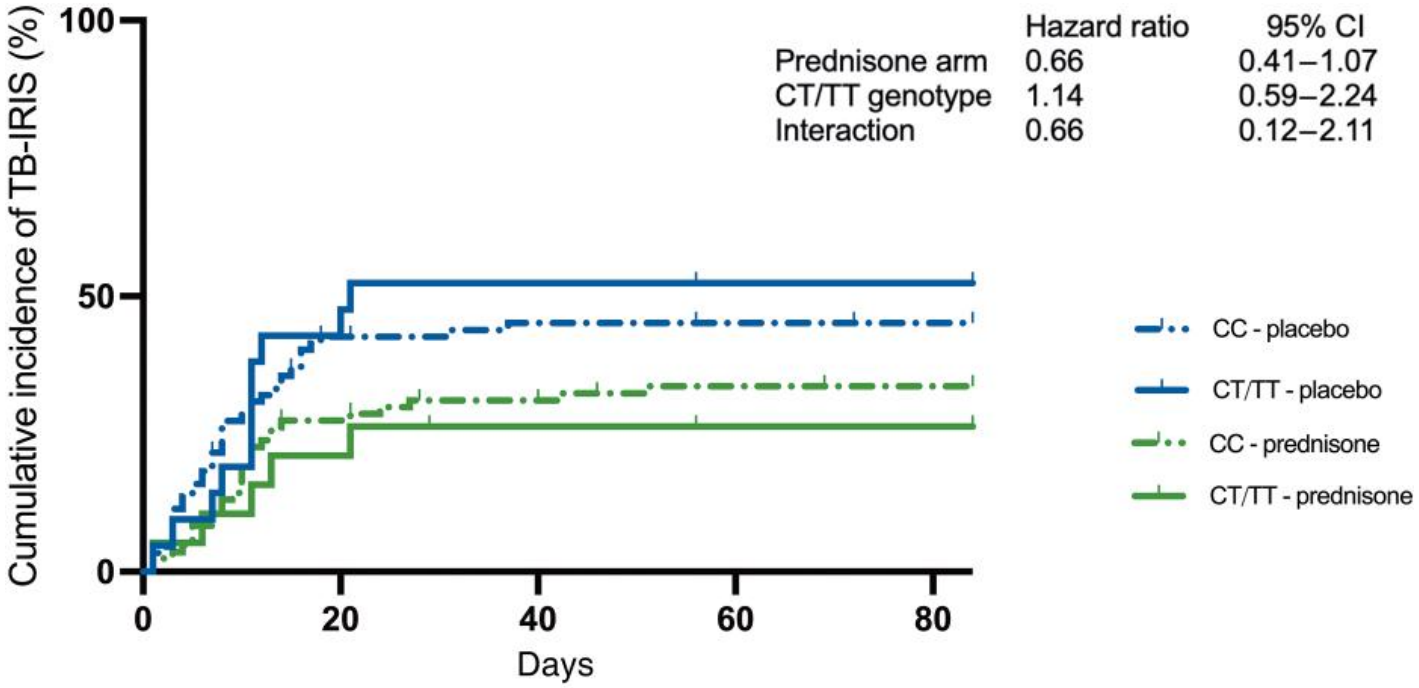
Genotype LTA4H associé à sévérité chez zebrafish et cohortes humaines soit par trop ou par pas assez d'inflammation

Applications thérapeutiques?



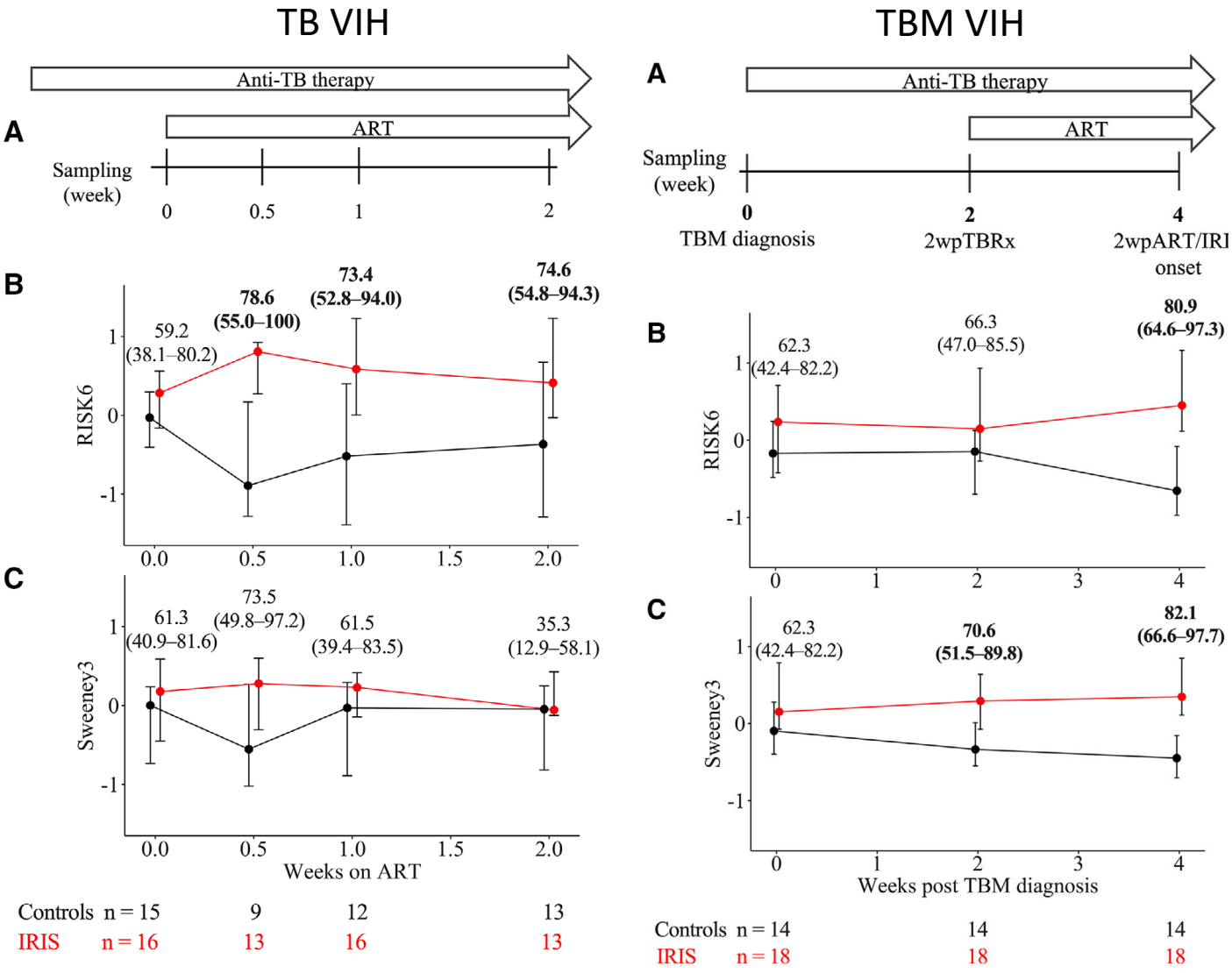
Tobin et al, Cell *148*, 434–446, February 3, 2012

LT4H IRIS et CTC préventifs



Stek op forum inf dis 2023

Applications diagnostiques? Facteurs prédictifs?



Mbandi EJI 2022

Diagnostic IRIS

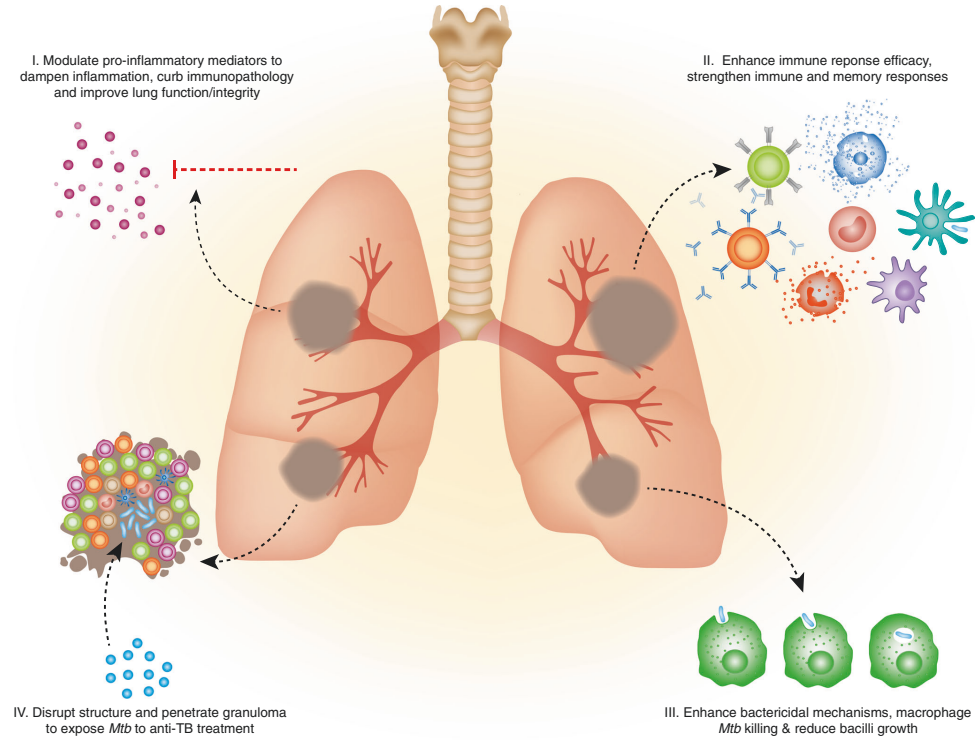
- Pas de test diagnostic positif spécifique
- Association d'éléments:
  - Cliniques:
    - Chronologie +++:
      - 7-15j apres debut HAART,
      - 3-6 semaines apres arret anti-TNF
      - 6-12 semaines apres debut traitement anti-TB
    - Manifestations atypiques car exacerbées et tres inflammatoires
  - Para cliniques: Arguments pour reconstitution immunitaire
    - Lymphocytes, CD4, IDR, sortie d'aplasie…

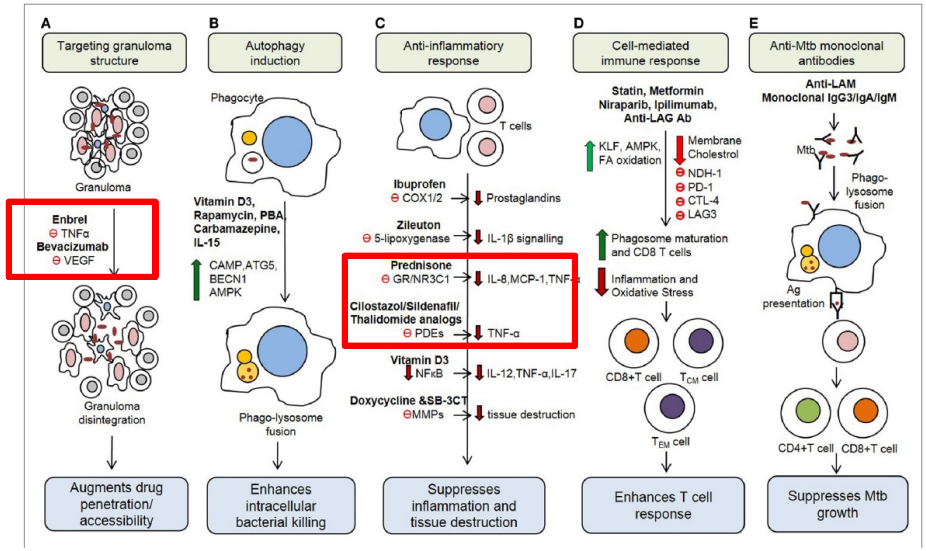
Ce que l'on sait déjà : traitement

Knowledge summary	
Incidence	Adults overall: 18% (95% CI 16–21%), with a range of 4–54%; higher rates in patients with lower CD4 counts (up to 57% in patients with CD4 count <200 cells/μl).
	South African children: 6.7% reported in a recent prospective study
Risk factors	Low CD4 count at ART initiation; High HIV viral load at ART initiation
	Shorter time between TB treatment initiation and ART initiation
	Disseminated TB/high mycobacterial load.
Clinical presentation	Systemic, pulmonary and lymph node presentations most common
	In a recent study, median days to symptom onset reported as 6 (range 1–23)
Mortality	All-cause mortality rate of 7% (95% CI 4–11%) and IRIS-attributable deaths of 2% (95% CI 1–3%)
	Higher mortality in CNS TB-IRIS
Pathogenesis	Innate immune cell activation, including neutrophils, monocytes and NK cells; Antigen-specific upregulation of cytotoxic mediators Inflammasome activation; Hypercytokinaemia (including IL-1β, IL-6 and TNF-α) and MMP upregulation/secretion
Treatment	Prednisone (1.5 mg/kg for 2 weeks followed by 0.75 mg/kg for 2 weeks) for treatment of paradoxical TB-IRIS reduced length of hospital admission and number of therapeutic procedures required, and improved symptoms in paradoxical TB-IRIS
	Consensus is not to stop ART, but to investigate fully for alternative causes, and provide symptomatic treatment
Prevention	Prednisone (40 mg daily for 2 weeks, followed by 20 mg daily for 2 weeks) from ART initiation reduces the risk of future paradoxical TB-IRIS by 30%
	Do not delay ART initiation beyond 2 weeks after TB treatment initiation in patients with CD4 count <50 cells/mm^3, unless CNS TB diagnosed (then delay 4–8 weeks). Early ART improves survival in patients with CD4 < 50 cells/mm^3 even though it increases TB-IRIS risk > two-fold

Walker curr op HIV 2018

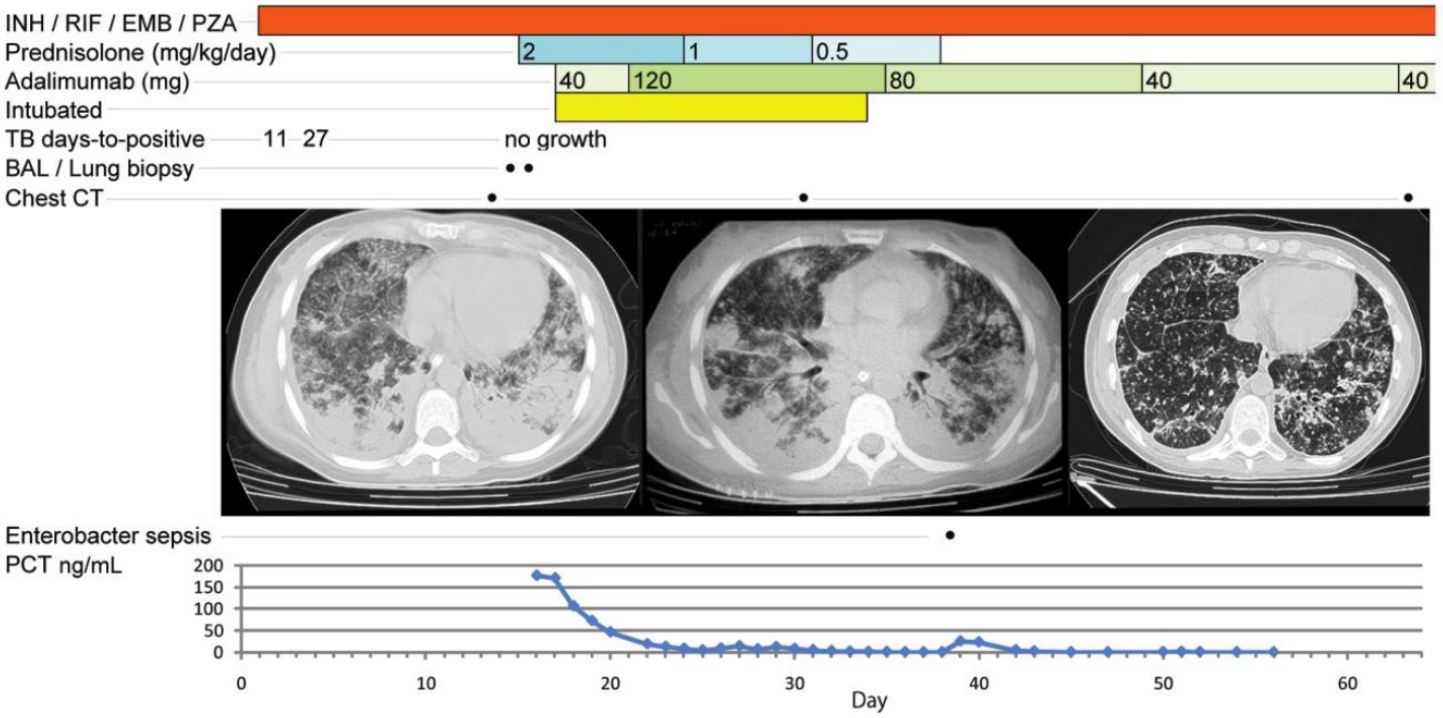
Host directed Therapies in TB





C Young Nature 2019

Anti-TNF et traitement de la tuberculose



Wallis, CID 2009

Tuberculose neuromeningée sévère traitées par Anti TNF-a: cohorte française de 18 patients

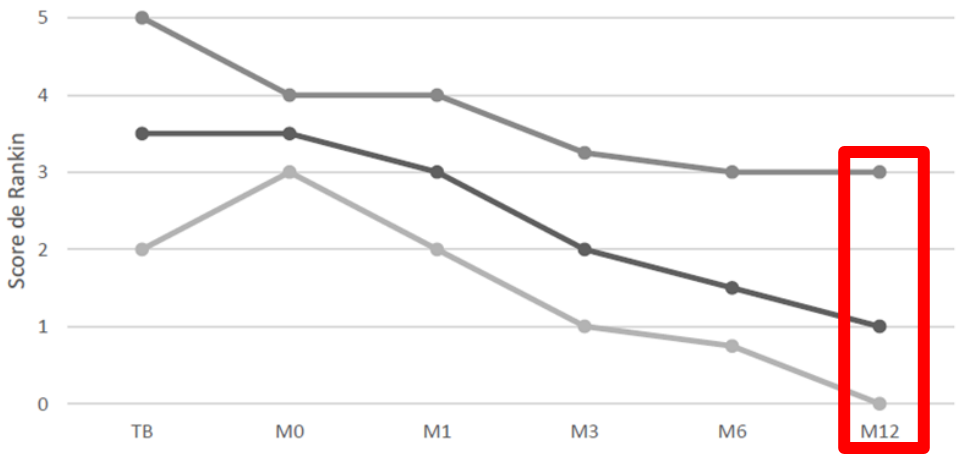
- de janvier 2017 à septembre 2021
- RCP mycobactéries CNR Pitié Salpétriere
- TBM avec aggravation paradoxale (ou aggravation d'emblee pour 2)
- Traités par Infliximab 5mg/kg/j J1, J15, J30, M2, M3 (M4, M5, M6)
- 25 jours à compter du diagnostic de RP
- 87 jours du début des ATT

Table 1: Characteristics of patients at baseline and at infliximab onset

Characteristics	TB diagnosis	At anti-TNF initiation
Age, median (IQR), years	34 (20-40)	-
Male sex, No (%)	11/18 (72)	-
HIV, No (%)	3/18 (17)	-
Blood CD4 /mm^3 median, (min-max)	183 (111-222)	215 (182-248)
Blood Viral load copies/mL, median, (min-max)	4,34 (2.33-4.88)	NA
Neurological symptoms, No (%)		
Cephalgia	15/18 (83)	5/18 (28)
Meningeal syndrome	8/18 (44)	2/18 (11)
Cerebral focal deficit	6/18 (33)	7/18 (39)
Spinal deficit	1/18 (6)	6/18 (33)
Cerebellar syndrome	4/18 (22)	3/18 (17)
Cranial nerve involvement	4/18 (22)	3/18 (17)
Seizure	3/18 (17)	3/18 (17)
Cognitive disorder	13/18 (72)	11/18 (61)
Coma	5/18 (28)	1/18 (6)
CNS TB		
TBM, No (%)	17/18 (94)	-
Probable TBM	3/17 (18)	-
[illegible]	[illegible]	[illegible]
MRC grade, No (%)		
I	3/17 (18)	-
II	7/17 (41)	-
III	7/17 (41)	-
Rankin scale, No (%)		
0-1	2/18 (11)	2/18 (11)
2-3	7/18 (39)	7/18 (39)
4-5	9/18 (50)	9/18 (50)
median (IQR)	3,5 (2-5)	3,5 (3-4)
Biological analysis		
Blood lymphocyte count/mm^3, median (IQR)	840 (655-1000)	1440 (1130-1740)
CSF cellularity/mm^3, median (IQR)	168 (94.5-486)	57 (27-180)†
CSF lymphocytosis, % (IQR)	51,5 (43.25-80)	92 (41.5-95.75)†
CSF proteinorachia g/L, median (IQR)	2,29 (1.49-3.39)	3,39 (1.48-20.6)†
Antibiotic susceptibility		
Unkown	5/18 (28)	-
Sensible	11/18 (61)	-
INH resistant	2/18 (11)*	-
MDR	0/18 (0)*	-
Radiological findings, No (%)		
Meningeal enhancement	15/18 (83)	13/18 (72)
Tuberculoma	9/18 (50)	15/18 (83)
Multiple tuberculomas	8/9 (89)	13/15 (87)
Abscess	0/18 (0)	4/18 (22)
Hydrocephalus	8/16 (50)	8/18 (44)
Spinal involvement	4/18 (22)	9/18 (50)
Myelitis	0/18 (0)	3/18 (17)
Tuberculoma	3/18 (17)	4/18 (22)
Abscess	0/18 (0)	3/18 (17)
Radiculitis	1/18 (6)	1/18 (6)
Ischemia	5/18 (28)	6/18 (33)
Vasculitis	2/18 (11)	6/18 (33)

Benhard J et al ECCMID 2023

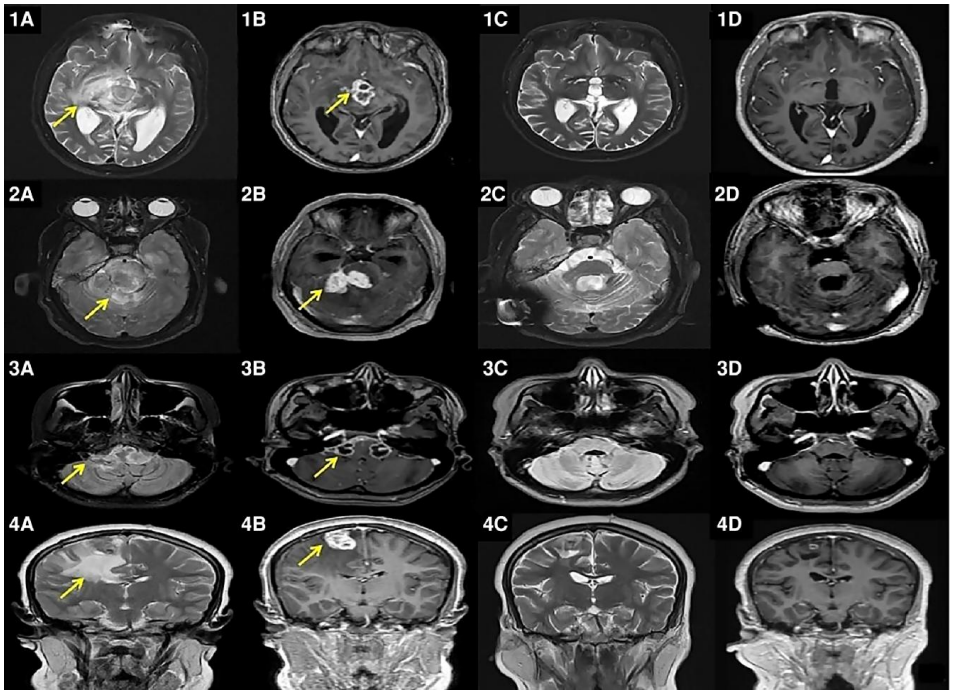
Résultats : évolution sous anti-TNF-α à M12



- mediane 8 injections, arret des ctc apres M8
- **94% Survie**
  - 1 DC à 1 an apres PVAM
- **72%** amelioration fonctionnelle
  - Rankin scale <=3
- **50% avec amelioration fonctionnelle complète** (Rankin <=1)
- **3 avec** Rankin >=4 at M12
  - 2 compression medullaire
  - 1 tetraparesie et troubles cognitifs
- 2 aggravations precoces
  - 1 infection DVE
  - 1 aggravation après arret des ATT

Effectiveness of Adjunctive High-Dose Infliximab Therapy to Improve Disability-Free Survival Among Patients With Severe Central Nervous System Tuberculosis: A Matched Retrospective Cohort Study

Abi Manesh,[1] Priyanka Gautam,[1] Selwyn Selva Kumar D,[1] Pavithra Mannam,[2] Anitha Jasper,[2] Karthik Gunasekaran,[3] Naveen Cherian Thomas,[4] Rohit Ninan Benjamin,[5] Leeberk Raja Inbaraj,[6] Emily Devasagayam,[1] Mithun Mohan George,[1] Rajiv Karthik,[1] Ooriapadickal Cherian Abraham,[3] Harshad A. Vanjare,[2] Ajith Sivadasan,[5] Prabhakar Thirumal Appaswamy,[5] Edmond Jonathan,[7] Joy S. Michael,[8] Prasanna Samuel,[9] and George M. Varghese[1]



10 mg/kg M1 M2 M3
Stopped if complete response or no response

- 3 inj n=19
- 2 n=7
- 1 n=4

Table 2. Treatment Outcomes for Cohort A and Cohort B at 6 Months

Variable	Total (N = 90)	Cohort A (n = 30)	Cohort B (n = 60)	RR (95% CI)	*P*
Successful outcome, post-therapy, mRS ≤2	38 (42.2)	19 (63.3)	19 (31.7)	2.3 (1.28–4.36)	.004
Unsuccessful outcome, post-therapy mRS 3–6	52 (57.8)	11 (36.7)	41 (68.3)		
Severe disability, post-therapy mRS scores 4 and 5	26 (28.9)	5 (16.7)	21 (35)	.4 (.21–1.14)	0.070
Mortality[a]	15 (16.7)	2 (6.7)	13 (21.7)	.3 (.09–1.34)	.081

Data are presented as n (%) unless otherwise indicated.

Abbreviations: CI, confidence interval; mRS, modified Rankin Scale; RR, Relative risk; TBM, tuberculosis meningitis.

[a]In cohort A, 1 patient died due to probable aspiration pneumonia and another had sudden death in sleep. In cohort B, of the 13 deaths, 11 patients died due to TBM disease progression. The other 2 died of unrelated causes, 1 due to acute *Escherichia coli* pyelonephritis with bacteremia and another because of enterococcal bacteremia.

- Autres études prospectives en cours:
  - Chez le PVVIH
  - date d'introduction
  - Molécule, forme, dose, fréquence, durée…

CID 2023

Quand ré-introduire les anti-TNF?

Systematic review

(Re-)introduction of TNF antagonists and JAK inhibitors in patients with previous tuberculosis: a systematic review

Thomas Theo Brehm [1, 2, 3, *], Maja Reimann [2, 3, 4], Niklas Köhler [1, 2, 3], Christoph Lange [2, 3, 4, 5, 6]

Reintroduction après 12 mois (8-13)

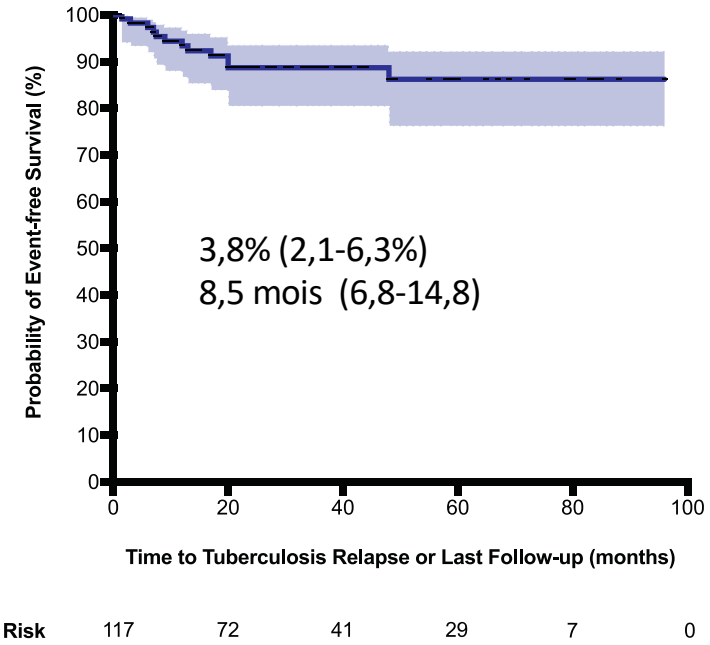


Fig. 3. Kaplan–Meier estimate of probability of event-free survival over time in tuberculosis patients (re-)introduced to TNF antagonists. An event was defined as documented tuberculosis relapse or tuberculosis treatment failure.

Réintroduction pour RP

Table 3
Baseline and clinical characteristics of tuberculosis patients introduced to TNF antagonists for prevention or treatment of paradoxical reactions ($n = 94$)

Age	
Median (y)	31.1
95% CI (y)	31.1–34.5
Sex	
Male, *n* (%)	49 (52.1)
Female, *n* (%)	45 (47.9)
Tuberculosis manifestation	
Pulmonary, *n* (%)	45 (47.9)
Central nervous system, *n* (%)	39 (41.5)
Disseminated, *n* (%)	6 (0.6)
Urogenital, *n* (%)	1 (0.1)
Ocular, *n* (%)	2 (0.2)
Data not available, *n* (%)	1 (0.1)
TNF antagonist after tuberculosis disease	
Infliximab, *n* (%)	49 (52.1)
Etanercept, *n* (%)	43 (45.7)
Adalimumab, *n* (%)	1 (0.1)
Adalimumab/infliximab, *n* (%)	1 (0.1)

CI, confidence interval; TNF, tumour necrosis factor.

Aucune rechute en cas de ttt pour RP

CMI 2024

Quand ré-introduire les anti-TNF?

Table 4. Demographic and Clinical Characteristics of 45 Patients Treated With Anti-TNFα for TB-IRIS

	Median (IQR) or No. (%)
Demographics	
Age, y	34.5 (27–43.5)
Male	22 (48.9)
Coming from endemic country for TB	21 (46.7)
Immunodepression factor	
None	24 (53.3)
HIV	9 (20)
CD4 level at TB diagnosis	124 (106–147)
Anti-TNFα treatment	11 (24.4)
Inflammatory bowel disease	7 (15.6)
Rheumatoid arthritis	1 (2.2)
Spondyloarthropathy	1 (2.2)
Psoriasis	1 (2.2)
Chronic juvenile arthritis	1 (2.2)
Treatment with mycophenolate mofetil	1 (2.2)
TB features	
Pulmonary tuberculosis only	3 (6.7)
Disseminated	29 (64.4)
Miliary	16 (35.6)
Neuromeningeal	25 (55.6)
TB treatment	
Anti-TB treatment	45 (100)
Corticosteroids	26 (57.8)
TB-IRIS or paradoxical reaction features	
Time between TB diagnosis and IRIS, d	36 (21–63)
Neuromeningeal IRIS	29 (64.4)
Aggravation of pulmonary lesions	6 (13.3)
Aggravation or onset of lymphadenopathy	10 (22.2)
Spondylodiscitis	3 (6.7)
Psoas abscess	2 (4.4)
Chylothorax	1 (2.2)
Intra-abdominal collection	1 (2.2)
Pancytopenia	1 (2.2)
Uveitis	1 (2.2)
IRIS treatment	
Intensive care unit hospitalization	5 (11.1)
Corticosteroids	42 (93.3)
Anti-TNFα	45 (100)
Infliximab	37 (82.2)
Adalimumab	9 (20)
Outcome	
Recovery without sequelae	28 (62)
Recovery with sequelae	15 (33.3)
Treatment failure	1 (2.2)
Death from IRIS	1 (2.2)

Patients: 40 from systematic literature review and 5 additional cases from the current study.

Abbreviations: anti-TNFα, anti–tumor necrosis factor α; IRIS, immune reconstitution inflammatory syndrome; TB, tuberculosis.

Amoura Op For inf Dis 2023

Ce que l'on sait déjà

Knowledge summary	
Incidence	Adults overall: 18% (95% CI 16–21%), with a range of 4–54%; higher rates in patients with lower CD4 counts (up to 57% in patients with CD4 count <200 cells/μl).
	South African children: 6.7% reported in a recent prospective study
Risk factors	Low CD4 count at ART initiation; High HIV viral load at ART initiation
	Shorter time between TB treatment initiation and ART initiation
	Disseminated TB/high mycobacterial load.
Clinical presentation	Systemic, pulmonary and lymph node presentations most common
	In a recent study, median days to symptom onset reported as 6 (range 1–23)
Mortality	All-cause mortality rate of 7% (95% CI 4–11%) and IRIS-attributable deaths of 2% (95% CI 1–3%)
	Higher mortality in CNS TB-IRIS
Pathogenesis	Innate immune cell activation, including neutrophils, monocytes and NK cells; Antigen-specific upregulation of cytotoxic mediators Inflammasome activation; Hypercytokinaemia (including IL-1β, IL-6 and TNF-α) and MMP upregulation/secretion
Treatment	Prednisone (1.5 mg/kg for 2 weeks followed by 0.75 mg/kg for 2 weeks) for treatment of paradoxical TB-IRIS reduced length of hospital admission and number of therapeutic procedures required, and improved symptoms in paradoxical TB-IRIS
	Consensus is not to stop ART, but to investigate fully for alternative causes, and provide symptomatic treatment
Prevention	Prednisone (40 mg daily for 2 weeks, followed by 20 mg daily for 2 weeks) from ART initiation reduces the risk of future paradoxical TB-IRIS by 30%
	Do not delay ART initiation beyond 2 weeks after TB treatment initiation in patients with CD4 count <50 cells/mm^3, unless CNS TB diagnosed (then delay 4–8 weeks). Early ART improves survival in patients with CD4 < 50 cells/mm^3 even though it increases TB-IRIS risk > two-fold

Walker curr op HIV 2018

En conclusion

- TB pathologie inflammatoire
  - Permet le controle mais est responsable de la pathogénie
  - Equilibre entre trop et pas assez
- Traitements:
  - Contrôler l'infection
  - Augmenter les capacités d'éradication de l'hôte
  - Diminuer les éffets délétères de la réponse immune
- IRIS:
  - Attention à restoration trop rapide d'une immunité fonctionnelle??
  - Traitements: Antiinflammatoires, autres traitements immunomodulateurs, traitements ciblés pour qui?
  - Prévention? Pour qui?
  - Problèmes de régulation? Et ne pas sur-immunodeprimer

En dehors VIH

- IRIS sous Anti-TNF
  - Ne pas arreter ou Reprendre anti-TNF
    - Pas de différence de réponse au TAT (Lortholary)
    - TB disséminée sous anti-TNF = IRIS demasquant?
  - Corticoides:
    - Pour maladie sous-jacente+++
    - Pour IRIS, mais ne previent pas la survenue d'IRIS
  - Prolongation du traitement anti-tuberculeux??
    - Aucun argument pour activité residuelle de la mycobactérie
    - Difficile mais non justifié
- IRIS TB disséminées: corticoïdes pour formes avec fort risque de complications:
  - Œdème cérébral, péricardite, compressions VAES
  - Prevention ? pericardite, meningite…