Management of latent tubertculosis infection (TBI) in solid organ transplant (SOT) recipients

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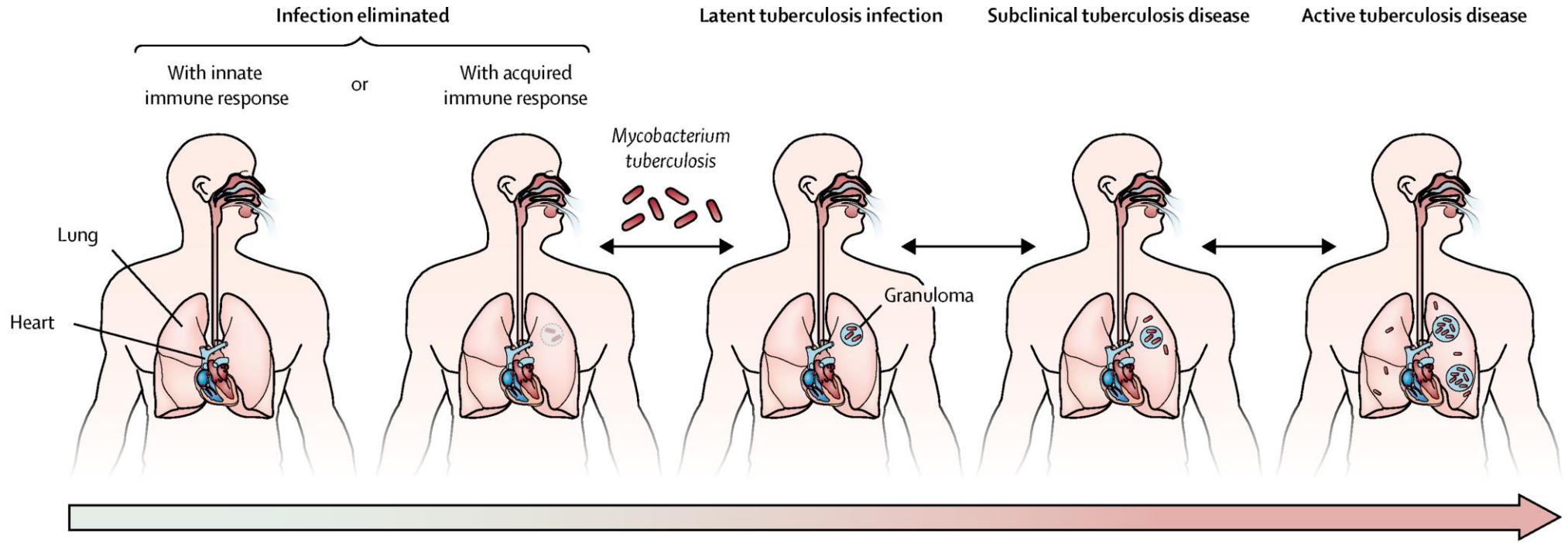
Outlines

- Tuberculosis (TB) in solid organ transplant (SOT) recipients
  - Epidemiology
  - Difficulties in diagnosis and treatment
- How to prevent TB in SOT recipeints?
  - Effectiveness of latent tuberculosis infection (TBI) prophylaxis
  - Adverse drug effects
  - Recommendations

Spectrum of tuberculosis infection and disease



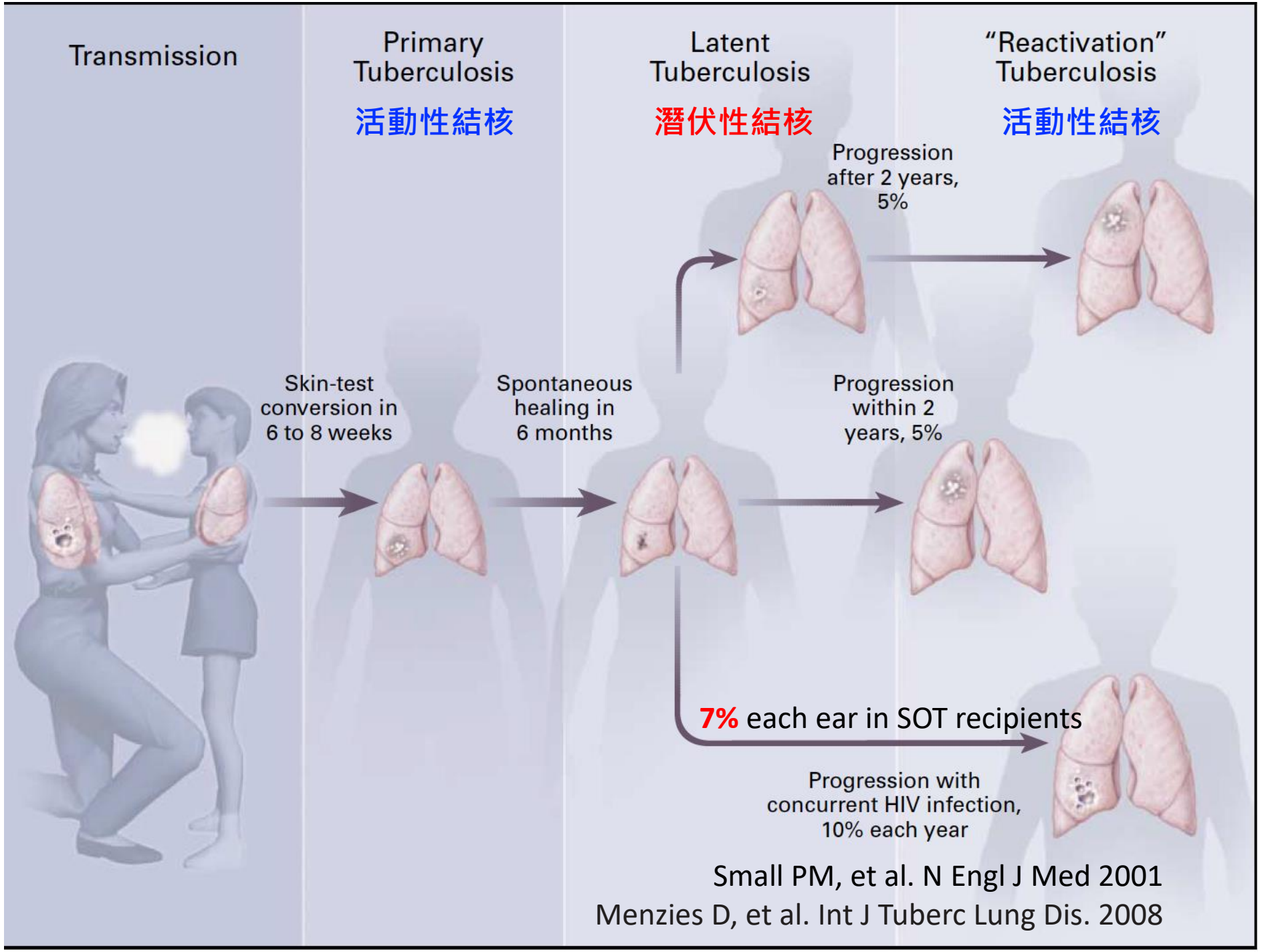
TST	Negative	Positive	Positive	Positive	Usually positive
IGRA	Negative	Positive	Positive	Positive	Usually positive
Culture	Negative	Negative	Negative	Intermittently positive	Positive
Sputum smear	Negative	Negative	Negative	Usually negative	Positive or negative
Infectious	No	No	No	Sporadically	Yes
Symptoms	None	None	None	Mild or none	Mild to severe
Preferred treatment	None	None	Preventive therapy	Multidrug therapy	Multidrug therapy

Furin J, et al. Lancet 2019

Epidemiology

- The prevalence of active TB among SOT recipients
  - 1.2%-6.4% in most developed countries
  - up to 12% in highly endemic areas
- The incidence
  - 24-74 times higher after transplantation

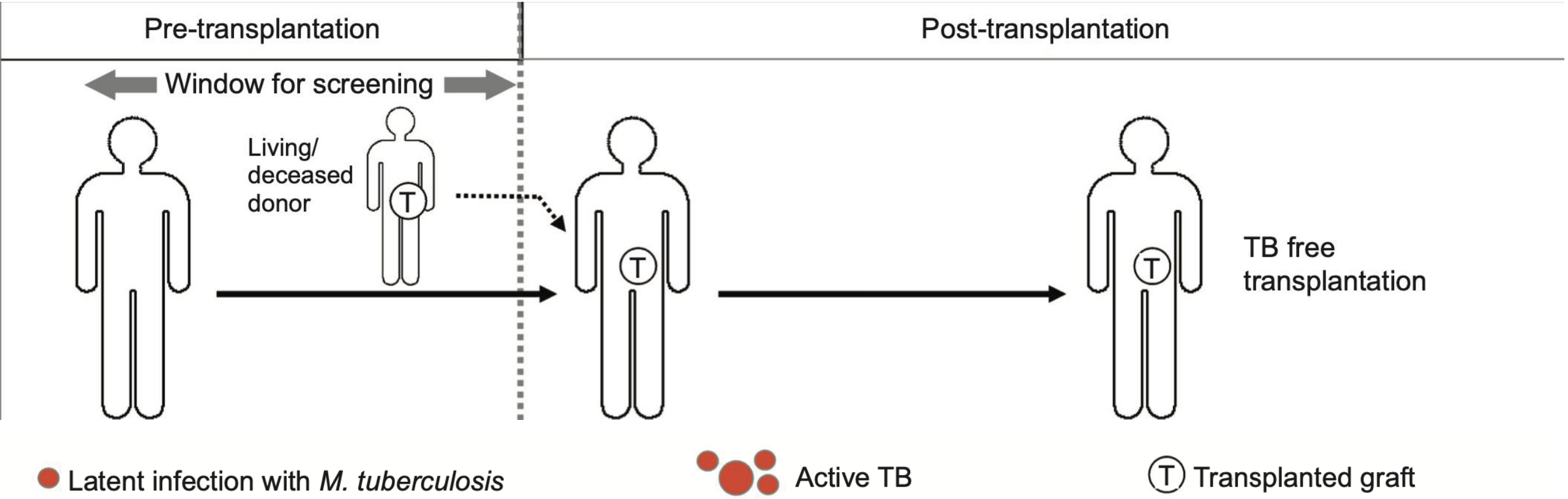
Subramanian AK, et al. *Clinical Transplantation.* 2019
Muñoz P, et al. *Clin Infect Dis* 2005



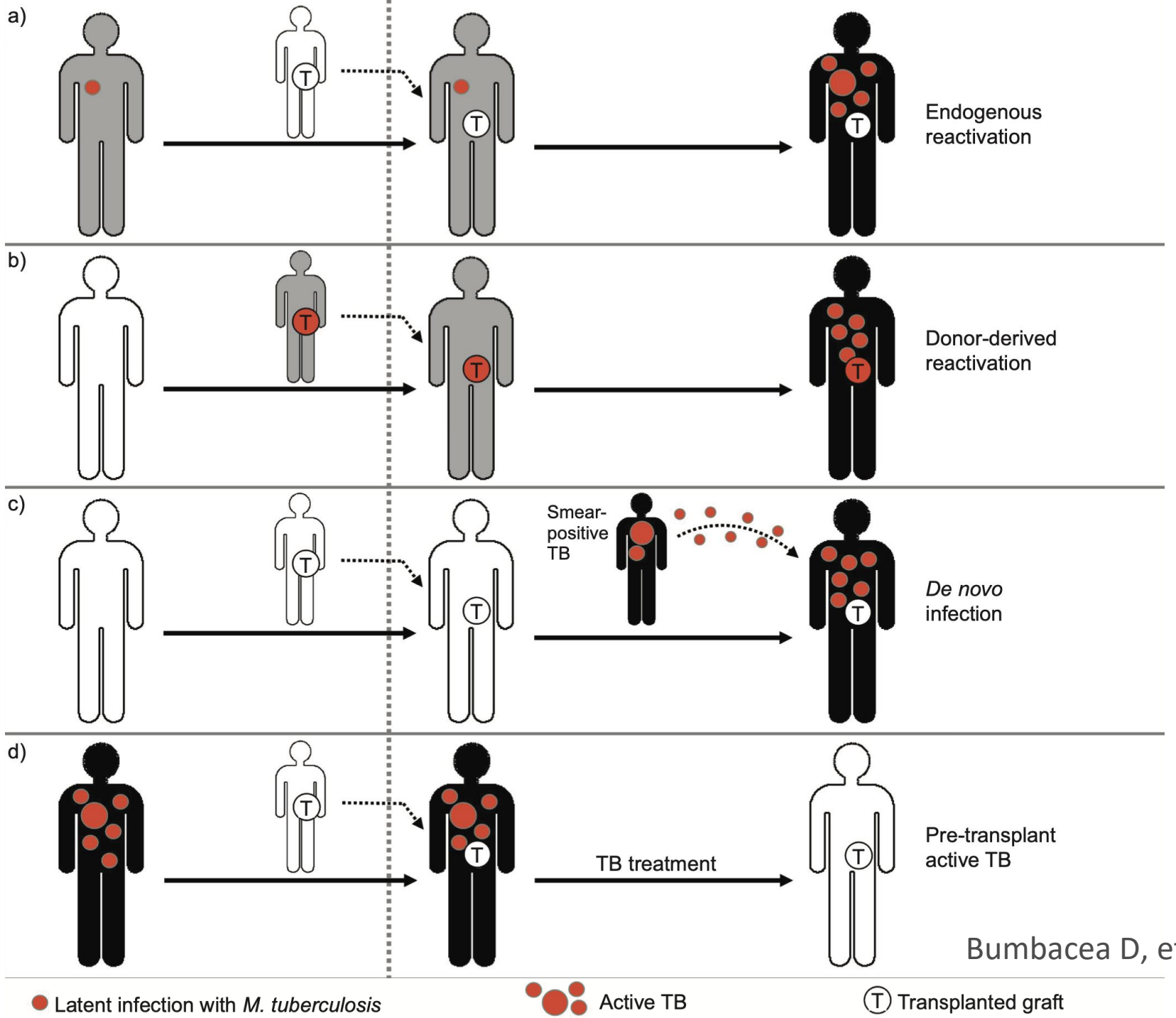
Small PM, et al. N Engl J Med 2001

Menzies D, et al. Int J Tuberc Lung Dis. 2008

The four different scenarios for infection with Mycobacterium tuberculosis in the transplant setting



Bumbacea D, et al. Eur Respir J 2012



Bumbacea D, et al. Eur Respir J 2012

Risk factors for tuberculosis

- History of untreated TB
- The presence of findings on chest radiographs suggestive of healed TB
- Intensified immunosuppression for treatment of allograft rejection
- Prior exposure to *M. tuberculosis*
  - positive tuberculin skin test [TST], positive interferon-γ [IFN-γ] release assay [IGRA]
  - and/or residual TB lesions in pre-transplantation chest imaging
- T-cell–depleting antilymphocyte antibodies
- Kidney transplant recipients
  - Longer pre-transplant hemodialysis and those with hepatitis C virus infection
- Liver transplant recipients
  - Mammalian target of rapamycin inhibitors (mTORis)
- Lung transplant recipients

Subramanian AK, et al. *Clinical Transplantation.* 2019
Chen CY, et al. *Am J Transplantation* 2005

Characteristics of TB infection, by type of transplant

Characteristic	Overall[a]	Kidney	Liver	Heart	Lung	Other
Age (y)	NA	43.75/47[d]	53/51	64/50	51/50	43.5
Gender, male	1301/2073 (62.76)	896/1316 (68.09)	78/106 (73.58)	20/22 (90.9)	10/19 (52.63)	1/2 (50)
Immunosuppression	1630	1165	45	21	7	2
CSA	685 (42.02)	572 (49.1)	12 (26.67)	17 (80.95)	4 (57.14)	0
Non-CSA	945 (57.98)	593 (51.9)	33 (73.33)	4 (19.15)	3 (42.86)	2 (100)
h/o acute rejection prior to TB	223/687 (32.46)	184/531 (34.65)	5/17 (29.41)	6/8 (75)	4/6 (66.67)	1 (50)
Time of onset, median (mos)						
Early <12 mos	417 (41.16)	255 (37.67)	43 (72.88)	14 (63.64)	15 (75)	0
Late >12 mos	596 (58.84)	422 (62.33)	16 (27.12)	8 (36.36)	5 (25)	2 (100)
Type of TB, n	1642	1257	63	22	19	2
PTB	890 (54.2)	678 (53.94)	23 (36.51)	12 (54.55)	15 (78.95)	1 (50)
EPTB	490 (29.84)	403 (32.06)	23 (36.51)	4 (18.18)	2 (10.53)	0
Disseminated	262 (15.96)	176 (14)	17 (26.98)	6 (27.27)	2 (10.53)	1 (50)
Fever	513/597 (86)	370/533 (69.42)	39/57 (68.42)	13/22 (60)	9/18 (50)	1 (50)

Abad CLR, et al. *Clinical Transplantation.* 2018

Anti-infective and immunosuppressant drug interactions

Antimicrobial	Immunosuppressant	Severity of Interaction[a]	Interaction	Mechanism of interaction	Suggested actions	GRADE[b]
Rifamycins						
Rifampin	CSA, TAC, **SRL**, EVR	+++	↓ Imm levels	CYP3A4 induction	Avoid/↑ Imm 2-fold and monitor	Strong, Moderate
	MMF, MPA	+		Induction of UGT and organic anion transporters	Utilize alternate rifamycin if possible	Strong, Moderate
	Prednisone	++		CYP3A4 induction	Monitor steroid efficacy, consider dose increase	Strong, Low
Rifabutin	CSA TAC, **SRL**, **EVR**	++		CYP3A4 induction	Monitor Imm levels	Strong, Moderate
Rifapentine	CSA, TAC, SRL, EVR, Prednisone	++		CYP3A4 induction	Monitor Imm levels	Weak, Very Low

CSA, cyclosporine; EVR, everolimus; Imm, immunosuppressant; MMF, mycophenolate mofetil; MPA, mycophenolic acid; SRL, sirolimus; TAC, tacrolimus
[b]GRADE: Strength of Recommendation (Strong, Weak) and Quality of the Evidence (High, Moderate, Low, Very Low)

Spark T, et al. *Clinical Transplantation.* 2019

Characteristic	Overall[a]	Kidney	Liver	Heart	Lung	Other
Treatment, n	1150	1058	57	15	18	2
4- or 5-drug therapy	647 (56.26)	752 (71.08)	39 (68.42)	9 (60)	11 (61.1)	2 (100)
3-drug therapy	198 (17.22)	172 (16.26)	16 (28.07)	5 (33.33)	5 (27.78)	0
HR-containing	783 (68.09)	723 (68.34)	41 (71.93)	9 (60)	9 (50)	1 (50)
Nonspecified or non-HR	323 (28.09)	134 (12.67)	8 (14.04)	7 (46.67)	7 (38.89)	1 (50)
Treatment duration (mean)						
Case reports	12.01	10.24	8.95	7.29	9.6	18
Cohort	10.54	11.16	9.45	NR	11	—
Morbidity						
Hepatotoxicity[b]	140/716 (19.56)	102/502 (20.32)	11/40 (27.5)	NR	NR	NR
Graft dysfunction/loss	188/1249 (15.05)	183/1090 (16.79)	2/57 (3.51)	0/13	0/13	0/2
Mortality	269/1428 (18.84)	229/1215 (18.85)	13/64 (20.31)	5/21 (23.81)	5/20 (25)	0/2

EPTB, extrapulmonary TB; HR, isoniazid/rifampin; NR—not reported; PTB, pulmonary TB.
[a]Denominator may include SOT recipients from combined cohort.
[b]Cohort data only.
[c]Included DDI cases.
[d]Cohort/case report.

Abad CLR, et al. *Clinical Transplantation.* 2018

Clinical features of tuberculosis in solid organ transplantation

Characteristic	Reactivation TB	Donor-derived infection
Organ Involvement	EPTB and DTB are more common	Allograft is commonly involved
Mode of transmission	Reactivation of latent infection in the recipient	Latent infection from the transplant allograft
Symptoms	Fever is most common	Fever or allograft pain
Time to reactivation after transplant	Usually >12 months in KT Earlier in non-KT	Early, usually within 3 months
Mortality	18%	25%

Abad CLR, et al. Expert Rev Anti Infect Ther. 2020

Difficulties in SOT recipiets with TB

- Difficulties in the diagnosis
  - High incidence
  - Non-specific presentations

- Difficulties in the treatment
  - Drug-drug interactions
  - Drug toxicities

How to prevent tuberculosis in SOT recipients?

Case

- A 22-year-old woman, who migrated to the US from Ethiopian in 2014
- December 2017
  - A living unrelated donor kidney transplant for end-stage renal disease caused by granulomatous interstitial nephritis with glomerulosclerosis and interstitial fibrosis
  - Induction therapy: alemtuzumab
  - Maintainance therapy: tacrolimus, mycophenolate mofetil, and prednisone
  - Prophylaxis: valganciclovir for CMV and TMP-SMX for PCP
  - Positive TST with negative CXR s/p 4-month rifampin DOT

Abad CLR, et al. *Transpl Infect Dis.* 2019

Case

- February 2018
  - Fever and fatigue
  - Physical examination: enlarged tender lymph nodes over the anterior and posterior cervical regions; tenderness on palpation of the parietal region
  - Lab data: WBC 7000 cells/mm3, Hb 11 g/dL, Plat 254K, serum Cr 1.6 mg/dL
  - CT of the head, chest, abdomen, and pelvis: a left temporo-occipital abscess
  - Histopathology of the cervical lymph node: granulomatous inflammation and multiple acid-fast bacilli
  - Cervical LN tissue was positive for *M. tuberculosis* complex PCR
  - M. tuberculosis was isolated from its culture
  - She was treated with isoniazid, ethambutol, pyrazinamide, and rifabutin

Abad CLR, et al. *Transpl Infect Dis.* 2019

Effectiveness of TBI prophylaxis in SOT recipients

- Among 41 cohort studies, active TB disease developed
  - only 1.8% of all recipients given prophylaxis (36/2010)
    - Before transplantation in 13 studies, after in 19, and either in two
  - 2.5% (250/9750) who were not on prophylaxis (relative risk [RR] = 0.69, $p < 0.04$)
- Among 6 randomized controlled trials (RCT), active TB developed
  - a total of 20 (3.1%) of 641 patients who received LTBI prophylaxis
  - 62 (11.4%) of 544 recipients who did not receive prophylaxis (RR = 0.25, $p < 0.00001$)

Abad CLR, et al. Expert Rev Anti Infect Ther. 2020

Adverse drug reactions (ADR) of TBI prophylaxis

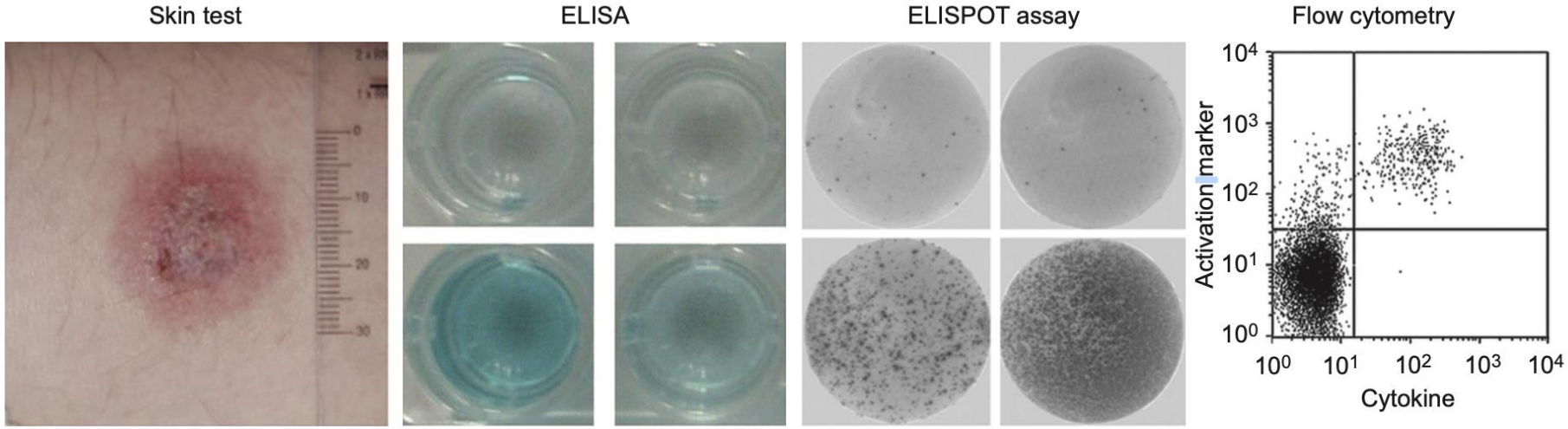
- Patients in 41 cohorts
  - INH, Levo/EMB, RIF, FQ, INH/RIF for 1 to 18 months
  - ADR: 149/1148 (12.9%)
    - Hepatitis: 68/149 (45.6%)
  - Risk of hepatitis in INH
    - 6% (68/1148)
- Patients in 6 RCT
  - INH for 9 months to 1 year
  - ADR: 73/641 (11.4%)
    - Hepatitis: 42/73 (57%)
  - Risk of hepatitis in INH
    - 6.6% (42/641)
- Liver transplant recipients
  - ADR: 56/266 (21%)
    - INH-related: 51.8% (29/56)
  - Risk of hepatitis in liver-only recipients
    - 10.9% (29/266)
  - There was no reported INH resistance

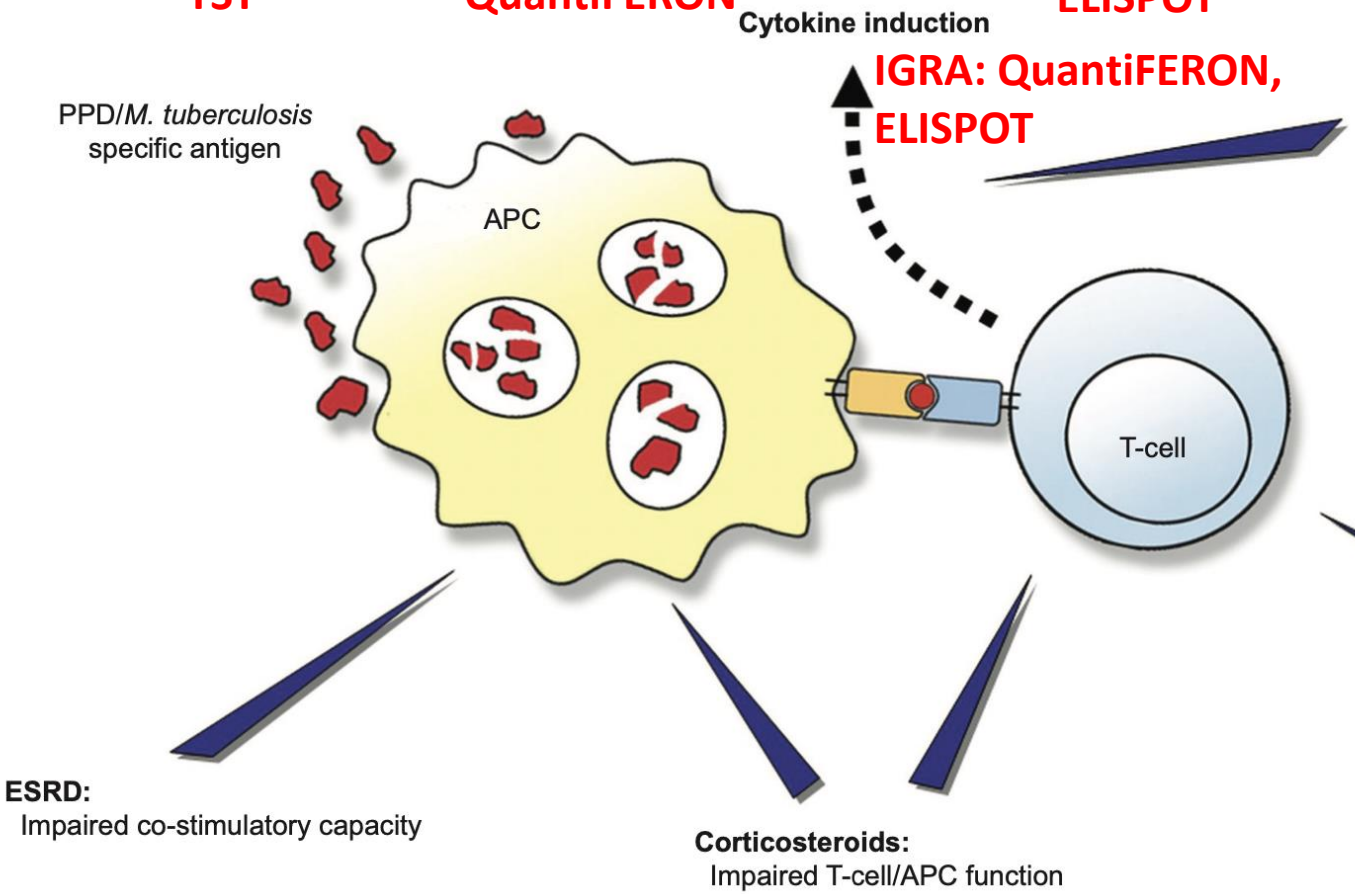
Abad CLR, et al. *Transpl Infect Dis.* 2019

Studies with candidates treated with 3HP

Author/ Year	Study Design	Organ type/ Country	Regimens	Case No. N (%)	Competetion rate N (%)	Adverse reactions (Ads) (hepatitis)	DC due to ADRs N (%)	Post-Tx TB N (%)
Simkins 2017	Retrosp. study of RCT	Renal candidates/ USA	3HP vs. 9H	43 (28%) vs. 110 (72%)	40 (93%) vs. 52 (47%)	0 (0%) vs. 6 (5%)	3 (7%) vs. 12 (11%)	0 (0%) (12 Tx F/U 367 d) vs. 0 (0%) (19 Tx F/U 512 d)
Knoll 2017	Prosp. study	Liver (8)/renal (4) candidates/USA	3HP	12	12 (100%)	1 (8.3%)	0 (0%)	0 (0%) 3 s/p Tx, No TB at 9, 22, 40 months
Castilla 2014	Prosp. study	SOT candidates/ USA	3HP	17	13 (76%)	0 (0%)		0 (0%) 4 s/p Tx, No TB at 20.4 mo

Simkins J, et al. *Transplantation* 2017
Knoll BM, et al. *Infection* 2017
Castilla *Transplantation* 2014





	2021/02/24 11:30
IGRA Result()	Indeterminate - Low Mitogen
IGRA:Nil(IU/mL)	0.032
IGRA:TB Antigen(IU/mL)	0.035
IGRA:Mitogen(IU/mL)	0.298

Bumbacea D, et al. *Eur Respir J* 2012

Regimens used for treatment of TBI

First-line regimens:

- 9H (INH × 9 mo)[76]
- 4R (RIF × 4 mo)[76]
- 3HP (weekly INH/RPT × 12 doses)[76]

Alternative regimens with disadvantages relative to first-line regimens:

- 6H (INH × 6 mo)[76]
- RFB × 4 mo[76]
- 3HR (INH/RIF × 3 mo)[74,77]
- 4HR (INH/RIF × 4 mo)[77]

INH, isoniazid; RFB, rifabutin; RIF, rifampin; RPT, rifapentine.

Subramanian AK, et al. *Clinical Transplantation.* 2019

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Spark T, et al. *Clinical Transplantation.* 2019

Recommendations

- Screening of deceased or living donors and recipients, and treating living donors and recipients with latent tuberculosis infection are effective strategies to reduce risk of TB disease in the recipient post-solid organ transplantation.
- In addition to assessment of TB exposure risk, tuberculin skin tests (TST) and interferon gamma release assays (IGRA) are indirect measures of TB infection in living donors and recipients.

Malinis M, et al. Curr Opin Organ Transplant 2021

Recommendations

- Whenever possible, completion of LTBI therapy is recommended before transplantation and donation of transplant candidates and living donors, respectively.
- Treatments of LTBI and TB disease are similar to general population in transplant candidates and recipients.
  - Potential drug–drug interactions and adverse effects have to be carefully evaluated prior to initiation of treatment.
- Tuberculosis may still occur despite TBI treatment.

Malinis M, et al. Curr Opin Organ Transplant 2021

Thank you!