TABLE RONDE
Complications et infections opportunistes

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prednisone for the Prevention of Paradoxical Tuberculosis-Associated IRIS

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- ECR supériorité, double aveugle, monocentrique (Afrique du Sud), n = 240
  - Objectif : prévention IRIS par glucocorticoïdes chez TB VIH
    - CJP : IRIS selon critères INSHI à 12 semaines d'ARV

- Naïf ARV
- CD4 < 100
- TB microbiologiquement confirmée ou diagnostic clinique avec réponse symptomatique aux anti-TB
- Anti TB < 30j avant ARV

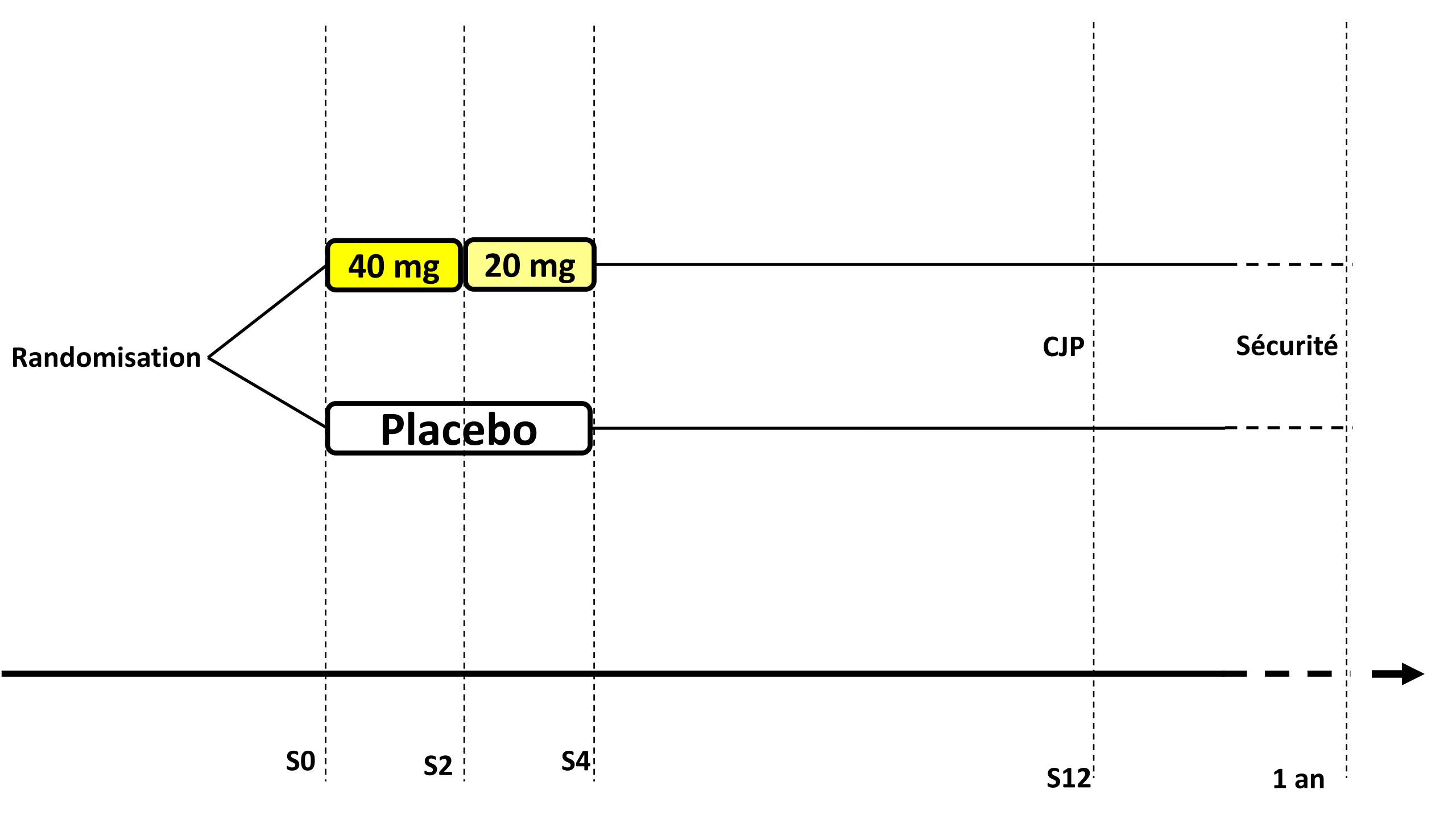
- TB neuro ou péricardique
- Anti TB non standards
- Pas de réponse aux anti-TB
- CTC 7 jours avant

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Prednisone Group (N=120)	Placebo Group (N=120)
Median age (IQR) — yr	36 (31–42)	36 (29–42)
Male sex — no. (%)	71 (59.2)	73 (60.8)
Median body-mass index (IQR)†	21 (19–24)	21 (19–24)
Median CD4 count (IQR) — no. of cells/μl	51 (27–84)	49 (23–88)
Median HIV-1 RNA viral load (IQR) — $\log_{10}$ copies/ml	5.5 (5.2–5.9)	5.6 (5.2–5.9)
Microbiologically confirmed TB — no. (%)‡	86 (71.7)	89 (74.2)
Median hemoglobin level (IQR) — g/dl	9.7 (8.8–11.1)	9.8 (8.5–10.9)
Median white-cell count (IQR) — $\times 10^{-9}$/liter	3.7 (2.9–5.1)	3.4 (2.6–5.0)
Median neutrophil count (IQR) — $\times 10^{-9}$/liter	2.3 (1.5–3.1)	2.0 (1.4–2.9)
Median platelet count (IQR) — $\times 10^{-9}$/liter	311 (259–413)	300 (226–396)
Median sodium level (IQR) — mmol/liter	136 (134–139)	137 (135–139)
Median creatinine level (IQR) — μmol/liter	57 (50–66)	59 (50–70)
Median total bilirubin level (IQR) — μmol/liter	6 (4–7)	6 (4–8)
Median alanine aminotransferase level (IQR) — IU/liter	26 (18–38)	28 (20–40)
Median alkaline phosphatase level (IQR) — IU/liter	113 (87–149)	115 (91–163)
Median C-reactive protein level (IQR) — mg/liter	10.9 (4.0–30.1)	10.7 (4.6–29.9)
Median Karnofsky performance score (IQR)§	90 (80–90)	90 (80–90)
Median duration of TB treatment before initiation of ART (IQR) — days	16 (15–22)	17 (15–21)

Critères INSHI

≥ 1 Major clinical criteria:	OR	≥ 2 Minor clinical criteria
- New or enlarging lymph nodes, cold abscesses, or other focal tissue involvement - New or worsening radiological features of TB - New or worsening CNS TB (meningitis or focal neurological deficit) - New or worsening TB serositis		- New or worsening constitutional symptoms - New or worsening respiratory symptoms - New or worsening abdominal pain accompanied by peritonitis, hepatomegaly, splenomegaly, or abdominal adenopathy


40 mg
20 mg
Randomisation
Placebo
CJP
Sécurité
S0
S2
S4
S12
1 an

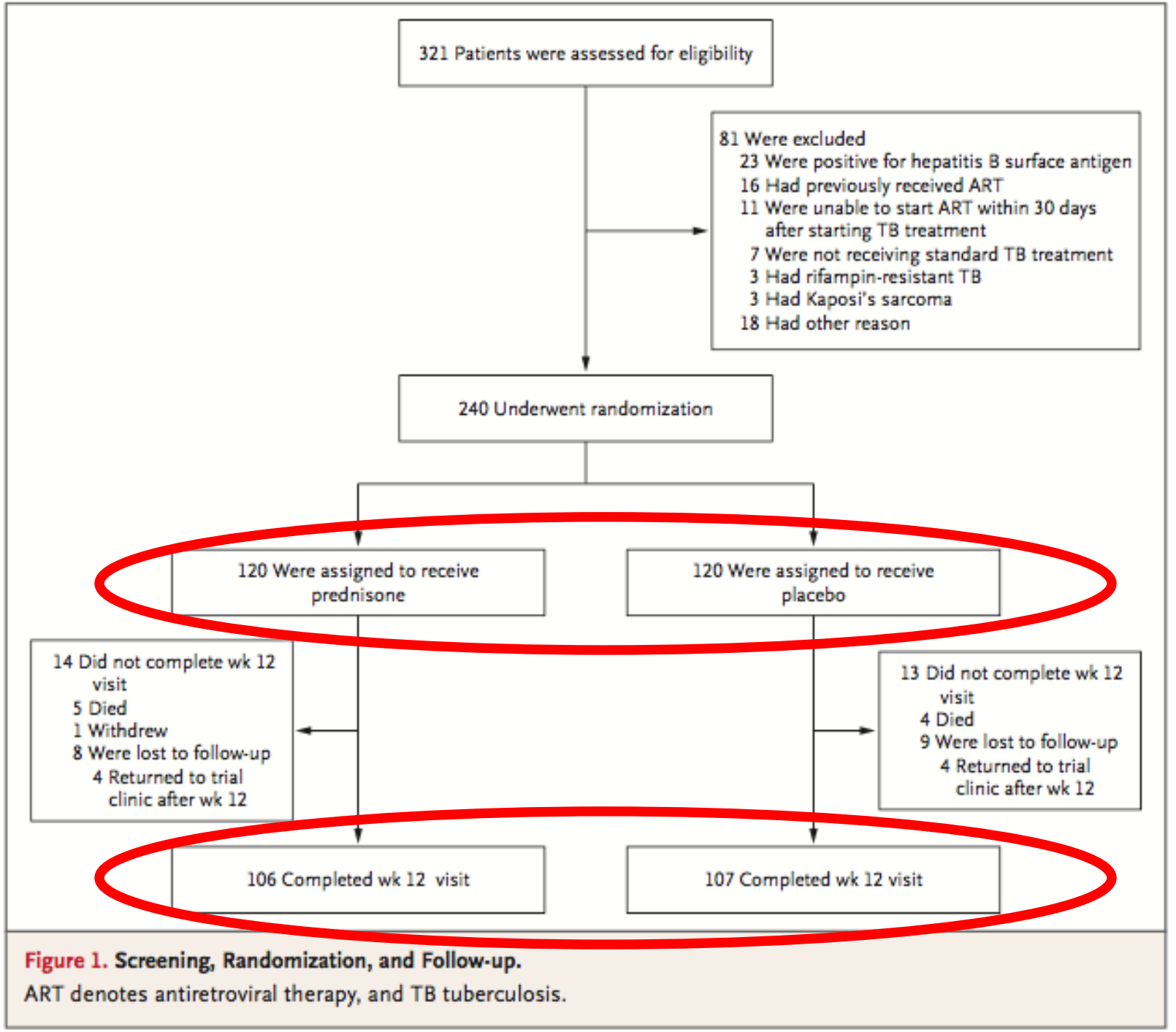
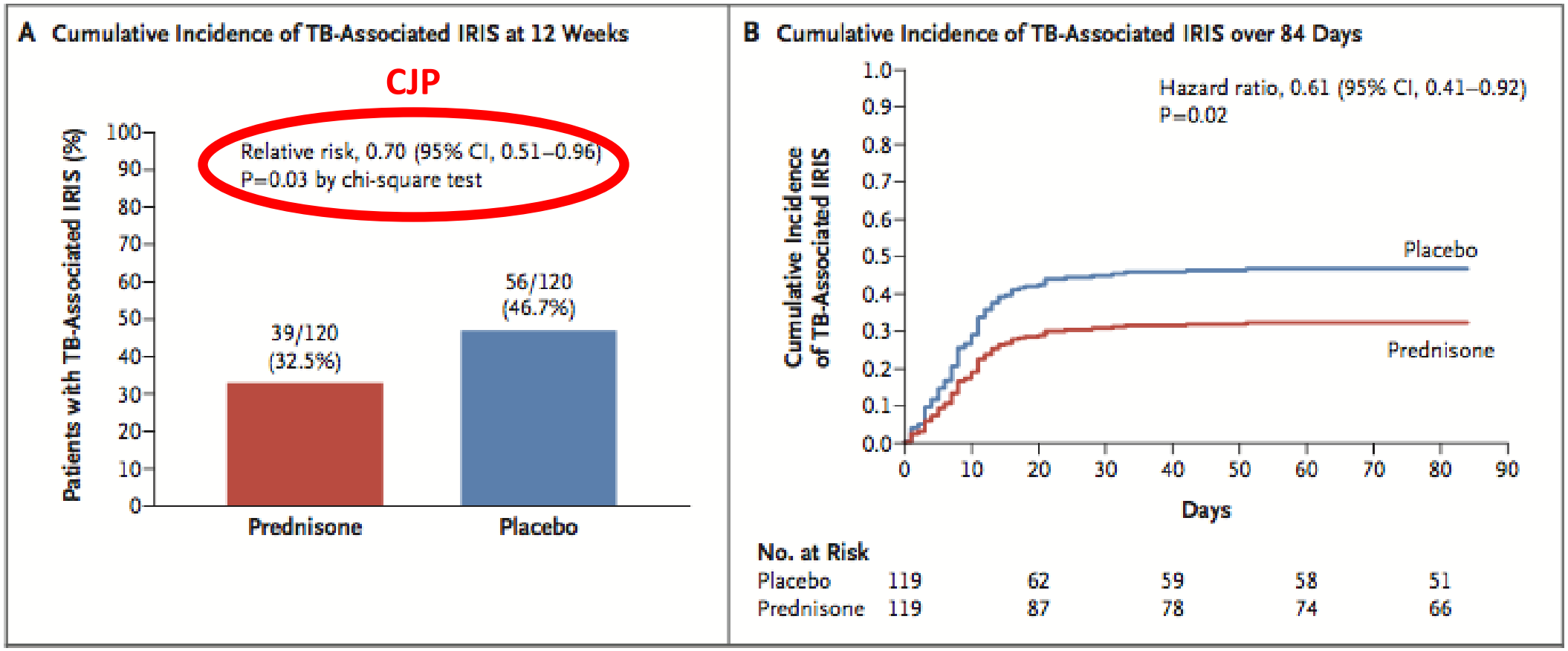


Figure 1. Screening, Randomization, and Follow-up.
ART denotes antiretroviral therapy, and TB tuberculosis.

Analyse CJP en ITT

Gestion données manquantes ?


A Cumulative Incidence of TB-Associated IRIS at 12 Weeks
CJP
Relative risk, 0.70 (95% CI, 0.51–0.96)
P=0.03 by chi-square test
Patients with TB-Associated IRIS (%)
100
90
80
70
60
50
40
30
20
10
0
39/120
(32.5%)
56/120
(46.7%)
Prednisone
Placebo
B Cumulative Incidence of TB-Associated IRIS over 84 Days
Hazard ratio, 0.61 (95% CI, 0.41–0.92)
P=0.02
Cumulative Incidence of TB-Associated IRIS
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Placebo
Prednisone
0
10
20
30
40
50
60
70
80
90
Days
No. at Risk
Placebo 119 62 59 58 51
Prednisone 119 87 78 74 66

Critères INSHI

10 vs 23 15 vs 26 0 vs 0 2 vs 2	**≥ 1 Major clinical criteria:** - New or enlarging lymph nodes, cold abscesses, or other focal tissue involvement - New or worsening radiological features of TB - New or worsening CNS TB (meningitis or focal neurological deficit) - New or worsening TB serositis	OR	**≥ 2 Minor clinical criteria** - New or worsening constitutional symptoms - New or worsening respiratory symptoms - New or worsening abdominal pain accompanied by peritonitis, hepatomegaly, splenomegaly, or abdominal adenopathy	14 vs 12

Table 2. Analysis of the Primary End Point in Prespecified Subgroups.*

Subgroup	Prednisone Group (N=120)	Placebo Group (N=120)	Relative Risk (95% CI)
	no./total no. (%)		
CD4 count at screening			
≤50 cells/μl	28/60 (46.7)	37/62 (59.7)	0.78 (0.56–1.10)
>50 cells/μl	11/60 (18.3)	19/58 (32.8)	0.56 (0.29–1.07)
HIV-1 RNA viral load at screening			
>100,000 copies/ml	36/102 (35.3)	50/99 (50.5)	0.70 (0.50–0.97)
≤100,000 copies/ml	3/17 (17.6)	5/20 (25.0)	0.71 (0.20–2.53)
Microbiologically confirmed TB†	33/86 (38.4)	43/89 (48.3)	0.79 (0.56–1.12)
No rifampin-resistant TB diagnosed after enrollment‡	39/118 (33.1)	55/119 (46.2)	0.72 (0.52–0.99)

NS

Table 3. Primary and Secondary End Points.*

End Point	Prednisone Group (N=120)	Placebo Group (N=120)	Relative Risk (95% CI)	P Value
Primary end point				
TB-associated IRIS meeting INSHI criteria — no. (%)	39 (32.5)	56 (46.7)	0.70 (0.51–0.96)	0.03
Secondary efficacy end points				
TB-associated IRIS meeting at least 1 major INSHI criterion — no. (%)	25 (20.8)	44 (36.7)	0.57 (0.37–0.87)	
Sustained TB-associated IRIS — no. (%)†	35 (29.2)	50 (41.7)	0.70 (0.49–0.99)	
Median duration of TB-associated IRIS (IQR) — days†	49 (31–97)	35 (19–82)		
Open-label glucocorticoid treatment of TB-associated IRIS — no. (%)	16 (13.3)	34 (28.3)	0.47 (0.27–0.81)	
Hospitalization for TB-associated IRIS — no. (%)	5 (4.2)	9 (7.5)	0.56 (0.19–1.61)	
Hospitalization for any cause — no. (%)	17 (14.2)	27 (22.5)	0.63 (0.36–1.09)	
Death from any cause — no. (%)	5 (4.2)	4 (3.3)	1.25 (0.34–4.54)	1.00
Death attributed to TB-associated IRIS — no. (%)	0	1 (0.8)	Could not be calculated	1.00
Composite end point of death, hospitalization, and hepatotoxicity — no. (%)	22 (18.3)	32 (26.7)	0.69 (0.43–1.11)	
Interruption of ART, TB treatment, or both owing to adverse event — no. (%)	10 (8.3)	19 (15.8)	0.53 (0.26–1.08)	
Interruption of ART, TB treatment, or both owing to drug-induced liver injury or rash — no. (%)	6 (5.0)	8 (6.7)	0.75 (0.27–2.10)	
Secondary safety end points‡				
Severe infection — no./total no. (%)§	11/119 (9.2)	18/119 (15.1)	0.61 (0.30–1.24)	0.23
Grade 3 clinical adverse event — no./total no. (%)¶	33/119 (27.7)	53/119 (44.5)	0.62 (0.44–0.89)	0.01
Grade 4 clinical adverse event — no./total no. (%)¶	8/119 (6.7)	10/119 (8.4)	0.80 (0.33–1.96)	0.81
Serious adverse event — no./total no. (%)‖	24/119 (20.2)	30/119 (25.2)	0.80 (0.50–1.28)	0.44
Adverse drug reaction — no./total no.**	22/119	21/119	1.05 (0.61–1.80)	1.00
Definitely related to trial regimen	0/22	0/21		
Probably related to trial regimen	1/22	2/21		
Possibly related to trial regimen	21/22	19/21		
CD4 count at week 12				
No. of patients in analysis	106	106		
Median (IQR) — no. of cells/μl	164 (97–226)	150 (100–226)		0.73
Decrease in HIV-1 RNA viral load of <2 $\log_{10}$ copies/ml at week 12 — no./total no. (%)	6/105 (5.7)	9/105 (8.6)	0.67 (0.25–1.81)	0.59

Suivi à 1 an

- Statut vivant/mort à 1 an, 239/240, 8 (CTC) vs 10 (placebo)
- Statut cancer à 1 an, 220/240, 0 (CTC) vs 1 (placebo)

Conclusion

- diminution significative du risque d IRIS
- Aucun impact sur mortalité
- population afrique du sud (prevalence TB VIH)

Original Article

Bacterial Factors That Predict Relapse after Tuberculosis Therapy

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BACKGROUND

Approximately 5% of patients with drug-susceptible tuberculosis have a relapse after 6 months of first-line therapy, as do approximately 20% of patients after 4 months of short-course therapy.

We postulated that by analyzing pretreatment isolates of *Mycobacterium tuberculosis* obtained from patients who subsequently had a relapse or were cured, we could determine any correlations between the minimum inhibitory concentration (MIC) of a drug below the standard resistance breakpoint and the relapse risk after treatment.

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METHODS

- Using data from the Tuberculosis Trials Consortium Study 22 (development cohort),
- we assessed relapse and cure isolates to determine the MIC values of isoniazid and rifampin that were below the standard resistance breakpoint (0.1 μg per milliliter for isoniazid and 1.0 μg per milliliter for rifampin).
- We combined this analysis with clinical, radiologic, and laboratory data to generate predictive relapse models, which we validated by analyzing data from the DMID 01-009 study (validation cohort).

RESULTS

- In the development cohort, the mean (—SD) MIC of isoniazid below the breakpoint was 0.0334 +/- 0.0085 µg per milliliter in the relapse group and 0.0286 +/-0.0092 µg per milliliter in the cure group, which represented a higher value in the relapse group by a factor of 1.17 (P = 0.02).
- The corresponding MIC values of rifampin were 0.0695 +/-0.0276 and 0.0453 ±0.0223 µg per milliliter, respectively, which represented a higher value in the relapse group by a factor of 1.53 (P<0.001).
- Higher MIC values remained associated with relapse in a multivariable analysis that included other significant between-group differences.

Table 2. Logistic-Regression Models Predicting Tuberculosis Relapse after Treatment.*

Variable	Univariate Model	Rifampin and Isoniazid MIC Model	All-Variable Model†	All-Variable Model without 8-Wk Sputum Culture	Full Model‡	Full Model without 8-Wk Sputum Culture	Composite Model§
Isoniazid MIC							NA
Odds ratio per increase of 0.01 μg/ml (95% CI)	1.83 (1.08–3.28)	2.14 (1.15–4.40)	2.81 (1.29–7.34)	2.43 (1.17–5.85)	2.65 (1.36–5.84)	2.41 (1.17–5.68)	
P value	0.02	0.02	0.01	0.02	0.008	0.02	
Rifampin MIC							NA
Odds ratio per increase of 0.01 μg/ml (95% CI)	1.47 (1.21–1.85)	1.38 (1.12–1.75)	1.44 (1.13–1.94)	1.45 (1.15–1.90)	1.43 (1.15–1.84)	1.44 (1.15–1.89)	
P value	<0.001	0.002	0.004	0.002	0.002	0.002	
Underweight by ≥10%		NA					
Odds ratio (95% CI)	2.53 (1.21–5.41)		4.06 (1.19–16.01)	3.21 (1.06–10.55)	3.99 (1.17–15.55)	3.21 (1.06–10.56)	3.03 (1.31–7.29)
P value	0.01		0.03	0.04	0.03	0.04	0.01
Cavitation on chest radiography		NA					
Odds ratio (95% CI)	2.81 (1.26–6.58)		2.75 (0.76–11.10)	3.92 (1.20–14.85)	2.71 (0.75–10.85)	3.92 (1.20–14.80)	1.88 (0.77–4.66)
P value	0.01		0.13	0.03	0.14	0.03	0.17
Bilateral disease on chest radiography		NA	NA	NA	NA	NA	NA
Odds ratio (95% CI)	3.42 (1.54–7.93)						
P value	0.003						
Positive 8-wk sputum culture		NA		NA		NA	
Odds ratio (95% CI)	4.06 (1.86–9.24)		7.46 (2.18–29.48)		6.85 (2.05–26.09)		3.87 (1.60–9.84)
P value	<0.001		0.002		0.003		0.003
White race		NA			NA	NA	NA
Odds ratio (95% CI)	2.31 (1.01–5.47)		0.60 (0.13–2.41)	0.93 (0.25–3.29)			
P value	0.05		0.48	0.91			
Treatment with rifapentine vs. rifampin		NA					
Odds ratio (95% CI)	1.94 (0.92–4.16)		1.14 (0.33–3.92)	1.34 (0.44–4.16)	1.09 (0.32–3.69)	1.33 (0.44–4.13)	1.66 (0.71–3.95)
P value	0.08		0.83	0.61	0.89	0.61	0.24
ROC AUC (95% CI)¶	NA	0.779 (0.680–0.877)	0.880 (0.806–0.954)	0.841 (0.756–0.925)	0.875 (0.798–0.952)	0.842 (0.756–0.927)	0.755 (0.663–0.847)

* Shown are the eight covariates that were included in models; there was no adjustment for additional covariates. Bilateral disease was included as a variable only in the univariate model, because it was collinear with cavitation on chest radiography. For the minimum inhibitory concentration (MIC) values of rifampin and isoniazid, the P values and 95% confidence intervals have been adjusted by the Bonferroni method; all other variables are exploratory, and the P values and 95% confidence intervals have not been adjusted for multiple comparisons. NA denotes not applicable.

† The all-variable model includes all the variables with the exception of bilateral disease.

‡ The full model includes the MIC values of rifampin and isoniazid, being underweight by 10% or more, cavitation on chest radiography, positive 8-week sputum culture, and randomized study treatment but does not include white race.

§ The composite model includes being underweight, cavitation on chest radiography, positive 8-week sputum culture, and randomized study treatment.

¶ Receiver-operating-characteristic (ROC) curves for relapse were examined to visualize the trade-off between sensitivity and specificity. The area under the curve (AUC) summarizes the overall biomarker performance in a single number, with 0.5 indicating no difference from chance and 1.0 indicating a perfect biomarker with sensitivity and specificity both equal to 100%.

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- In pretreatment isolates of *M. tuberculosis* with decrements of MIC values of isoniazid or rifampin below standard resistance breakpoints, higher MIC values were associated with a greater risk of relapse than lower MIC values.