方法

- eThekwini HIV-tuberculosis clinic in Durban,South Africa
- 2005年6月28日〜2008年7月11日
- 結核とHIVの重複感染者642名
  （喀痰塗抹抗酸菌検査陽性、CD4+＜500mm³）
- Open-label,ramdomized,controlled trial
- 割り付け
①結核治療中に抗レトロウイルス治療開始群
               integrated therapy group
                    →early群、late群に分かれる
②結核治療後に抗レトロウイルス治療開始群
               sequential therapy group

- 結核治療の方法
- 　　2週間（3）intensive combination-drug regimen
　　4週間（5）continuation regimen

- Endpoint
　→The primary endpoint　あらゆる原因による死亡
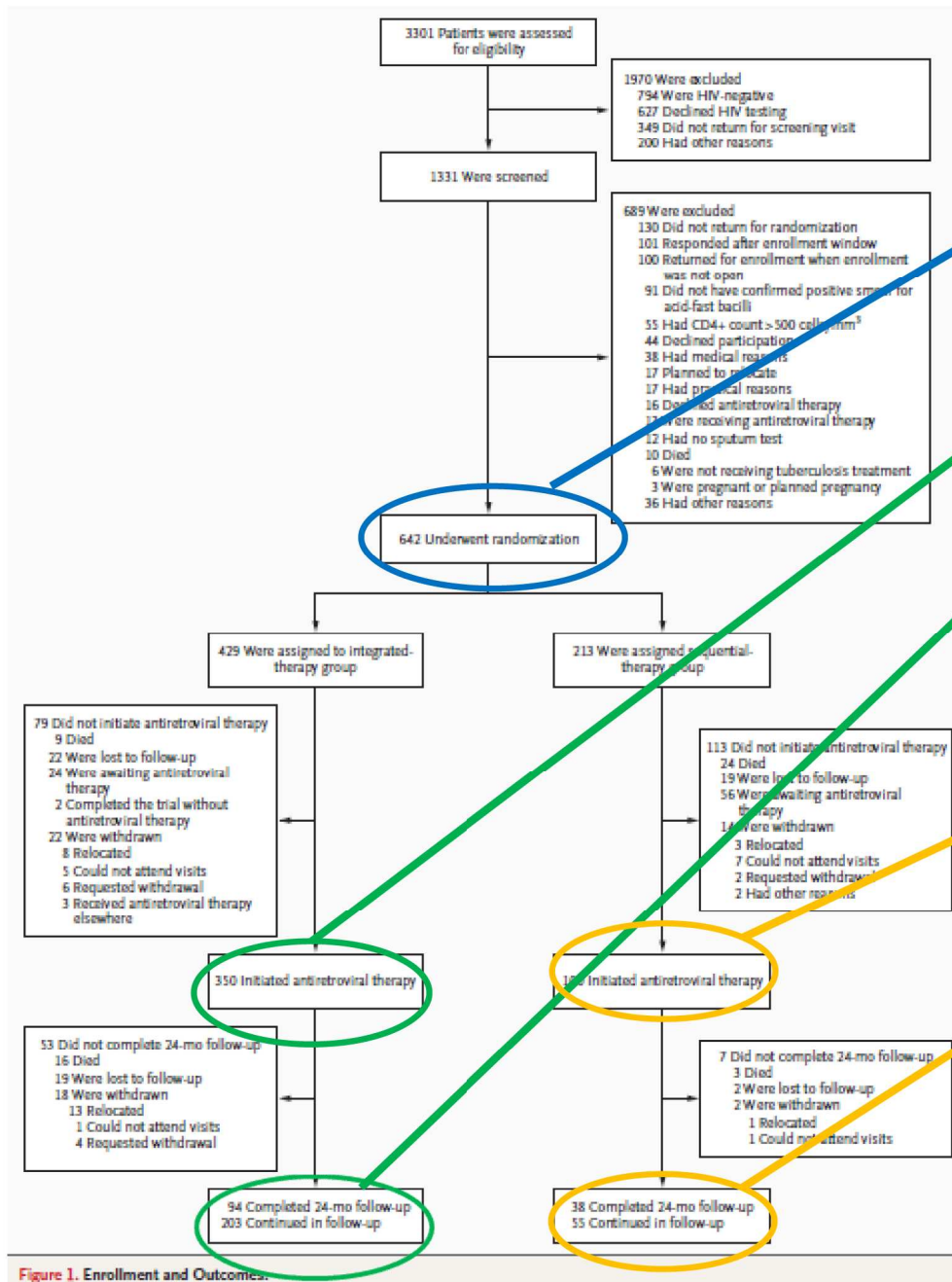

　→The secondary endpoint
　　　　　　　　中毒
　　　　　　　　　HIV RNA量
　　　　　　　　　結核の治療結果
　　　　　　　　　免疫再構築症候群

3301 Patients were assessed for eligibility

1970 Were excluded
　794 Were HIV-negative
　627 Declined HIV testing
　349 Did not return for screening visit
　200 Had other reasons

1331 Were screened

689 Were excluded
　130 Did not return for randomization
　101 Responded after enrollment window
　100 Returned for enrollment when enrollment was not open
　91 Did not have confirmed positive smear for acid-fast bacilli
　55 Had CD4+ count >500 cells/mm³
　44 Declined participation
　38 Had medical reasons
　17 Planned to relocate
　17 Had practical reasons
　16 Declined antiretroviral therapy
　12 Were receiving antiretroviral therapy
　12 Had no sputum test
　10 Died
　6 Were not receiving tuberculosis treatment
　3 Were pregnant or planned pregnancy
　36 Had other reasons

642 Underwent randomization

429 Were assigned to integrated-therapy group

213 Were assigned sequential-therapy group

79 Did not initiate antiretroviral therapy
　9 Died
　22 Were lost to follow-up
　24 Were awaiting antiretroviral therapy
　2 Completed the trial without antiretroviral therapy
　22 Were withdrawn
　　8 Relocated
　　5 Could not attend visits
　　6 Requested withdrawal
　3 Received antiretroviral therapy elsewhere

113 Did not initiate antiretroviral therapy
　24 Died
　19 Were lost to follow-up
　56 Were awaiting antiretroviral therapy
　14 Were withdrawn
　　3 Relocated
　　7 Could not attend visits
　　2 Requested withdrawal
　　2 Had other reasons

350 Initiated antiretroviral therapy

100 Initiated antiretroviral therapy

53 Did not complete 24-mo follow-up
　16 Died
　19 Were lost to follow-up
　18 Were withdrawn
　　13 Relocated
　　1 Could not attend visits
　　4 Requested withdrawal

7 Did not complete 24-mo follow-up
　3 Died
　2 Were lost to follow-up
　2 Were withdrawn
　　1 Relocated
　　1 Could not attend visits

94 Completed 24-mo follow-up
203 Continued in follow-up

38 Completed 24-mo follow-up
55 Continued in follow-up

Figure 1. Enrollment and Outcomes.

合計642人

Integrated therapy
350人

24か月後
297人

Sequential therapy
100人

24か月後
93人

結果

Table 1. Baseline Characteristics of the Patients.*

Variable	Integrated Therapy (N=429)	Sequential Therapy (N=213)	P Value
Age — yr			0.48
Mean	34.4±8.38	33.9±8.18	
Range	19–72	19–60	
Male sex — %	48.7	52.1	0.45
Educational level — no./total no. (%)			0.03
Primary school or less	92/427 (21.5)	48 (22.5)	
Some secondary school	205/427 (48.0)	80 (37.6)	
Completed secondary school	130/427 (30.4)	85 (39.9)	
Employed — no./total no. (%)	251/428 (58.6)	116 (54.5)	0.35
History of tuberculosis — no. (%)	144 (33.6)	64 (30.0)	0.42
Karnofsky score — no./total no. (%)			0.44
90 or 100	251/425 (59.1)	132/209 (63.2)	
70 or 80	165/425 (38.8)	75/209 (35.9)	
<70	9/425 (2.1)	2/209 (1.0)	
Median CD4+ count (interquartile range) — cells/mm³†	150 (77–254)	140 (69–247)	0.32
Median log viral load (interquartile range) — copies/ml‡	5.2 (4.5–5.6)	5.2 (4.7–5.6)	0.22
WHO stage 4 HIV infection — no. (%)§	21 (4.9)	10 (4.7)	1.00
Presence of extrapulmonary tuberculosis — no. (%)	24 (5.6)	10 (4.7)	0.71
Median no. of days of tuberculosis therapy at randomization (interquartile range)	9 (1–14)	9 (7–16)	0.15

* Plus–minus values are means ±SD.
† Patients underwent randomization on the basis of the CD4+ count at screening (criterion for study enrollment, <500 cells per cubic millimeter). However, for 16 patients, the CD4+ count at enrollment was more than 500 cells per cubic millimeter.
‡ The viral load at baseline was measured in 397 patients in the integrated-therapy group and in 201 patients in the sequential-therapy group.
§ The remainder of patients had stage 3 infection, according to criteria of the World Health Organization (WHO).

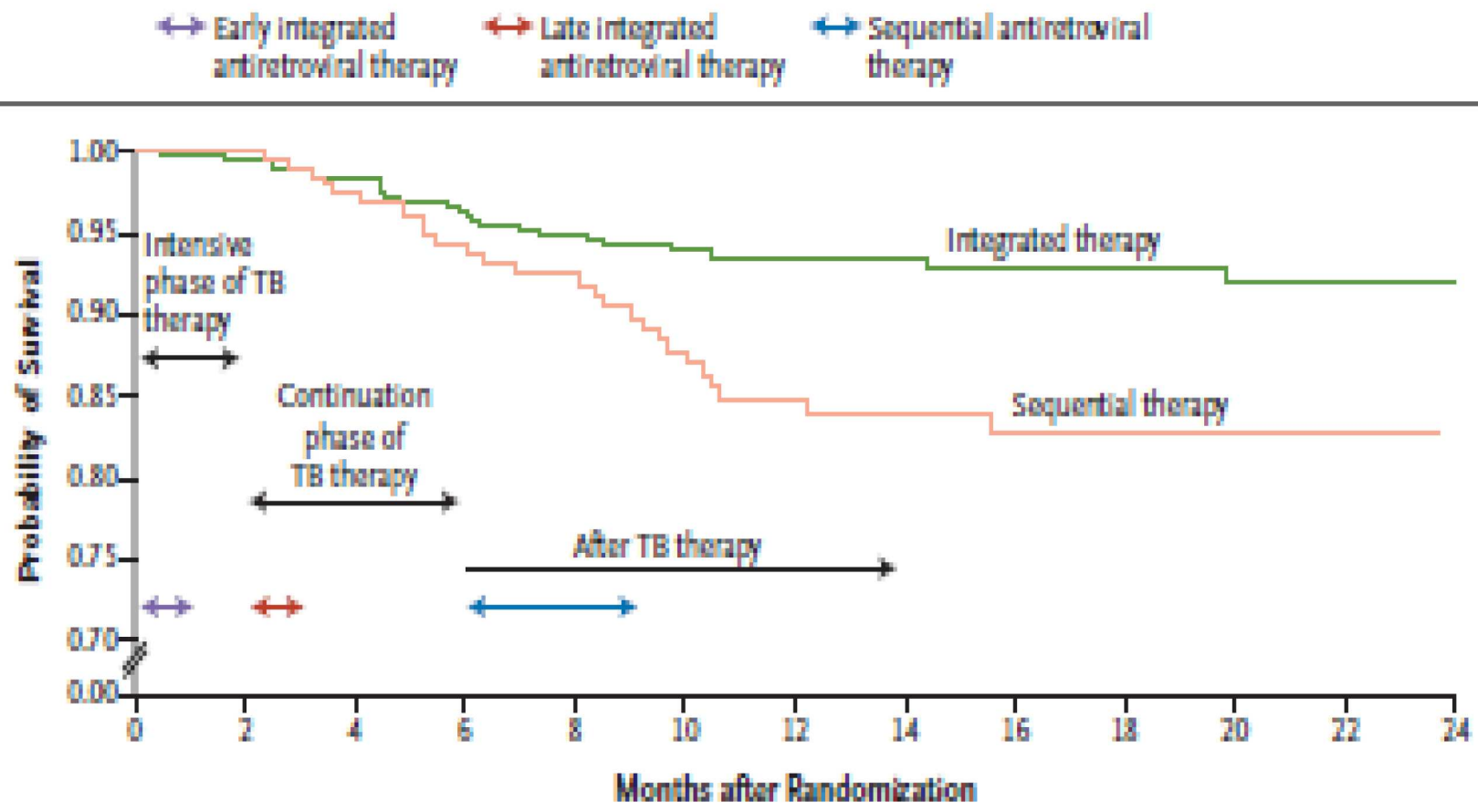**Table 2. Death Rates and Hazard Ratios, Stratified According to CD4+ Cell Count.**

CD4+ Count	Integrated Therapy				Sequential Therapy				Hazard Ratio (95% CI)*	P Value
	No. of Patients	No. of Person-Yr	No. of Deaths	Death Rate/ 100 Person-Yr (95% CI)	No. of Patients	No. of Person-Yr	No. of Deaths	Death Rate/ 100 Person-Yr (95% CI)		
All patients	429	467	25	5.4 (3.5–7.9)	213	223	27	12.1 (8.0–17.7)	0.44 (0.25–0.79)	0.003
≤200 cells/mm³	273	281	23	8.2 (5.2–12.3)	138	137	21	15.3 (9.6–23.5)	0.54 (0.30–0.98)	0.04
>200 cells/mm³	156	186	2	1.1 (0.1–3.9)	75	86	6	7.0 (2.6–15.3)	0.16 (0.03–0.79)	0.02

* Hazard ratios are for the integrated-therapy group, as compared with the sequential-therapy group.

Primary endpoint(死亡)

Integrated therapyの方が、死亡率は低い。

CD4+ cellの数で層別しても、死亡率は
integrated therapyの方が低い。

Figure 2. Kaplan–Meier Survival Curves.

TB denotes tuberculosis.

Secondary endpoint
結核治療の結果

Table 3. Clinical Outcomes of Tuberculosis Therapy.*					
Outcome	Integrated Therapy (N=343)		Sequential Therapy (N=171)		P Value
	Repeated Therapy of Tuberculosis (N=116)	First Episode of Tuberculosis (N=227)	Repeated Therapy of Tuberculosis (N=58)	First Episode of Tuberculosis (N=113)	
	number (percent)				
Tuberculosis cure†	67 (57.8)	131 (57.7)	31 (53.4)	67 (59.3)	1.00
Successful completion‡	16 (13.8)	42 (18.5)	5 (8.6)	16 (14.2)	0.20
Therapy success (cure plus successful completion)	83 (71.6)	173 (76.2)	36 (62.1)	83 (73.5)	0.07
Died before completion of therapy	7 (6.0)	12 (5.3)	6 (10.3)	9 (8.0)	0.19
Therapy interruption	2 (1.7)	3 (1.3)	3 (5.2)	7 (6.2)	0.01
Therapy failure§	0	0	0	1 (0.9)	0.33
Loss to follow-up	13 (11.2)	13 (5.7)	6 (10.3)	6 (5.3)	1.00
Therapy outcome unknown because of transfer to another clinic	1 (0.9)	5 (2.2)	2 (3.4)	1 (0.9)	1.00
Other outcome	1 (0.9)	1 (0.4)	0	0	
Outcome pending (still receiving therapy at time of analysis)	9 (7.8)	20 (8.8)	5 (8.6)	6 (5.3)	0.49

* Only patients who were enrolled in the study at least 7 months before the date of the analysis are included. Percentages may not total 100% because of rounding.
† Tuberculosis cure was defined as a sputum smear that was negative for acid-fast bacilli close to the time of therapy completion.
‡ Successful completion of therapy was defined as the use of more than 85% of the prescribed medication.
§ Therapy failure was defined as the presence of a positive smear or culture for *Mycobacterium tuberculosis* obtained at least 5 months after the initiation of tuberculosis therapy.

Integrate therapyと sequential therapy の結果に違いはない。

First episodeと repeated therapyの患者でも結果に違いはない。