Early Clinical Toxicity of Antiretroviral Therapy in a Home-based AIDS Care Program in Rural Uganda

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Background

- Antiretroviral therapy (ART) prolongs lives of people living with HIV/AIDS
- Access expanding in sub-Saharan Africa
- ART associated with multiple toxicities
  - Stavudine
    - Peripheral neuropathy, lactic acidemia
  - Nevirapine
    - Rash, hepatotoxicity
- Limited information about toxicity from treatment programs in Africa

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Objective

- Describe clinical toxicities associated with ART in the home-based AIDS care program (HBAC) in rural Uganda

Methods - Participants

- Eligibility criteria for HBAC
  - The AIDS Support organization (TASO) clients
  - CD4 cell count ≤ 250 cells/μL or symptomatic AIDS
- Included in this analysis
  - ART-naïve adults
  - Started ART May 2003 through December 2004
- Provided with
  - ART (Stavudine + Lamivudine + Nevirapine or Efavirenz)
  - Cotrimoxazole
  - Tuberculosis (TB) treatment

Methods - HBAC

- Initial comprehensive visit
  - Physical examination and laboratory evaluation
    - HIV viral load, CD4 cell count, complete blood count, creatinine, liver transaminases
- Field officers visit patients weekly at home
  - Distribute medications
  - Provide adherence support
  - Assess potential symptoms of antiretroviral failure or toxicity
  - Provide triage and feedback to medical officers
- Patients referred to clinic if illness or toxicity suspected

Methods - Toxicity

- Clinically apparent toxicities
  - Confirmed by medical officer
- Toxicities graded according to 1992 NIH Division of AIDS table for grading severity of adult adverse events
  - Grade 1 = Mild
  - Grade 2 = Moderate
  - Grade 3 = Severe
  - Grade 4 = Life-threatening
- Severe toxicities
  - Any grade 3 or 4 toxicity
  - Any cases of hypersensitivity reaction, anemia, acute hepatitis, pancreatitis, or death

Methods - Statistical Analysis

- Kaplan-Meier analyses
  - Time to first occurrence of any toxicity
  - Time to first occurrence of severe toxicity
  - Time to first toxicity-related single-drug substitution
- Univariate and multivariate Cox proportional hazards models

Baseline characteristics of patients started on ART in HBAC between May 2003 and December 2004

Characteristic	N=1037
Female (%)	761 (73)
Median age, years (range)	38 (20-72)
Age ≥ 35 (%)	683 (66)
Body mass index (BMI), kg/m^2 (range)	20 (12-35)
BMI < 18 (%)	269 (26)
Median CD4 cell count, cells/μL (range)	126 (0-343)
CD4 cell count (%):	
≥ 250	37 (4)
200-249	189 (18)
50-199	599 (58)
0-49	212 (20)
Median viral load, copies/mL (range)	220,500 (399-750,001)
TB treatment (%)	80 (8)
ART regimen (%):	
Stavudine + Lamivudine + Nevirapine	1000 (96)
Stavudine + Lamivudine + Efavirenz	37 (4)

Patients with clinically diagnosed toxicity in HBAC between May 2003 and December 2004

Toxicity	Grade 1/2/3/4 No. (%)	Grade 3/4 No. (%)
Peripheral Neuropathy*	325 (36)	86 (10)
Asthenia	67 (6)	16 (2)
Rash	59 (6)	25 (2)
Vomiting	30 (3)	2 (0.2)
Nausea	28 (3)	2 (0.2)
Psychiatric Disorder	7 (1)	1 (0.1)
Hypersensitivity Reaction	17 (2)	
Acute Hepatitis	5 (0.5)	
Anemia	4 (0.4)	
Pancreatitis	3 (0.3)	
Toxicity-related Death	1 (0.1)	
Any Toxicity	414 (40)	140 (14)

* Among 900 patients without evidence of peripheral neuropathy at baseline

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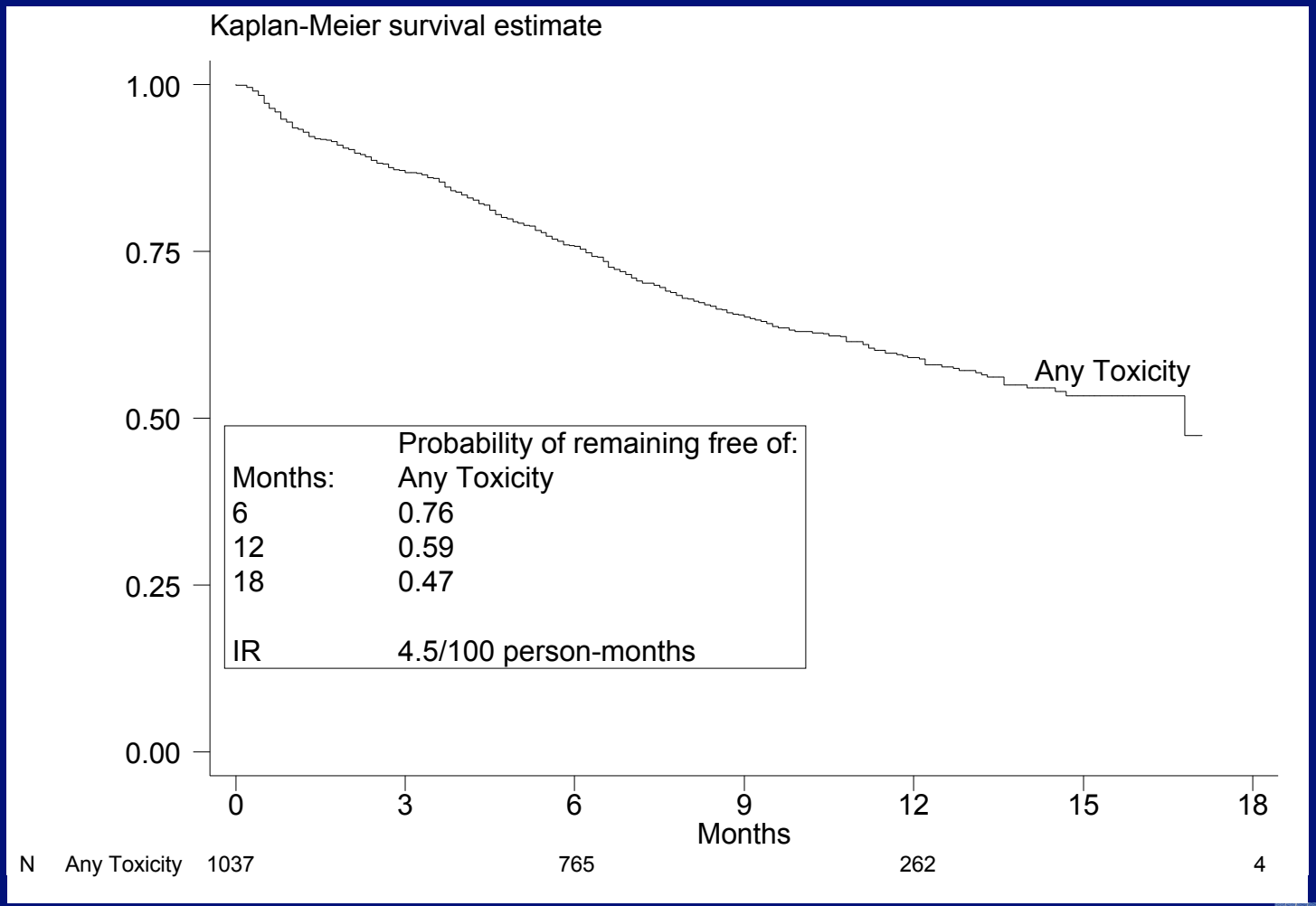
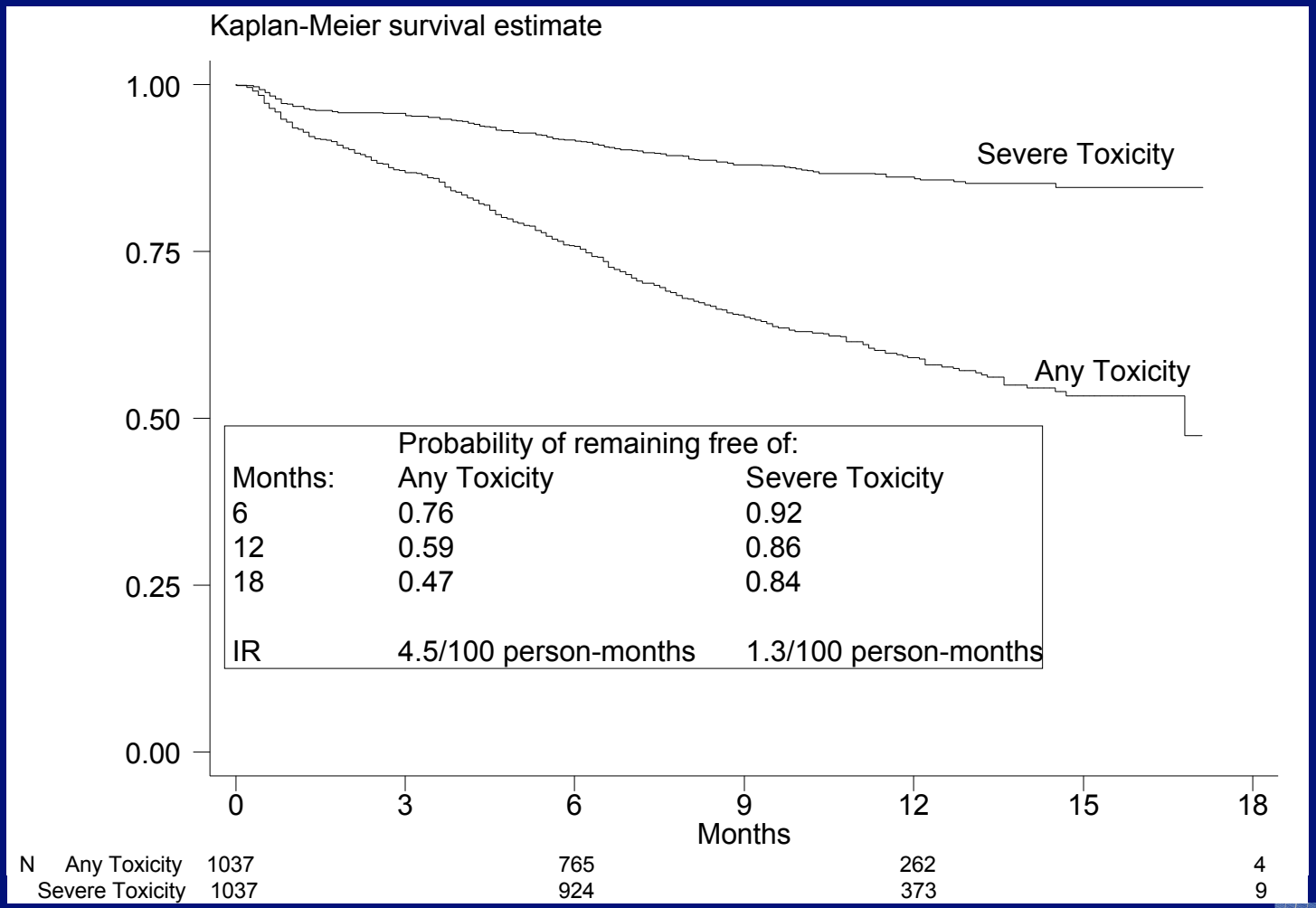
Probability of remaining free of any toxicity in HBAC between May 2003 and December 2004



Probability of remaining free of any toxicity and severe toxicity in HBAC between May 2003 and December 2004



Multivariate analysis of toxicity among 1037 patients started on ART in HBAC between May 2003 and December 2004

		Adjusted Cox proportional hazard ratio (95% Confidence Interval)	
Variable		Any Toxicity	Severe Toxicity
Gender	Female	1.25 (0.99 - 1.58)	1.11 (0.76 - 1.64)
	Male	ref	ref
BMI	< 18	0.92 (0.72 - 1.17)	1.11 (0.75 - 1.64)
	≥ 18	ref	ref
Age	≥ 35	1.72 (1.38 - 2.16)	1.82 (1.22 - 2.71)
	< 35	ref	ref
CD4	≥ 250	0.62 (0.33 - 1.16)	0.36 (0.08 - 1.49)
	200-249	0.90 (0.66 - 1.24)	1.15 (0.68 - 1.94)
	50-199	0.92 (0.72 - 1.18)	0.95 (0.62 - 1.46)
	0-49	ref	ref
TB treatment	Yes	1.16 (0.79 - 1.69)	1.59 (0.91 - 2.78)
	No	ref	ref

Multivariate Analysis – Individual Toxicities

- Any Peripheral Neuropathy
  - Age ≥ 35 years (HR 1.80; 95% CI: 1.39 - 2.32)
- Severe Peripheral Neuropathy
  - Age ≥ 35 year (HR 2.88; 95% CI:1.59 - 5.22)
  - TB treatment at baseline (HR 2.10; 95% CI: 1.06 - 4.17)

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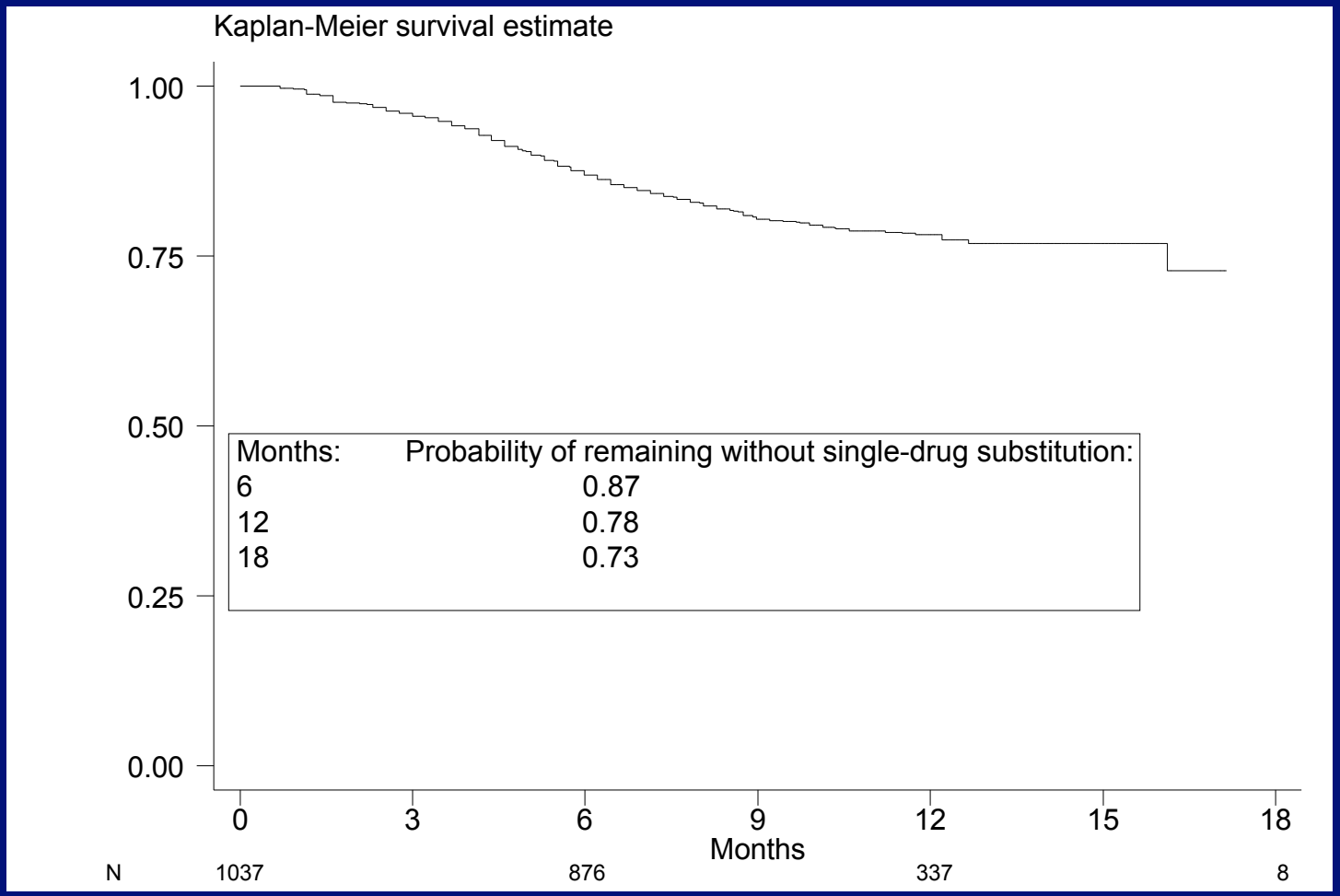
Toxicity-related single-drug substitutions among patients in HBAC from May 2003 to December 2004

Drug	Toxicity-related single-drug substitutions n (%)
Stavudine	181 (17)
Nevirapine	39 (4)
Lamivudine	0 (0)
All	220 (21)

Probability of remaining on the original regimen without single-drug substitution in HBAC from May 2003 to December 2004



Limitations

- Under-report toxicity
  - Clinically apparent toxicities
- No standardized physical exams for neuropathy
- Other toxicity-related deaths

Conclusions

- Toxicity manageable barrier to use of regimen containing stavudine, lamivudine, and nevirapine
- Neuropathy and rash accounted for most events
- Age ≥ 35 years associated with increased hazard of toxicity
- Tuberculosis treatment associated with increased hazard of severe neuropathy

Recommendations

- Increase attention to neuropathy
  - Age ≥ 35 years
  - TB therapy
- Expand drug formularies

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HBAC Field Officer on Motorcycle
Tororo, Uganda

Hepatitis

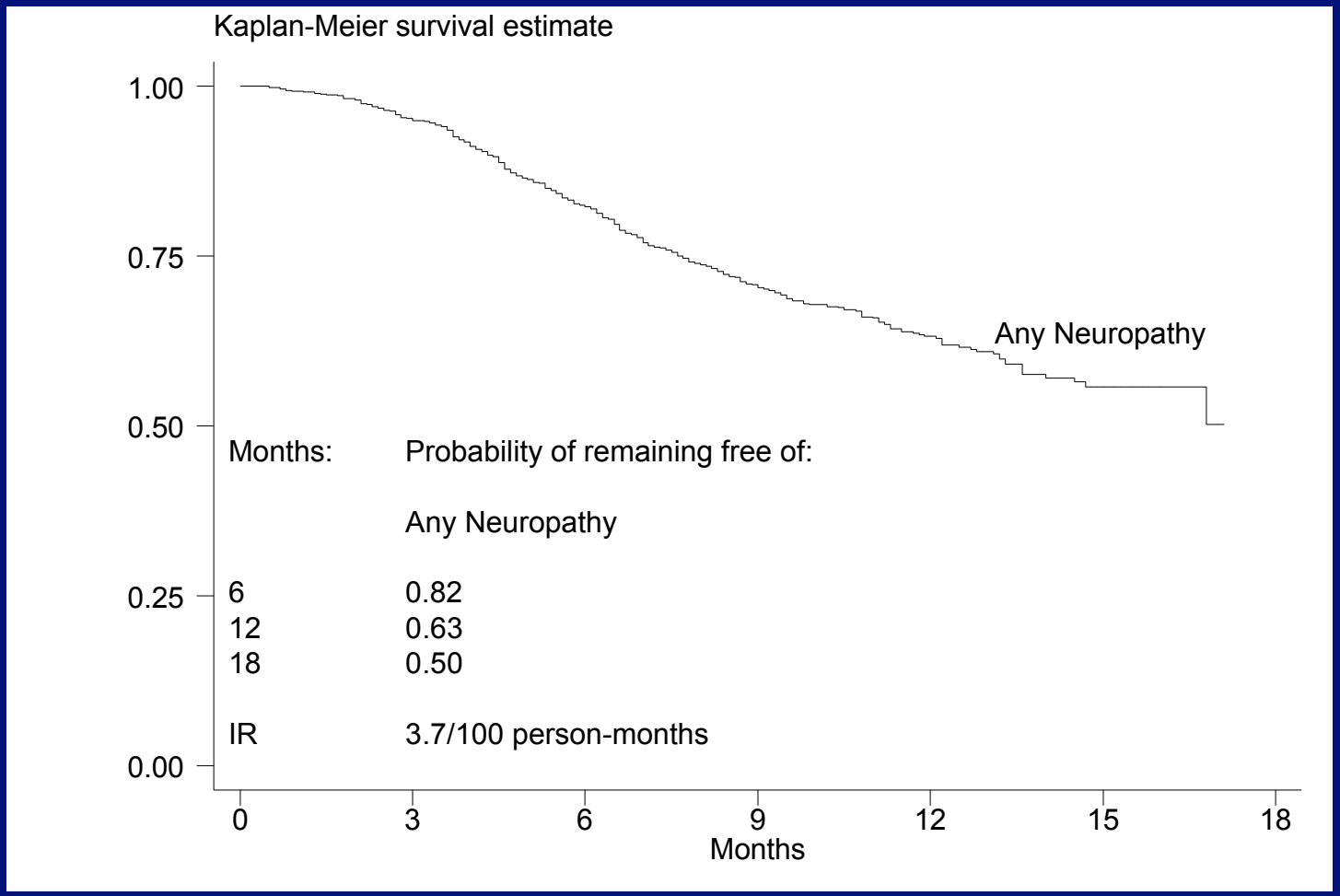
- 5 patients (0.5%) developed acute hepatitis
  - 2 had abnormal liver function tests at baseline
  - 3 also developed severe rash
- 1 toxicity-related death
  - 37 year-old woman with hepatitis and rash
  - Hypersensitivity reaction to nevirapine
  - Baseline CD4 cell count: 247 cells/μL; AST: 25 units/L; ALT: 15 units/L

Rash

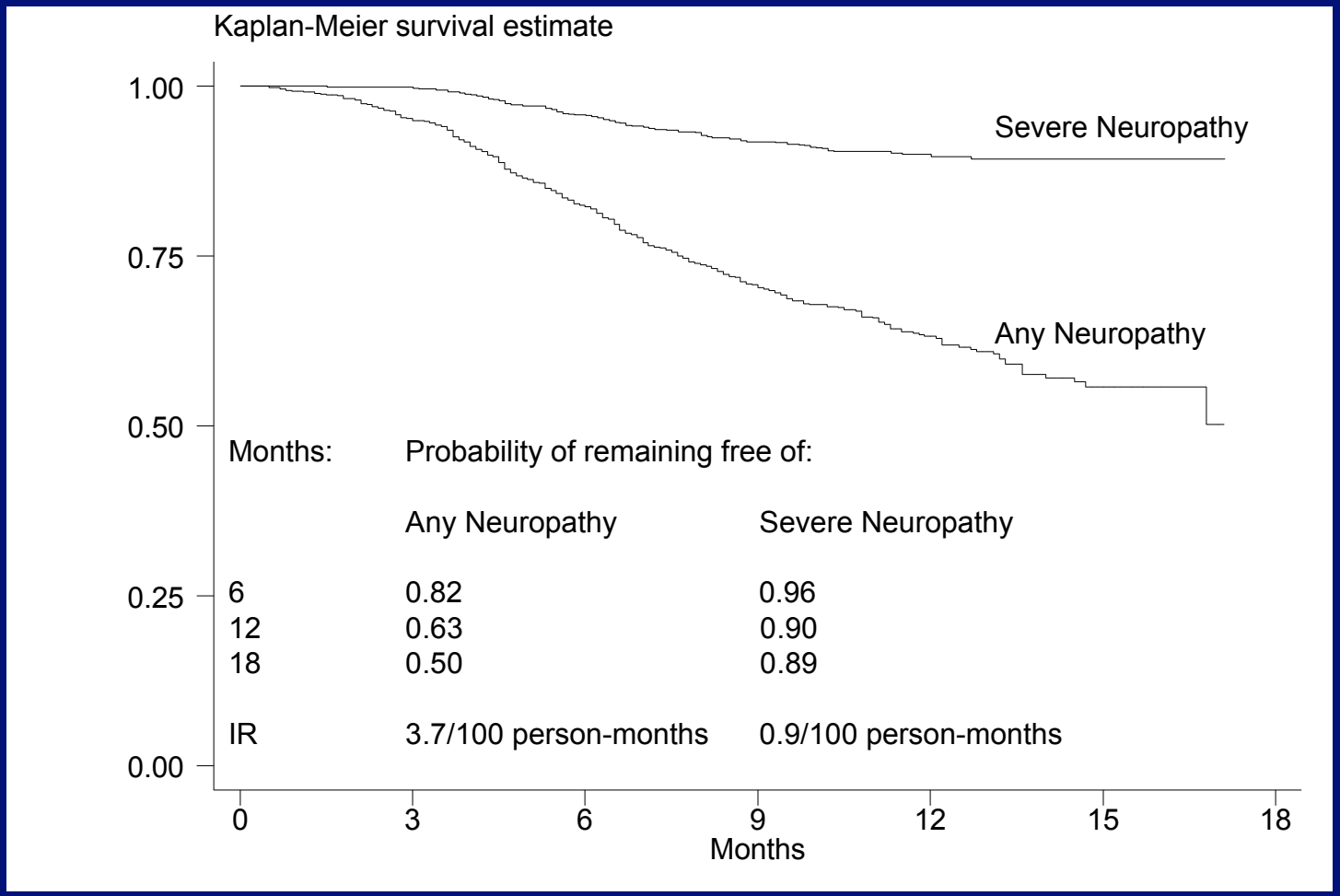
- 59 patients (6%) developed rash
  - 17 hypersensitivity reaction
- 25 patients (2%) developed severe rash
  - 9 Stevens-Johnson syndrome

- 2/37 patients with baseline CD4 cell count ≥ 250 developed rash
  - Both male

Probability of remaining free of any peripheral neuropathy in HBAC between May 2003 and December 2004



Probability of remaining free of any peripheral neuropathy and severe peripheral neuropathy in HBAC between May 2003 and December 2004



Methods - Toxicity

- Peripheral neuropathy
  - Grade 1: mild pain or weakness; no interference with ambulation; mild sensory impairment in extremities
  - Grade 2: moderate pain or weakness; minimal interference with ambulation; mild weakness in feet; moderate sensory impairment in extremities
  - Grade 3: severe pain or weakness; moderate interference with ambulation; moderate weakness in feet; severe sensory impairment in extremities
  - Grade 4: incapacitated; substantial impairment with ambulation; marked distal weakness; sensory impairment in limbs and trunk