Adverse Events in HIV-Infected Patients Receiving Antiretroviral Therapy in a Treatment Program in a Nairobi Slum, Kenya, February 2003 – June 2005

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Background

- An estimated six million persons in developing countries have advanced HIV disease and would benefit from antiretroviral (ARV) therapy
- Through large initiatives, HIV treatment programs that provide ARV therapy are rapidly expanding
- Tolerability to ARV therapy is well described in developed countries
  - e.g. - Nevirapine
    - Clinical hepatic events 4%
    - Severe rash in first 6 weeks 1.5%
- There is little information on tolerability to these medications in African populations

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Study Objective

- An observational study to describe toxicities associated with ARV therapy among HIV-infected patients receiving care in a community clinic in a large informal settlement in Nairobi, Kenya

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Kibera ARV Treatment Program

Kibera Community Clinic

- Kibera
  - Largest informal settlement in Nairobi, Kenya with a population of ~700,000
- Kibera ARV Treatment Program
  - Pilot program established in February 2003
  - Integrated into a community clinic
  - Free HIV medication for eligible persons

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Methods: Kibera ARV Program

- Enrollment Criteria
  - AIDS defining illness or symptomatic HIV disease
  - CD4+ T-cell count < 200 cells/mm^3
- ARV program managed by mid-level clinical officers and medical officers
- Data collected on patient forms and entered into an electronic clinic database

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Methods: Simplified and Standardized Antiretroviral Drug Regimens

- Two ARV drug regimens consistent with guidelines from the World Health Organization (WHO) and Kenya Ministry of Health
  - 1st line regimen
    - Stavudine (d4T), lamivudine (3TC), nevirapine (NVP)
    - In the event of drug toxicity, single drug substitutions:
      - Nevirapine to efavirenz
      - Stavudine to zidovudine (ZDV)
  - 2nd line regimen: In the event of failure
    - Zidovudine, didanosine (ddI), lopinavir/ritonavir

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Methods: Adverse Event Assessment

- Based on history and clinical examination
  - Routine examinations at 2, 4 weeks, and monthly thereafter
  - Interim visits
- Laboratory
  - Assessed at 1, 2, 6 month and 6 monthly thereafter
  - Serum aspartate aminotransferase (AST) levels
  - Complete blood counts
- Graded on standardized scale of 1-4 (Division of AIDS, US National Institutes of Health)
  - 1 = mild
  - 2 = moderate
  - 3 = severe
  - 4 = life threatening

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Methods: Data Analysis

- Data analyzed through June 30, 2005
- Simple frequencies
  - Demographics
  - Clinical adverse events
  - Laboratory adverse events
- Kaplan-Meier analysis to estimate cumulative probability of time to first:
  - Any clinical adverse event (grade 1-4)
  - Severe clinical adverse event (grade 3-4)
  - AST elevation
  - ARV regimen change

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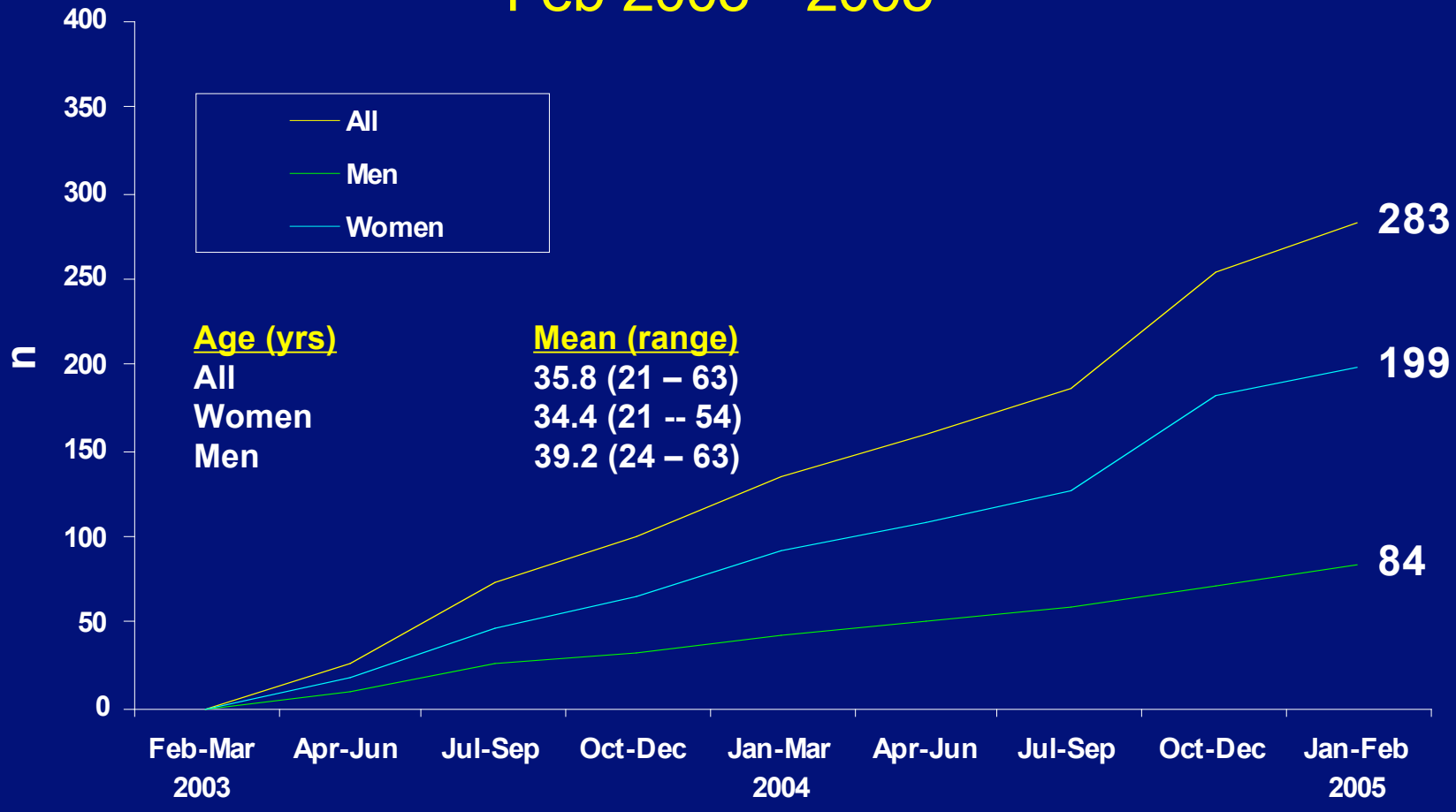
Results: Cumulative Number of HIV-Infected Patients Receving ARV Therapy: Feb 2003 - 2005



254 patient-years of observation (median: 0.9 years per patient)

Characteristics of HIV-Infected Patients Receiving ARV Therapy, Kibera ARV Program

Baseline	
• Median CD4+ cell count (n=267) [IQR]	157 [67-293] cells/mm
• Median Viral Load (n=254)	~ 144,500 copies/ml
• WHO Stage (n=283)	
◦ I/II	82 (29%)
◦ III	66 (23%)
◦ IV	135 (48%)
First line therapy (n=283):	
d4T/3TC/NVP	267
d4T/3TC/EFV	12
ZDV/3TC/NVP	1
ZDV/dDI/Lopinovir/Ritonovir	3

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Patient Response to Therapy

12 months on therapy:

- Cumulative probability of remaining in care 0.87
- Cumulative probability of survival 0.93
- Median CD4+ cell count increase 125 cells/mm^3
- Viral load < 400 copies/ml 73%

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Distribution and Frequency of Clinical Adverse Events among HIV-Infected Patients Receiving ARV Therapy, Kibera ARV Program

Adverse Event	Any (n=283)	Grade 3-4 (n=283)
Any adverse event	184 (65%)	18 (6%)
Neuropathy	65 (23%)	7 (3%)
Rash	58 (20%)	4 (1%)
Nausea	46 (16%)	1 (0.4%)
Asthenia	11(3.9%)	0
Diarrhea	5 (1.8%)	1 (0.4%)
Clinical hepatitis	4 (1%)	4 (1%)
Lipodystrophy	2 (1%)	1 (0.4%)

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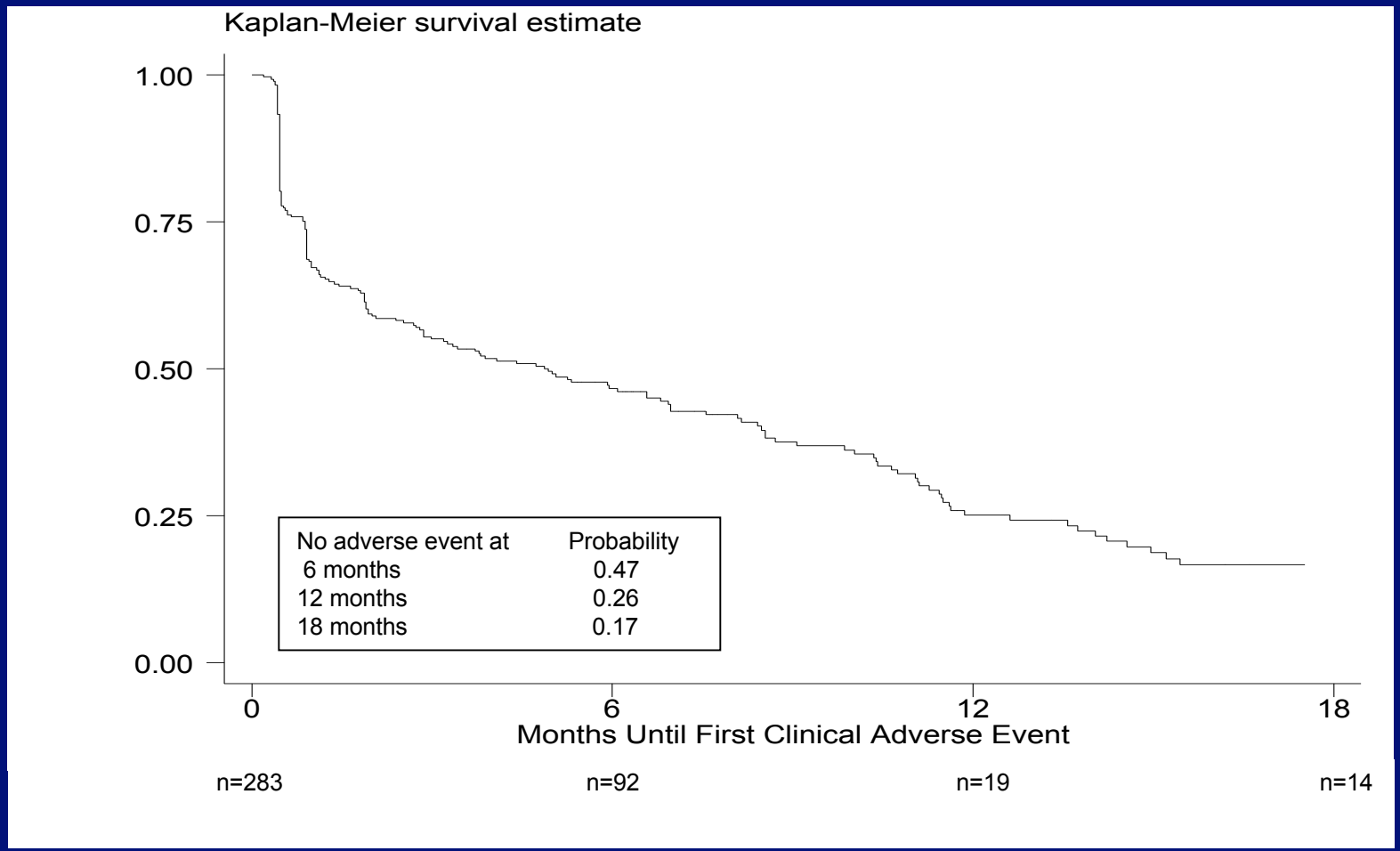
Time to First Adverse Event among HIV-Infected Patients Receiving ARV Therapy, Kibera ARV Program



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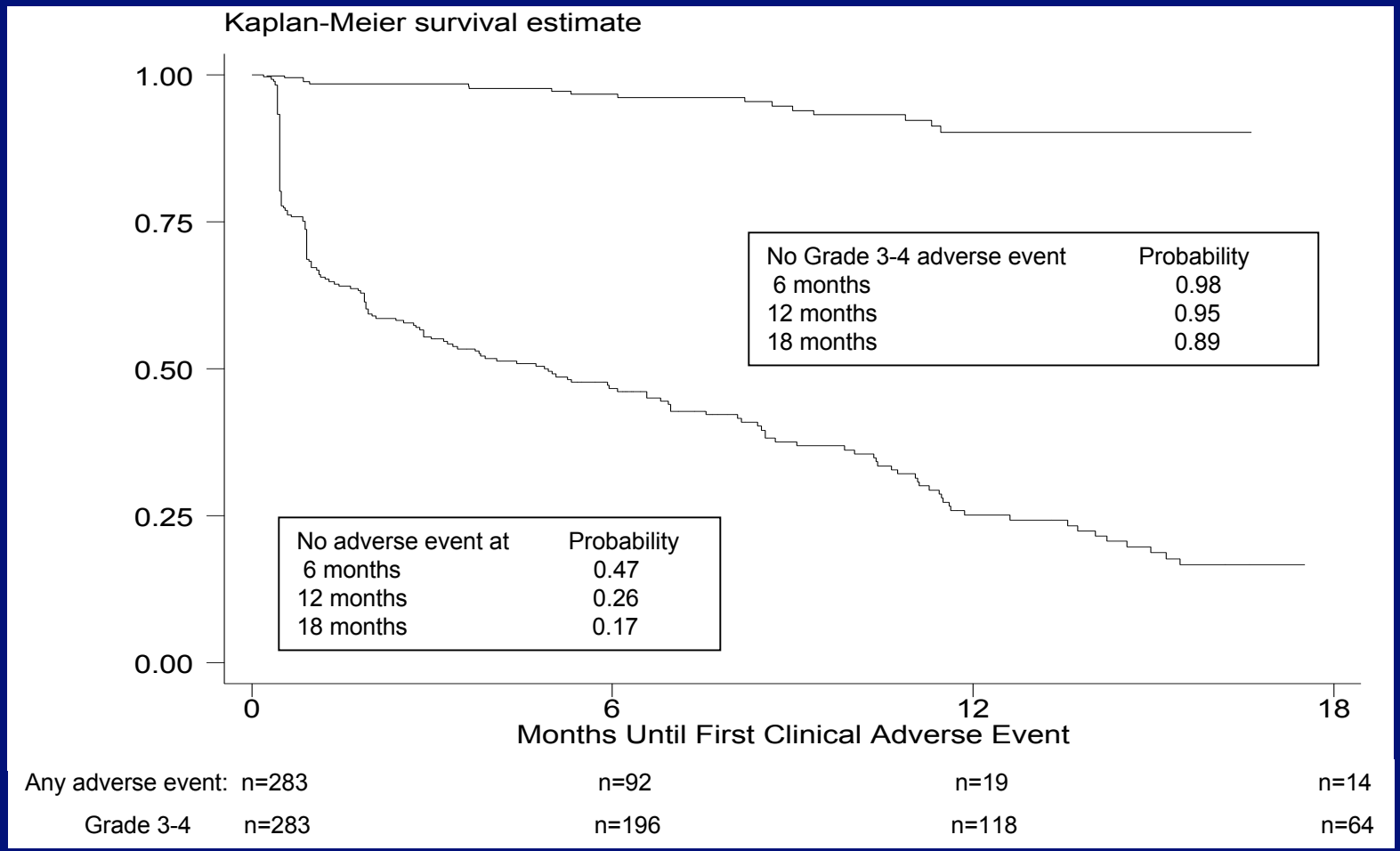
Time to First Grade 3-4 Adverse Event among HIV-Infected Patients Receiving ARV Therapy, Kibera ARV Program



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ARV Regimen Change Due to Clinical Toxicity

Single drug change (n=13)

NVP → EFV (n=8)	4 due to rash 4 due to hepatitis
d4T → ZDV (n=5)	4 due to neuropathy 1 due to lipodystrophy

Regimen change (n=1)

ZDV, ddI, ritonavir/lopinavir → d4T, 3TC, NVP	1 due to diarrhea/nausea

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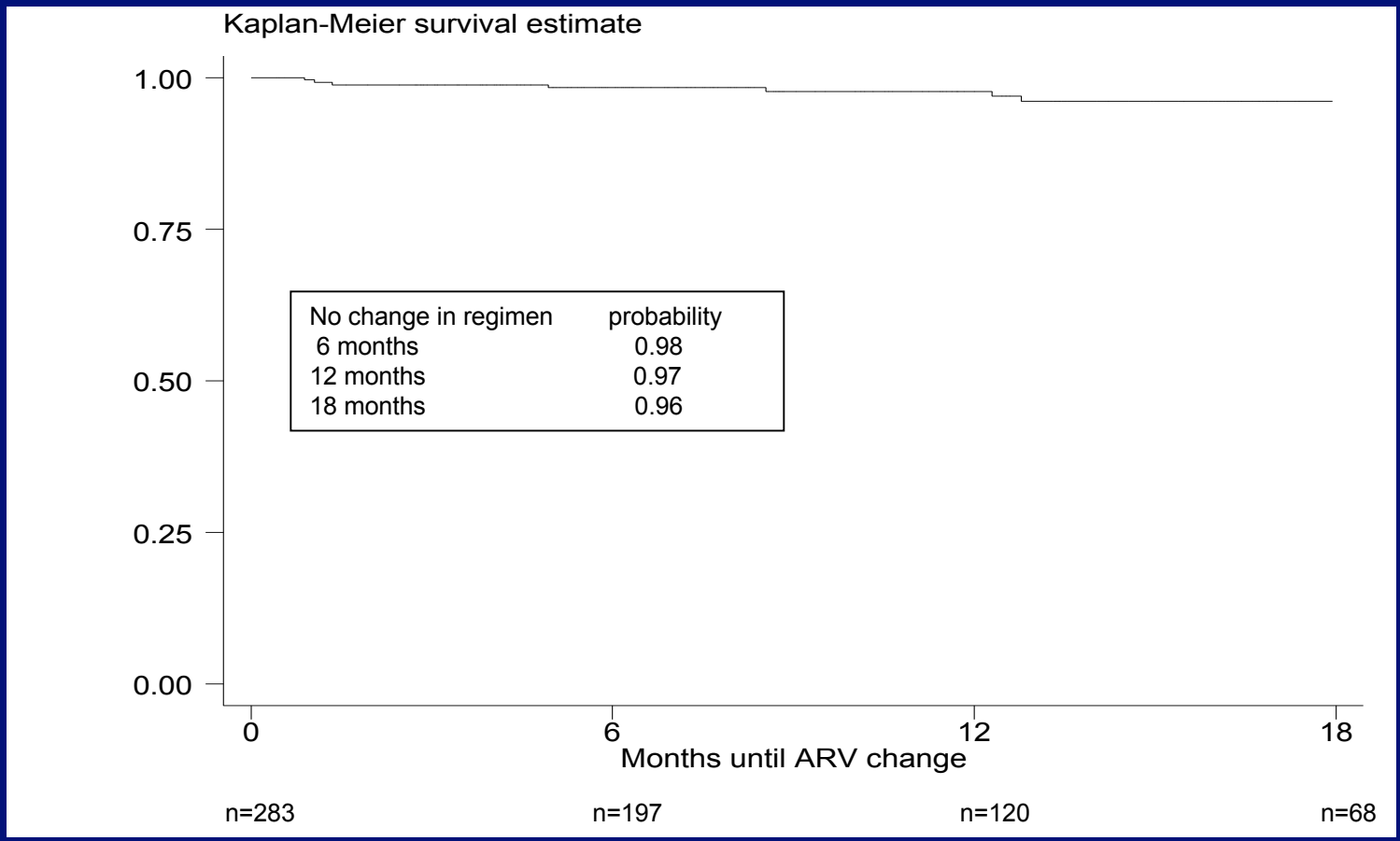
Time to First Change in Regimen Due to Toxicity among HIV-Infected Patients Receiving ARV Therapy, Kibera ARV Program



Evaluation of AST Values among HIV-Infected Patients Receiving ARV Therapy, Kibera ARV Program

	AST Grade				
	Normal	**1** **1.25 – 2.5 x ULN****	**2** **> 2.5 – 5 x ULN**	**3** **> 5 – 10 x ULN**	**4** **> 10 x ULN**
Baseline (n=242)	184 (76%)	51 (21%)	7 (3%)	0	1 (0.4%)
Highest AST on ARVs (n=233)*	86 (37%)	98 (42%)	47 (20%)	2 (1%)	0

*Among patients with ≥ 1 lab test after ARV initiation

**ULN = upper limits of normal

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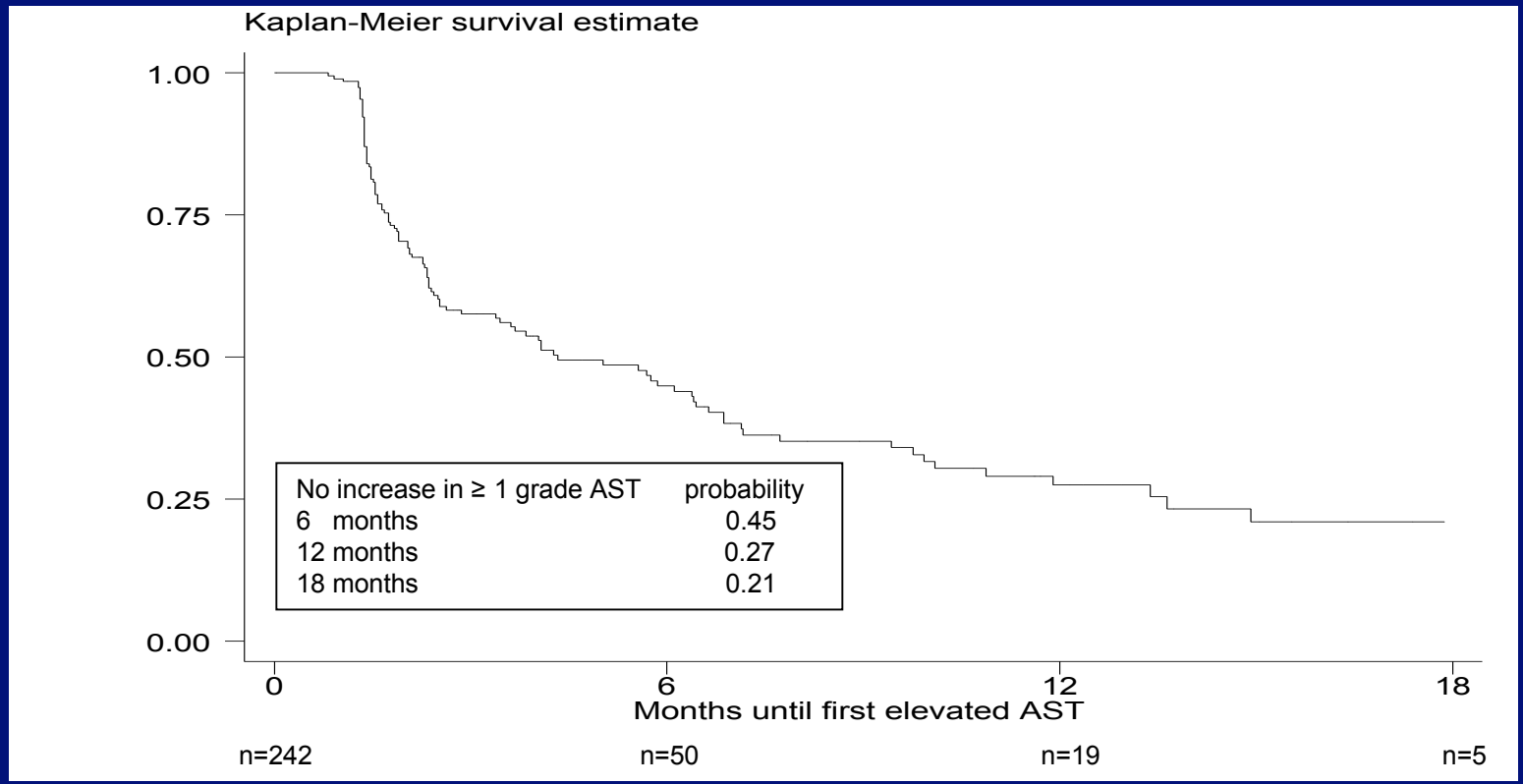
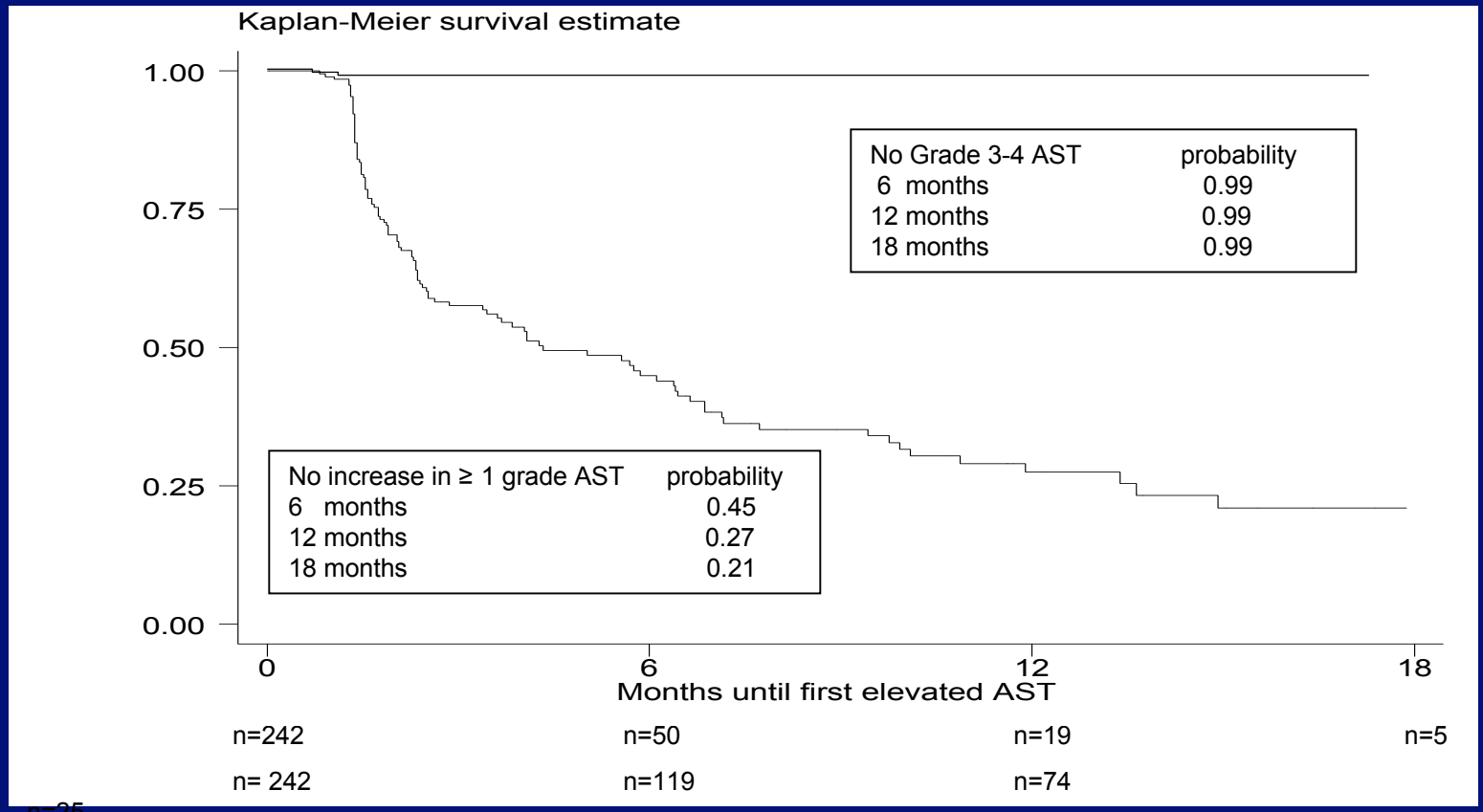
Time to First Increase of ≥ 1 Grade AST from Baseline among HIV-Infected Patients Receiving ARV Therapy, Kibera ARV Program



Time to First Grade 3-4 AST from Baseline among HIV-Infected Patients Receiving ARV Therapy, Kibera ARV Program



Limitations

- This is an observational study using routinely collected data
- Lack of comparison group limited ability to assess which adverse events were associated to ARVs
- Data estimates subject to imprecision due to small sample sizes

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Summary

- Clinical adverse events were frequent, but severe events were uncommon
- There were frequent and early elevation of liver enzymes, but few episodes of clinical hepatitis
- Rates of adverse events appear to be in a range consistent with those of industrialized countries

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Conclusion

- Known and expected risks of adverse events due to ARVs exist, but risks are modest in comparison to benefits gained
- Adverse events to ARVs do not represent a significant barrier to providing ARVs in this African setting

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