A Randomized Trial of Protease Inhibitor-based Antiretroviral Therapy for AIDS-associated Kaposi's Sarcoma in Sub-Saharan Africa



Jeffrey Martin[1], Miriam Laker-Oketta[1,2], Victoria Walusansa[3], Jackson Orem[3], John Bennett[1], Adrienne Mocello[1], Toby Maurer[1], Peter Hunt[1], Andrew Kambugu[2], and Edward Mbidde[2,4]

[1]University of California, San Francisco; [2]Infectious Diseases Institute, Kampala, Uganda; [3]Uganda Cancer Institute, Kampala, Uganda; and [4]Uganda Virus Research Institute, Entebbe, Uganda

Correspondence:
Jeffrey Martin
University of California, San Francisco
martin@psg.ucsf.edu

Background

- With advent of ART, quickly shown that some patients with KS who received ART without chemotherapy had lesion regression.
- All early "HAART" regimens contained protease inhibitors (PIs), which is what distinguished them from pre-HAART era.
- Led to belief, by some, that PIs had special/specific activity in treating KS.
- PIs, at levels achievable in blood of humans, can:
  - Block the development of KS-like lesions in mice inoculated with KS cells (from primary cell cultures)
  - Promote the regression of KS-like lesions in mice who had developed such lesions after inoculation with KS cells
  - Block macroscopic growth of angiogenic lesions & microscopic spindle-cell growth in mice inoculated with bFGF or bFGF/VEGF
  - Block angiogenesis induced by both bFGF & VEGF in the chorioallantoic membrane assay (comparable to paclitaxel)
  - Block bFGF-induced invasion of human umbilical-vein endothelial cells (relevant as invasion essential for angiogenesis)
- Hypothesized mechanism of PI effect on KS:
  - Inhibition of the conversion of matrix metalloproteinase-2 (MMP-2) from latent to active form
    - MMP-2 mediates degradation of blood vessel basement membranes, which allows for endothelial cell invasion -- an essential step in angiogenesis
  - Inhibition of the cellular proteasome
    - proteasome involved in several cell pathways

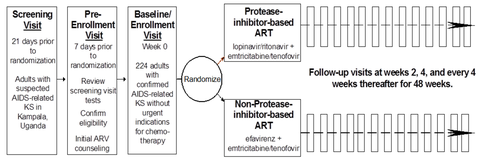
Sgadari *Nat Med* 2002; Pati *Blood* 2002

Objective

To determine whether:

PI-based ART is superior to non-PI-based ART (e.g., NNRTI-based) in prolonging survival in persons with AIDS-related KS in sub-Saharan Africa

Schema



- Doubtful if RCT feasible in US given decline in KS incidence
- RCT theoretically feasible and *relevant* in Africa
  - Cannot simply recommend PIs for KS without justification
    - PIs more complicated, expensive, drug-drug interactions
  - Given lack of chemo salvage, critical to optimize initial Rx

Participants

- Age 18 years or older
- Untreated HIV-1 infection, confirmed with antibody testing
- Biopsy-confirmed untreated KS
  - At least one 0.6 x 0.6 cm lesion
  - Exception: characteristic oral lesions not amenable to biopsy
- No urgent indication for chemotherapy, defined as:
  - Oral lesions which interfere with chewing/swallowing
  - Shortness of breath, hemoptysis, or moderate/severe cough
  - Bleeding from mouth or rectum
  - Bulky cutaneous lesions (≥ 5 cm wide by ≥3 cm tall)
  - Painful/functionally disabling facial/genital/peripheral edema (<85% range of motion)
- No untreated OI, malignancy other than KS, or temp ≥ 38.5°C
- Karnofsky performance score ≥ 70

Measurements

- **Questionnaire-based:** Sociodemographic characteristics; ART adherence; Non-ART medication use; Physical symptoms and co-morbidity; Alcohol/Recreational drug use; Sexual behavior; Mental health; Quality of Life; Chemotherapy indications; Cause of death
- **Physical examination:**
  - Counting Lesions
  - Digital Caliper Measurement
  - Digital Photography



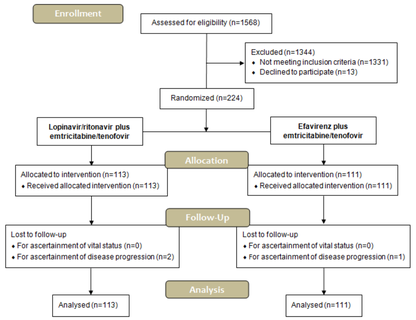


- **Laboratory-based:** CD4+ T cell count, plasma HIV RNA, complete blood cell count, serum creatinine and liver function tests – all performed at the College of American Pathologists-certified clinical laboratory at the IDI.

Primary Outcome

1. **Composite of:**
   - Death or
   - Indication for chemotherapy (chemotherapy provided for free by study if indicated)
     - Progression of cutaneous lesions (size, number, ulceration, superinfection)
     - Oral: difficulty swallowing or chewing
     - Pulmonary: cough, dyspnea, and/or hemoptysis along with suggestive radiographic findings
     - GI: early satiety, abdominal pain, hematemesis, melena, hematochezia, or ascites, not otherwise explained
     - Pericardial: dyspnea and/or cough with suggestive radiography
     - Edema: pain or functional disability (<85% range of motion)
2. **Death Alone**

Flow of Participants



Recruitment



Participant Characteristics at Time of ART Initiation

	Lopinavir/ritonavir + emtricitabine/tenofovir (N = 113)	Efavirenz + emtricitabine/tenofovir (N = 111)
Sociodemographic/Economic		
Age, years	33 (28 to 38)*	34 (28 to 40)
Female	50%	38%
Education, highest grade		
None	7.1%	8.1%
Primary	50%	39%
Secondary	28%	40%
University/vocational	15%	14%
Household income, monthly $US	$45 ($21 to $86)	$57 ($24 to $119)
Clinical history		
Tuberculosis	12%	13%
Any opportunistic infection	19%	19%
Hospitalization in past 3 months	7.1%	11%
Physical health summary score †	50.9 (38.1 to 57.4)	55.3 (37.3 to 58.4)
Physical Examination		
Body mass index, kg/m^2	21.2 (19.4 to 22.9)	21.5 (19.4 to 23.2)
Karnofsky performance, %	90 (85 to 90)	90 (80 to 90)
Laboratory		
Hemoglobin, g/dl	11.5 (10.1 to 13.3)	11.6 (10.3 to 13.2)
CD4+ T cells/mm^3		
<50	30%	38%
50 to 199	35%	34%
200 to 350	19%	18%
> 350	16%	10%
HIV RNA, $\log_{10}$ copies/ml	5.3 (4.9 to 5.6)	5.4 (5.1 to 5.6)

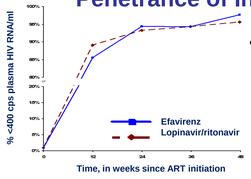
*median (interquartile range) † derived from the Medical Outcomes Study instrument

KS-Specific Characteristics at Time of ART Initiation

	Lopinavir/ritonavir + emtricitabine/tenofovir (N=113)	Efavirenz + emtricitabine/tenofovir (N=111)
Clinical History		
Duration of lesions, in months	4.5 (3.0 to 7.0)*	5.0 (3.0 to 8.0)
Change in lesion number past 30 days		
More	21%	20%
Less	0	1.8%
Unchanged	79%	78%
Physical Examination		
No. of anatomic skin sites with lesions †	6 (3 to 10)	6 (2 to 9)
Total no. of lesions ≥ 50	25%	23%
No. of lesions in 3 rep. regions	26 (4.5 to 43)	20 (7 to 39)
Raised lesions in oral cavity	20%	25%
Edema present	55%	53%
Staging		
T1	70%	73%
I1	66%	72%
S1	59%	62%
No. of "poor risk" criteria		
0	6.3%	7.4%
1	36%	32%
2	46%	55%
3	12%	6.5%

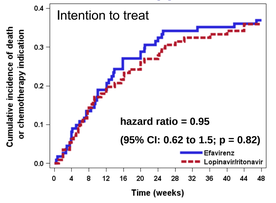
*median (interquartile range) † 15 potential sites

Penetrance of Intervention for HIV

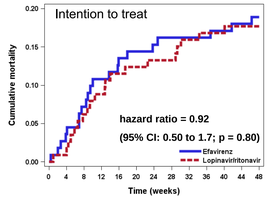


- Discontinuation of originally assigned drug class thru 48 weeks:
  - PI arm: 7.1%
  - NNRTI arm: 8.1%

Death or Chemotherapy Indication



Death Alone



Indications for Chemotherapy During Follow-up

Indication/Area of Involvement	Lopinavir/ritonavir + emtricitabine/tenofovir (n = 28)	Efavirenz + emtricitabine/tenofovir (n =28)	p value*
Cutaneous progression	10 (36%)	8 (29%)	0.78
Symptomatic oral	2 (7.1%)	3 (11%)	0.66
Symptomatic pulmonary	10 (36%)	11 (39%)	0.78
Symptomatic abdominal	3 (11%)	4 (14%)	0.70
Symptomatic pericardial	1 (3.6%)	0	1
Functionally disabling edema	14 (50%)	9 (32%)	0.28

* Fisher's exact test

Conclusions

In East Africa:

- It is challenging to identify patients with KS in early stages without urgent indications for chemotherapy
- Among patients with KS with no urgent chemotherapy indications who are treated with ART alone:
  - Overall high incidence of subsequent indications for chemotherapy and/or death
  - No evidence for superiority of PI-based ART (at least lopinavir) in terms of survival or need for subsequent chemotherapy
    - This is despite ample biologic plausibility

Implications

- While incidence of failure is high with ART alone, there is a substantial fraction who do well
  - We need robust prediction rules to identify who they are
- For all others (i.e., those predicted not to do well), we need:
  - Greater availability of potent chemo to serve as salvage
  - Or, better yet, use of potent chemo upfront until additional research (e.g., ACTG 5264/AMC 067) proves or disproves this strategy
- We need to find patients with KS earlier… but when we don't, we need to make potent chemotherapy more widely available

Acknowledgements

R01 CA119903
D43 CA153717

Infectious Diseases Institute
- IDI Directors: Keith McAdam & Alex Coutinho
- Ann Akiteng, Philippa Easterbrook, Andrew Kambugu, Christine Kihembo, Mitterand Kiirya, Esther Lubwama, Yuka Manabe, Jane Frances Nalubega, Sam Obul, and David Thomas

Uganda Cancer Institute
- Jackson Orem & Victoria Walusansa

Univ. of Manitoba
- Allan Ronald

Makerere Univ.
- Henry Wabinga

UCSF
- Donald Abrams, John Bennett, Dana Clutter, Steven Deeks, Debbie Garcia, Warner Greene, Janet Ho, Peter Hunt, David Janka, Melissa Kanchanapoomi, Toby Maurer, Mike McGrath, Abigail Phillips, Paul Volberding, Megan Wenger, and John Ziegler

