Evaluation of four chemotherapy regimens for treatment of advanced AIDS-associated Kaposi sarcoma in Kenya: a cost-effectiveness analysis

Esther E Freeman, Nicole C McCann, Aggrey Semeere, Krishna P Reddy, Miriam Laker-Oketta, Helen Byakwaga, Pamela P Pei, Maya E Hajny Fernandez, Samson Kiprono, Naftali Busakhala, Jeffery N Martin, Toby Maurer, Ingrid V Bassett, Kenneth A Freedberg, Emily P Hyle

Summary

Background The most effective treatment for advanced AIDS-associated Kaposi sarcoma is paclitaxel or pegylated liposomal doxorubicin (PLD); neither is routinely used in sub-Saharan Africa due to limited availability and high cost. We examined the clinical impact, costs, and cost-effectiveness of paclitaxel or PLD in Kenya, compared with etoposide or bleomycin–vincristine.

Methods In this study, we use the Cost-Effectiveness of Preventing AIDS Complications (CEPAC)—International Model to project clinical outcomes and costs among people living with HIV and advanced Kaposi sarcoma on antiretroviral therapy. We compared four different treatment strategies: etoposide, bleomycin–vincristine, paclitaxel, or PLD. We derived cohort characteristics and costs from the Kenyan Academic Model for Providing Access to Healthcare network, and adverse events, efficacy, and mortality from clinical trials. We projected model outcomes over a lifetime and included life expectancy, per-person lifetime costs, and incremental cost-effectiveness ratios (ICERs). We conducted budget impact analysis for 5-year total costs and did deterministic and probabilistic sensitivity analyses to evaluate the effect of uncertainty in input parameters.

Findings We found that paclitaxel would be more effective than bleomycin–vincristine and would increase life expectancy by 4·2 years per person. PLD would further increase life expectancy by 0·6 years per person. Paclitaxel would be the most cost-effective strategy (ICER US$380 per year-of-life-saved compared with bleomycin–vincristine) and would remain cost-effective across a range of scenarios. PLD would be cost-effective compared with paclitaxel if its price were reduced to $100 per cycle (base case $180 per cycle). Implementing paclitaxel instead of bleomycin–vincristine would save approximately 6400 life-years and would increase the overall 5-year Kenyan health-care costs by $3·7 million; increased costs would be primarily related to ongoing HIV care given improved survival.

Interpretation Paclitaxel would substantially increase life expectancy and be cost-effective compared with bleomycin–vincristine for advanced AIDS-associated Kaposi sarcoma in Kenya and should be the standard of care. PLD would further improve survival and be cost-effective with a 44% price reduction.

Funding US National Institutes of Health and Massachusetts General Hospital.

Introduction

Antiretroviral therapy (ART) has markedly improved survival in people with AIDS-associated Kaposi sarcoma.[1] However, Kaposi sarcoma remains a substantial contributor to mortality in low-income and middle-income countries (LMICs). Even in the ART era, only 54% of people with AIDS-associated Kaposi sarcoma in LMICs are alive at 3 years following diagnosis.[2,3] Poor Kaposi sarcoma survival is multifactorial, including delayed diagnosis and suboptimal linkage to care,[3–5] as well as limited access to the most efficacious chemotherapy regimens to treat advanced Kaposi sarcoma.[5,6] Prevalence of advanced Kaposi sarcoma, defined as AIDS Clinical Trials Group (ACTG) T1 disease and characterised by tumour-associated oedema or ulceration, extensive oral Kaposi sarcoma, or visceral Kaposi sarcoma, was found to be high (82%) among a cohort of people with Kaposi sarcoma in Kenya.[7,8]

For treatment of advanced Kaposi sarcoma in people living with HIV, clinical trials in both high-income countries and LMICs have shown superior clinical response for paclitaxel compared with etoposide or bleomycin–vincristine.[6] Additional clinical trials have shown similar efficacy for paclitaxel and pegylated liposomal doxorubicin (PLD) but fewer adverse events with PLD.[9] Paclitaxel and PLD are now the standard of care for Kaposi sarcoma in the USA and Europe.[10,11] Many high-income country guidelines favour PLD given its better side-effect profile.[10] Treatment guidelines in sub-Saharan Africa continue to recommend several regimens as first line, depending on availability and feasibility.[12–14] Bleomycin–vincristine remains the

Lancet Glob Health 2022; 10: e1179–88

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For the Swahili translation of the abstract see **Online** for appendix 1

Department of Dermatology (E E Freeman MD), **Medical Practice Evaluation Center** (E E Freeman, N C McCann BA, K P Reddy MD, P P Pei PhD, M E Hajny Fernandez BA, I V Bassett MD, K A Freedberg MD, E P Hyle MD), **Division of Pulmonary and Critical Care Medicine** (K P Reddy), **Division of Infectious Disease** (I V Bassett, K A Freedberg, E P Hyle), **and Division of General Internal Medicine** (K A Freedberg), **Massachusetts General Hospital, Boston, MA, USA; Harvard Medical School, Harvard University, Boston, MA, USA** (E E Freeman, K P Reddy, I V Bassett, K A Freedberg, E P Hyle); **Infectious Diseases Institute, Kampala, Uganda** (A Semeere MMed, M Laker-Oketta MBChB, H Byakwaga MBChB); **Department of Epidemiology and Biostatistics, University of California, San Francisco, CA, USA** (A Semeere, J N Martin MD); **Department of Internal Medicine** (S Kiprono MMed, N Busakhala MBChB) **and Department of Pharmacology and Toxicology** (N Busakhala), **Moi University School of Medicine, Eldoret, Kenya; Department of Dermatology, Indiana University School of Medicine, Indianapolis, IN, USA** (T Maurer MD)

Correspondence to: Dr Esther Freeman, Department of Dermatology, Massachusetts General Hospital, Boston, MA 02114, USA **efreeman@mgh.harvard.edu**

Research in context

Evidence before this study

AIDS-associated Kaposi sarcoma remains a substantial contributor to mortality in low-income and middle-income countries (LMICs), even in the treat-all antiretroviral therapy (ART) era. Limited access to the most efficacious chemotherapy regimens to treat advanced Kaposi sarcoma contributes to poor survival in these settings. Currently, bleomycin–vincristine remains a commonly used regimen in sub-Saharan Africa despite its clinical inferiority. Pegylated liposomal doxorubicin and paclitaxel are considered standard of care in high-income settings but are not widely used in LMICs. In 2020, the first trial comparing different chemotherapy regimens in combination with ART for treatment of Kaposi sarcoma in LMICs was published. In this paper, authors noted that future research on the cost-effectiveness of different regimens in LMICs would be crucial.

To identify existing literature related to the cost-effectiveness of chemotherapy regimens for Kaposi sarcoma, we searched PubMed for articles on July 31, 2021, published in English with no date restrictions, using the search terms "chemotherapy" AND "cost-effectiveness" AND "Kaposi Sarcoma". We identified 14 papers, conducted both in high-income countries and LMICs. We found that previous analyses had evaluated cost-effectiveness of chemotherapy for Kaposi sarcoma, but none of these analyses compared all three regimens evaluated in the 2020 trial. More generally, when searching the literature with the search terms "cancer" AND "chemotherapy" and "cost-effectiveness" AND "sub-Saharan Africa", we identified an additional 25 papers focused on breast cancer, colorectal cancer, childhood cancers, Burkitt lymphoma, and large B-cell lymphoma, but these did not provide additional information on cost-effectiveness of chemotherapy for Kaposi sarcoma in this setting.

Added value of this study

Our study evaluates the longer-term clinical outcomes, cost-effectiveness, and budget impact of four different chemotherapy regimens (ie, oral etoposide, bleomycin-vincristine, paclitaxel, and pegylated liopsomal doxorubicin) for advanced Kaposi sarcoma in Kenya using the Cost-effectiveness of Preventing AIDS Complications (CEPAC)—International Model. We found that paclitaxel would lead to higher life expectancy than the most commonly used regimen, bleomycin–vincristine, and would be cost-effective. This conclusion remains the same over a wide range of variations in model input parameters, including cohort characteristics, chemotherapy efficacy, loss-to-follow-up rates, relapse rates, and costs. At the population level, we project that using paclitaxel instead of bleomycin–vincristine would save approximately 6400 years of life over 5 years. Our budget impact analysis revealed that paclitaxel would be affordable; replacing bleomycin–vincristine with paclitaxel would cost an additional US$3·7 million over 5 years, which is only about 0·15% of Kenya's HIV care budget and about 0·32% of Kenya's 5-year county allocations for drug procurement over the same period.

Implications of all the available evidence

Paclitaxel is life-saving, cost-effective, and affordable at current prices and should be rolled out more broadly as a first-line treatment for advanced Kaposi sarcoma in Kenya. Additionally, pegylated liposomal doxorubicin would be cost-effective compared with paclitaxel, if a 44% price reduction were achieved. The results of this study provide evidence for policy guidelines and implementation plans to increase availability of the most effective and cost-effective chemotherapy regimens for people with advanced Kaposi sarcoma in LMICs. Similar to how negotiations on ART prices contributed to substantial reductions in the price of ART in LMICs over the past 20 years, advocacy is urgently needed to decrease the prices of life-saving chemotherapy regimens in LMICs.

most commonly used regimen in Kenya due to its lower price and greater availability than paclitaxel or PLD; etoposide is also sometimes used.[3,12,15–18]

There are no published evaluations of the cost-effectiveness of paclitaxel or PLD for treatment of advanced Kaposi sarcoma in LMICs. In this analysis, we evaluated the clinical impact, costs, and cost-effectiveness of four different chemotherapy regimens (oral etoposide, bleomycin–vincristine, paclitaxel, and PLD) for treatment of advanced Kaposi sarcoma in people living with HIV on ART in Kenya.

See Online for appendix 2

Methods

Study design and participants

In this study, we used the Cost-Effectiveness of Preventing AIDS Complications (CEPAC)–International Model, a validated microsimulation model of HIV disease and treatment.[19,20] We simulated a cohort of adults based in Kenya eligible for chemotherapy according to ACTG stage based on data from the Academic Model for Providing Access to Healthcare (AMPATH) network.[3,8] We derived cohort characteristics from AMPATH, including age (median 35 years [IQR 30–42]), sex (women 32%), and CD4 count at chemotherapy initiation (239 cells per uL [IQR 87–408]; table 1, appendix 2 p 16).[8] We assumed that all people living with HIV with advanced Kaposi sarcoma were on ART for 1 month or longer at chemotherapy initiation (appendix 2 p 3).[8] We compared four treatment strategies: oral etoposide, bleomycin–vincristine, paclitaxel, and PLD. We estimated treatment efficacy from two clinical trials in LMICs and the USA.[6,9] Additional details about HIV care and the CEPAC—International Model are available in appendix 2 (pp 2–4) and online.[21] The research was reviewed and approved by the Mass General Brigham Human Research Committee under protocol 2014P002708.

Model structure

At the start of the model, simulated individuals draw randomly from user-defined distributions of age, sex, and initial CD4 count based on Kenya-specific data.[20] Patients initiate chemotherapy at the start of the model and draw for two possible treatment responses based on regimen-specific probabilities: progression-free survival (PFS) or progressive Kaposi sarcoma. The PFS group has no Kaposi sarcoma-specific mortality while on treatment but could relapse post-treatment (appendix 2 pp 4, 23); people with progressive Kaposi sarcoma face Kaposi sarcoma-associated monthly mortality.[22] While on chemotherapy, individuals face a regimen-specific probability of adverse events (table 1, appendix 2 pp 4–5).

Individuals on chemotherapy have a monthly probability of loss to follow-up from Kaposi sarcoma treatment. If lost to follow-up, their probability of PFS decreased (appendix 2 pp 3, 23).

After chemotherapy completion, people with progressive Kaposi sarcoma continue to face Kaposi sarcoma-associated monthly mortality. Those with PFS after treatment completion could subsequently experience Kaposi sarcoma relapse (appendix 2 p 23). Those without relapse have life expectancy equal to people living with HIV without Kaposi sarcoma (table 1).[27]

The model incorporates costs, including chemotherapy drug price and delivery costs, chemotherapy-related adverse events, ART, and routine HIV care (appendix 2 pp 6–7, 16–17).

Model calibration and validation

We calibrated the model to trial-based 48-week PFS and overall survival for each chemotherapy regimen.[6,9] We validated the model against 2-year survival data from the AMPATH cohort of people living with HIV with Kaposi sarcoma receiving bleomycin–vincristine (appendix 2 pp 4, 10).[22]

Model input parameters

We estimated mortality from progressive Kaposi sarcoma (2·8% per month) from AMPATH-specific survival of people living with HIV with untreated, advanced Kaposi sarcoma (table 1, appendix 2 p 5).[22]

We defined efficacy in terms of 48-week PFS, a composite measure of complete, partial, or stable response to chemotherapy.[6,7,9] We derived 48-week PFS from the trial of etoposide (22%), bleomycin–vincristine (45%), and paclitaxel (66%) by Krown and colleagues,[6] and from the trial of PLD (66%) by Cianfrocca and colleagues[9] (table 1, appendix 2 pp 4, 15).[6,9] We estimated the probability of adverse events from these trials (etoposide 16% per month, bleomycin–vincristine 15% per month, paclitaxel 14% per month, and PLD 11% per month; appendix 2 pp 4–5).[6,9]

Using observational AMPATH and clinical trial data, we derived probabilities of loss to follow-up from chemotherapy (etoposide 9% per month, bleomycin–vincristine

	Value	Range examined
Cohort characteristics		
Age, years[8]	35 (30–42)	..
Women[8]	32%	..
Men[8]	68%	..
CD4 count at chemotherapy initiation, cells per μL[8]	239	87–408
Mortality		
Progressive Kaposi sarcoma, monthly probability[1,22–26]	0·03	0·01–0·05*
Non-Kaposi sarcoma AIDS, CD4 and ART stratified, monthly probability[27]	$1·2\times10^{-5}$ to $1·1\times10^{-5}$	..
Chemotherapy treatment characteristics		
Progression-free survival at 48 weeks, probability		
Etoposide[6]	0·22	..
Bleomycin–vincristine[6]	0·45*	..
Paclitaxel[6]	0·66	0·45–0·66*
PLD[6,9]	0·66†	0·66–0·80*
Adverse events, monthly probability		
Etoposide[6]	0·16	..
Bleomycin–vincristine[6]	0·15*	..
Paclitaxel[6]	0·14*	..
PLD[6,9]	0·11	0·00–0·14*
Loss to follow up, monthly probability		
Etoposide[28]	0·09	0·00–0·09*
Bleomycin–vincristine[28]	0·09	0·03–0·27*
Paclitaxel[28]	0·09	0·03–0·27*
PLD[28,29]	0·07	0·00–0·21*
Relapse by 50 months after treatment, overall probability[30]	0·14‡	0·05–0·41*
Chemotherapy-related costs, US$		
Chemotherapy drug price, per cycle§		
Etoposide	$40	..
Bleomycin–vincristine	$50	..
Paclitaxel	$60	$50–380*
PLD	$180	$90–180*
Adverse event cost, per adverse event		
Etoposide	$38	$19–76*
Bleomycin–vincristine	$32	$16–64*
Paclitaxel	$35	$18–70*
PLD	$35	$18–70*
HIV-related costs, US$		
First-line ART, monthly[31]	$6	$3–12
Routine HIV care (non-ART), monthly[32]	$12	$6–24

Data are median (IQR), unless stated otherwise. Costs are reported as per 2019 US dollars. ART=antiretroviral therapy. PLD=pegylated liposomal doxorubicin. *These parameters were varied in probabilistic sensitivity analysis using beta, lognormal, or fixed distributions (appendix 2 pp 7–8). †We assumed that PLD has the same 48-week progression-free survival value as paclitaxel based on data from Cianfrocca and colleagues[9], a trial that found no difference in progression-free survival between paclitaxel and PLD. We assumed PLD has the same progression-free survival value as paclitaxel in the trial done in low-income and middle-income countries by Susan E Krown and colleagues.[6] ‡We assumed that relapse among those with progression-free survival is the same for all chemotherapy regimens and examined this assumption in sensitivity analysis by assessing the implications of a higher relapse risk with paclitaxel than PLD. §Personal communication between the International epidemiology Databases to Evaluate AIDS (IeDEA) staff in Kenya and the AMPATH pharmacy team.

Table 1: **Model input parameters for a cost-effectiveness analysis comparing four chemotherapy regimens for people living with HIV and AIDS-associated Kaposi sarcoma in Kenya**

9% per month, paclitaxel 9% per month, PLD 7% per month; table 1, appendix 2 pp 5–6).[28,29]

We estimated that 13·5% of participants experienced relapse, with 60% of these relapses occurring in the first year after completing chemotherapy (table 1, appendix 2 p 5).[30] We assumed that relapse risk was the same among anyone with PFS, regardless of chemotherapy regimen (appendix 2 p 5). No second-line treatment was modelled for relapse.

Costs

We derived chemotherapy-related costs from AMPATH pharmacy data (via personal communication between the International epidemiology Databases to Evaluate AIDS [IeDEA] staff in Kenya and the AMPATH pharmacy team). Chemotherapy drug prices were based on generic (non-branded) drugs: etoposide, US$40 per treatment cycle; bleomycin–vincristine, $50 per cycle; paclitaxel, $60 per cycle; and PLD, $180 per cycle. We calculated costs of adverse events: etoposide, $38 per event; bleomycin–vincristine, $32 per event; paclitaxel, $35 per event; and PLD, $35 per event, based on regimen-specific adverse event type and frequency (table 1, appendix 2 pp 6–7, 17).[6] Additional Kaposi sarcoma and HIV-related costs, including costs of tubing and supportive medications, are summarised in appendix 2 (p 16).

Outcomes

Model outcomes were projected over a lifetime and included life expectancy, HIV and Kaposi sarcoma-associated costs from the health-sector perspective (as per 2019 US$), and incremental cost-effectiveness ratios (ICERs, difference in costs divided by the difference in life expectancy between strategies).[33] We considered a strategy to be cost-effective if its ICER was less than 0·5 times the annual per capita gross domestic product (GDP) in Kenya (ie, US$910 per year-of-life-saved [YLS]; appendix 2 p 2).[34–36] We simulated 1 million individuals to obtain stable outcome estimates (appendix 2 p 24).

Sensitivity analyses

We did sensitivity analyses to evaluate the implications of varying input parameters and determine thresholds at which cost-effectiveness conclusions would change (appendix 2 pp 7, 21).

Although etoposide is rarely used compared with bleomycin–vincristine, it is still recommended by WHO as an acceptable option; some believe its oral administration could be preferred by patients and could reduce loss to follow-up compared with intravenous regimens.[37] We examined a scenario in which etoposide would lead to no loss to follow-up, as an extreme.

We first compared paclitaxel with bleomycin–vincristine and did one-way sensitivity analyses in which we varied mean CD4 at chemotherapy initiation, mortality from progressive Kaposi sarcoma, chemotherapy PFS, loss to follow-up from Kaposi sarcoma care, Kaposi sarcoma relapse, and chemotherapy prices. In two-way sensitivity analyses, we varied paclitaxel efficacy and price simultaneously (table 1).

We then compared PLD with paclitaxel and did the same one-way sensitivity analyses as previously described. Additionally, we varied assumptions regarding loss to follow-up, adverse events, and relapse (figure 1, appendix 2 pp 5–6, 18) and did multi-way sensitivity analyses (appendix 2 p 7).

In probabilistic sensitivity analysis, we simultaneously varied key parameters across various distributions to understand the impact of uncertainty around multiple model input parameters on our results (appendix 2 pp 7–8). These parameters were PFS, mortality from progressive Kaposi sarcoma, relapse, adverse event probability, loss to follow-up, adverse event costs, and chemotherapy prices. We generated cost-effectiveness acceptability curves (appendix 2 pp 28–29).

Budget impact analysis

We did a budget impact analysis for advanced Kaposi sarcoma in Kenya over 5 years, comparing use of etoposide, bleomycin–vincristine, paclitaxel, PLD at current prices, and PLD with a 44% price reduction. We projected HIV and Kaposi sarcoma-related costs incurred with each strategy from the health-sector perspective and total YLS for 19 150 people living with HIV treated with chemotherapy over 5 years (3830 per year or 19 150 per 5 years; appendix 2 p 8).[8,38,39] Additional scenarios for budget impact analysis are available in appendix 2 (pp 30–32).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

We projected the overall survival for people treated with etoposide, bleomycin–vincristine, and paclitaxel, which closely approximated the trial-reported survival at 30 months in the study by Krown and colleagues[6] (appendix 2 p 25). The model-projected 2-year survival among people receiving bleomycin–vincristine was 65%, compared with 59% in the AMPATH clinical cohort (appendix 2 p 10).[22]

We projected undiscounted life expectancy to be 6·8 years for etoposide, 11·2 years for bleomycin–vincristine, 15·4 years for paclitaxel, and 16·0 years for PLD, and lifetime, per-person discounted costs to be $2340 for etoposide, $3180 for bleomycin–vincristine, $4150 for paclitaxel, and $4830 for PLD. Bleomycin–vincristine would be cost-effective compared with etoposide (ICER $350 per YLS), and paclitaxel would be cost-effective compared with bleomycin–vincristine (ICER $380 per YLS); however, PLD would not be cost-effective compared with paclitaxel (ICER $2080 per YLS;

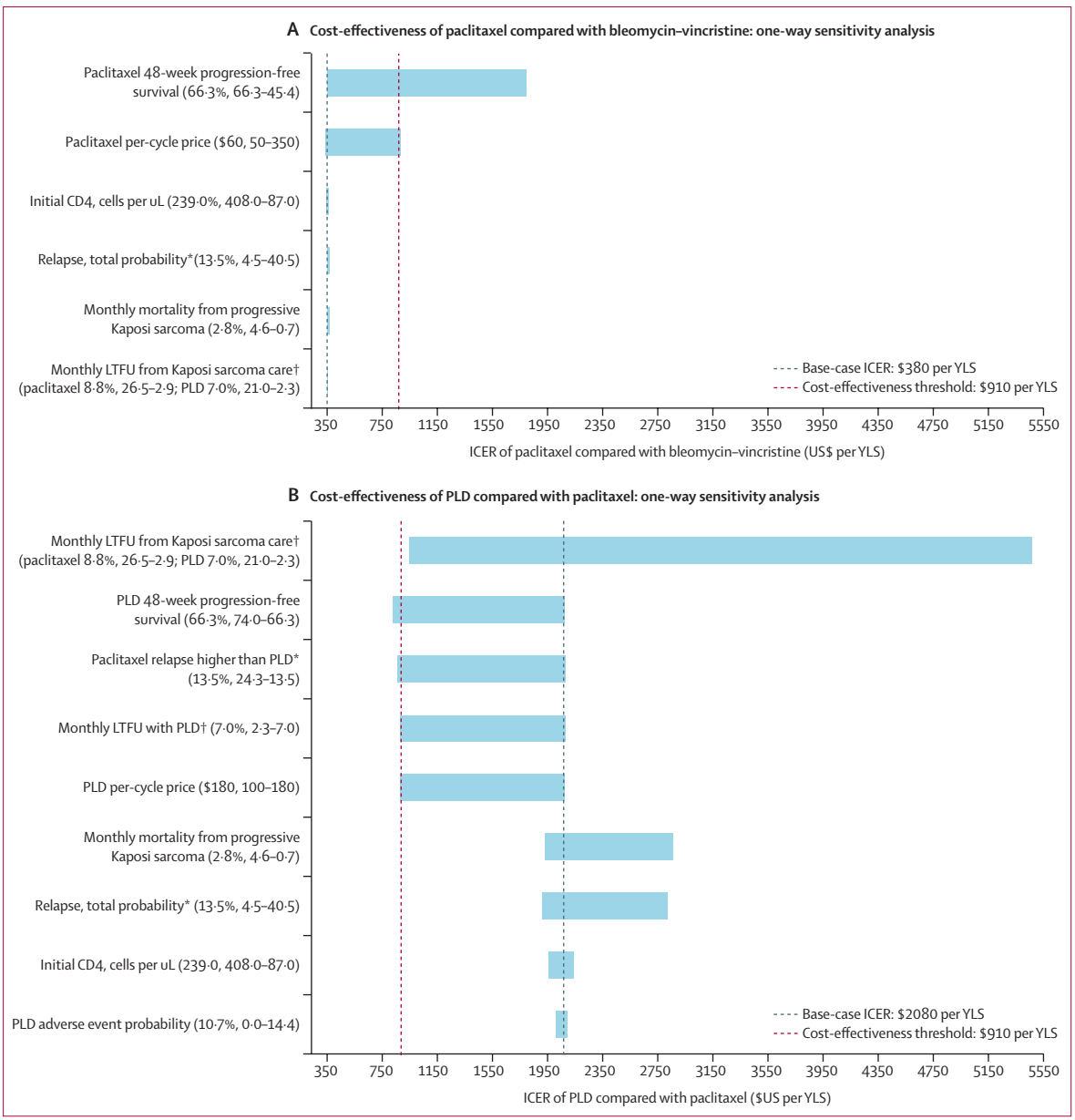

Figure 1: **One-way sensitivity analyses comparing the cost-effectiveness of paclitaxel with bleomycin–vincristine and the cost-effectiveness of PLD with paclitaxel**
This figure shows the ICER of paclitaxel compared with bleomycin–vincristine (A), and the ICER of PLD compared with paclitaxel (B) across a range of model input parameters. On the vertical axis, we describe each parameter varied in sensitivity analysis followed by its base-case value and the range over which it was varied. The parameter estimate that resulted in the lowest ICER is listed first, followed by the parameter estimate that resulted in the highest ICER. Each blue horizontal bar represents the ICER that resulted from the range of estimates examined. The black vertical bar represents the base-case ICER, and the red vertical bar represents the cost-effectiveness threshold in Kenya (0·5 times the per capita gross domestic product, $910 per YLS). Costs are reported as per 2019 US$. ICER=incremental cost-effectiveness ratio. LTFU=loss to follow-up. PLD=pegylated liposomal doxorubicin. YLS=year of life saved. *This models an equal reduction or increase in relapse across all strategies, while paclitaxel relapse higher than PLD models differential relapse between PLD and paclitaxel. †LTFU from Kaposi sarcoma care models an equal reduction or increase in LTFU across all strategies, where LTFU with PLD models a reduction or increase in the difference in LTFU between PLD and paclitaxel.

table 2). Therefore, paclitaxel would be the most cost-effective strategy, with an ICER well below the threshold of $910 per YLS.

If people treated with oral etoposide experienced no loss to follow-up given better adherence, etoposide would remain clinically inferior to bleomycin–vincristine, with an undiscounted life expectancy of 8·0 years (base case 6·8 years), compared with 11·2 years with bleomycin–vincristine.

In one-way sensitivity analyses, paclitaxel remained cost-effective compared with bleomycin–vincristine across a wide range of initial CD4 counts, relapse rates,

	Undiscounted per-person life expectancy, years	Discounted per-person life expectancy, years*	Discounted per-person lifetime cost, US$*	ICER (US$/YLS)†
Etoposide	6·8	5·0	$2340	..
Bleomycin–vincristine	11·2	7·4	$3180	350
Paclitaxel	15·4	9·9	$4150	380
Pegylated liposomal doxorubicin	16·0	10·3	$4830	2080

Costs are reported as per 2019 US$. ICER=incremental cost-effectiveness ratio. YLS=year of life saved. *A discount rate of 3% was used for both life-years and costs, and ICERs were calculated from the discounted values. †ICERs are defined as the difference in cost divided by the difference in life expectancy between a given strategy and the next, least costly strategy. In competing-choice analysis, the most effective strategy with an ICER below the defined threshold is the preferred, cost-effective strategy. We considered the cost-effectiveness threshold to be 0·5 times the annual Kenyan per capita gross domestic product (threshold=US$910 per YLS).

Table 2: **Base-case model outcomes for life expectancy, cost, and cost-effectiveness comparing four chemotherapy regimens for people living with HIV and AIDS-associated Kaposi sarcoma in Kenya**

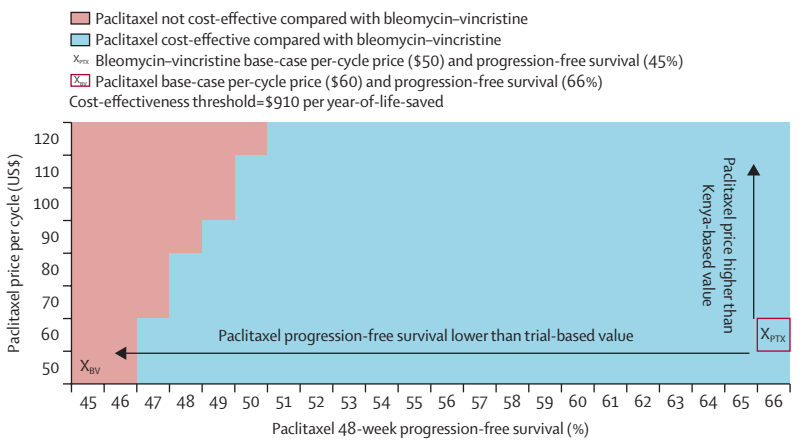

Figure 2: **Cost-effectiveness of paclitaxel compared with bleomycin–vincristine: two-way sensitivity analysis of 48-week paclitaxel's progression-free survival and price**

This figure shows the cost-effectiveness of paclitaxel compared with bleomycin–vincristine, while simultaneously varying paclitaxel's 48-week progression-free survival and per-cycle price. The base-case values for progression-free survival and price are displayed for paclitaxel (X_{PTX}) and bleomycin–vincristine (X_{BV}). The area in blue represents the combinations of paclitaxel's progression-free survival and the price at which paclitaxel is cost-effective at 0·5 times the per capita gross domestic product threshold. The area in red represents the combinations of paclitaxel's progression-free survival and the price at which paclitaxel is not cost-effective at this threshold. The leftward-pointing horizontal arrow shows the 48-week progression-free survival for paclitaxel becoming progressively lower than the trial-based base-case value (<66%). The upward-pointing vertical arrow shows the paclitaxel per-cycle price increasing compared with the Kenya-based base-case value (>$60 per cycle). Costs are reported as per 2019 US$.

mortality from progressive Kaposi sarcoma, and loss to follow-up rates (figure 1). Paclitaxel would no longer be cost-effective only if 48-week PFS was substantially less than that observed in the trial (≤46%; base case 66%) or if its price increased more than 5-fold (≥$350 per cycle; base case $60 per cycle; appendix 2 p 19).[6] In two-way sensitivity analyses, paclitaxel would remain cost-effective compared with bleomycin–vincristine across a broad range of combinations of paclitaxel PFS and price (figure 2).

At current estimates of PFS and price, PLD would not be cost-effective compared with paclitaxel. In one-way sensitivity analyses, PLD would be cost-effective compared with paclitaxel in the following situations: first, 48-week PFS with PLD was 8% greater than with paclitaxel (≥74%; base case 66%); second, PLD loss to follow-up was 2% or less per month (base case 7% per month); third, PLD per-cycle price was reduced by 44% ($100 per cycle; base case $180 per cycle; figure 1, appendix 2 p 19); or fourth, paclitaxel relapse was 1·8 times higher than PLD (24%, base case 13·5%). When PLD adverse events were reduced to 0% per month, PLD would still not be cost-effective. Cost-effectiveness conclusions did not change when examining additional assumptions about loss to follow-up with PLD (appendix 2 p 18) or in multi-way sensitivity analysis (appendix 2 pp 26–27).

In probabilistic sensitivity analysis, there was an 85% probability that paclitaxel offered the highest net monetary benefit at the willingness-to-pay threshold of $910 per YLS (appendix 2 p 28).

Over 5 years, using paclitaxel instead of bleomycin–vincristine to treat 19 150 people living with HIV with advanced Kaposi sarcoma initiating chemotherapy in Kenya would save 6400 years of life (figure 3). Paclitaxel would increase cumulative health-care expenditures by approximately $3·7 million over 5 years compared with bleomycin–vincristine. Overall, HIV-related costs would contribute to 57% of this total expenditure increase due to prolonged life expectancy among people living with HIV. The price of paclitaxel itself would contribute less than $1 million to the overall cost increase. Compared with paclitaxel, PLD would save an additional 380 years of life over 5 years but would cost an additional $11 million; if the price of PLD was reduced to $100 per cycle, PLD would add only $3·6 million in costs.

Discussion

We found that paclitaxel would be the most cost-effective strategy for treatment of advanced AIDS-associated Kaposi sarcoma among people living with HIV in Kenya compared with etoposide, bleomycin–vincristine, or PLD. Because paclitaxel is more clinically effective than bleomycin–vincristine and offers excellent value, it should be the standard of care in Kenya and implemented widely instead of bleomycin–vincristine, which is currently the most frequently used regimen in Kenya.[3,18] PLD is currently included as the first-line treatment by the Kenya Ministry of Health and other guidelines, but thus far is rarely in use in Kenya; we projected that PLD would increase life expectancy but was cost-effective compared with paclitaxel only with a 44% price reduction.[13,14]

Although clinical trial evidence and guidelines support the use of clinically efficacious chemotherapy regimens such as paclitaxel and PLD, to our knowledge this is the first study to analyse the cost-effectiveness of these four regimens for the treatment of advanced Kaposi sarcoma in sub-Saharan Africa.[6] A few cost-effectiveness analyses have compared chemotherapy regimens for Kaposi sarcoma in other countries and included some, but not

all, regimens examined in this analysis. A US-based study[40] compared paclitaxel with PLD and found that paclitaxel was more cost-effective than PLD, but did not include bleomycin–vincristine. In 2006, a Brazil-based analysis[41] concluded that a bleomycin–vincristine-based regimen was the "most reasonable" treatment option for advanced Kaposi sarcoma in LMICs due to its lower cost compared with more effective PLD but did not evaluate paclitaxel. Additionally, it estimated substantially higher costs for PLD in Brazil than estimated for Kenya in our analysis ($450–880 per cycle in Brazil *vs* $180 per cycle in Kenya).[41]

International and national chemotherapy guidelines for treatment of advanced Kaposi sarcoma in sub-Saharan Africa are not uniform. Although the 2014 WHO guidelines list all four regimens examined in this analysis as acceptable, depending on availability and feasibility, our model-based analysis showed that etoposide would be markedly inferior to other regimens.[12] The more recent 2017 National Comprehensive Cancer Network (NCCN) guidelines for sub-Saharan Africa list PLD as the first line, with paclitaxel as the alternate first line.[13] Kenya's 2019 Ministry of Health guidelines recommend PLD as the first-line treatment and paclitaxel, bleomycin–vincristine, and adriamycin–bleomycin–vincristine (a bleomycin–vincristine-based triple regimen) as alternate first-line treatments.[14] Despite NCCN and Kenyan guidelines recommending these more efficacious regimens, neither paclitaxel nor PLD is widely used in most sub-Saharan African settings.[3,15–17] Even despite a clinical trial[3] showing the superior efficacy of paclitaxel compared with bleomycin–vincristine in LMICs, cost and availability remain barriers to widespread use.

Our results show that paclitaxel would improve life expectancy by 4·2 years compared with bleomycin–vincristine, and PLD would improve life expectancy by an additional 0·6 years compared with paclitaxel. These findings show that, in addition to improvements in short-term survival evident in clinical trials, these regimens would also improve life expectancy. These projections for long-term clinical outcomes show the importance of implementing paclitaxel for people living with HIV and Kaposi sarcoma in Kenya and other LMICs and should prompt reconsideration of current guidelines.

We found PLD to be cost-effective compared with paclitaxel only when certain conditions were met: if the per-cycle price of PLD were reduced by at least 44%—from $180 to $100 or less per cycle. Better tolerability of PLD could also affect its cost-effectiveness compared with paclitaxel, if fewer adverse events substantially reduces loss to follow-up.[9,29] The favourable side-effect profile of PLD has led several guidelines, including NCCN, to recommend its use instead of paclitaxel. We evaluated this in our analysis by varying the probability of adverse events and loss to follow-up with PLD. Paclitaxel would remain the most cost-effective strategy unless improved tolerability of PLD led to loss to follow-up of 2% or less per month compared with 9% per month with paclitaxel and bleomycin–vincristine. More recently, paclitaxel had a lower incidence of adverse events than noted in previous trials, which authors attributed to less frequent dosing (every 3 weeks, rather than every 2 weeks).[6] More data are needed to determine implications of dosing frequency on adverse event profiles of chemotherapy regimens and their impact on loss to follow-up. However, adverse events had no impact on conclusions of this analysis due to their low costs. Additionally, we found in PSA that paclitaxel would be the preferred chemotherapy strategy 85% of the time at the 50% annual per capita GDP threshold (appendix 2 p 2) and remained the strategy most likely to provide the highest net monetary benefit even when its current price was doubled (appendix 2 p 28). PLD would be the most likely strategy to provide the highest net monetary benefit only if its price were reduced or if willingness-to-pay was higher than the 50% annual per capita GDP threshold (appendix 2 p 29).

The finding that PLD would be cost-effective at a lower per-cycle price should inform price negotiations, as has been achieved in past negotiations of ART prices.[42] In the early 2000s, there was reluctance to provide ART in LMICs due to cost and perceived complexity of implementation given limited infrastructure.[43] However, advocacy from local and global communities coupled with evidence for ART feasibility and efficacy in LMICs led to reduced ART prices from $10 000 per person per year in 2000 to $100 per person per year in 2016.[44]

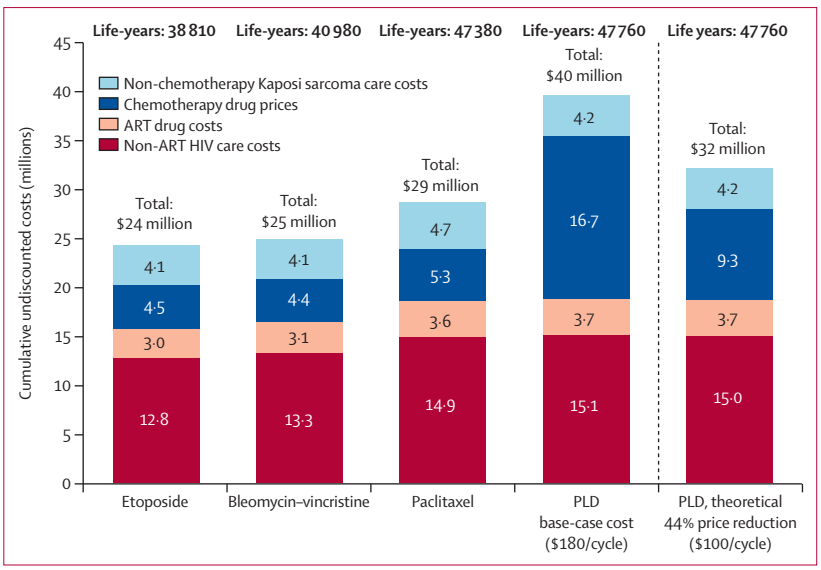

Figure 3: **5-year budget impact analysis of etoposide, bleomycin–vincristine, paclitaxel, PLD, and PLD with a 44% price reduction**

Costs are reported as per 2019 US$. The vertical axis shows projected, cumulative health-care costs over 5 years, assuming 19 150 people living with HIV and Kaposi sarcoma are eligible and initiate chemotherapy over these 5 years. The first four bars represent the 5-year cumulative health-care costs among these people if oral etoposide, bleomycin–vincristine, paclitaxel, or PLD were used as the chemotherapy treatment strategy at current costs. The bar to the far right, after the vertical line, represents the 5-year cumulative health-care costs if PLD had a theoretical 44% price reduction. Total life-years associated with each treatment over 5 years are shown above each corresponding bar. ART=antiretroviral therapy. PLD=pegylated liposomal doxorubicin.

Price reductions achieved for ART can serve as a model for chemotherapy. In 2017, an effort to increase access to chemotherapy in sub-Saharan Africa resulted in a deal between manufacturers and non-governmental organisations that made several chemotherapy drugs available at steep discounts; this deal did not include paclitaxel or PLD.[45] Further efforts are crucial to reduce prices for these life-saving chemotherapy drugs.

Cost-effectiveness does not ensure affordability but results from our budget impact analysis provide insight into cumulative costs of using paclitaxel compared with the most used regimens. We found that 5-year health-care costs would increase by $3·7 million when using paclitaxel instead of bleomycin–vincristine, which is only 0·15% of the 5-year Kenyan HIV budget (figure 3, appendix 2 pp 30–32) and 0·32% of Kenya's 5-year county allocations for drug procurement (2019–20 budget: $232·79 million).[46,47] Additionally, only 25% of these costs are due to paclitaxel itself; most of the increased costs are due to increased life expectancy among people with HIV and HIV treatment costs. A hypothetical paclitaxel price reduction of 10% per year would have only a marginal impact on the 5-year budget (appendix 2 p 32). Conversely, PLD at its current price would increase costs by $15 million over 5 years compared with bleomycin–vincristine, which is equivalent to 0·60% of the 5-year Kenyan HIV budget[46] and 1·27% of Kenya's 5-year county allocations[47] for drug procurement (as per the Kenya Ministry of Health). If PLD per-cycle price were reduced by 44%, total costs would increase by $7·3 million over 5 years, or 0·30% of the 5-year Kenyan HIV budget and 0·63% of Kenya's 5-year county allocations for drug procurement.

Although our analysis is specific to Kenya, our results could be generalisable to a range of LMICs across sub-Saharan Africa. Specifically, our findings were consistent over a wide range of estimates of CD4 counts at chemotherapy initiation and rates of Kaposi sarcoma mortality and loss to follow-up. For example, mean CD4 count of a population with AIDS-associated Kaposi sarcoma in Botswana was 274 per uL, which is within the range we examined in sensitivity analysis.[48] In Mozambique, the price of PLD is lower than in Kenya ($170 per cycle), which is also within the range we examined; PLD would still not be cost-effective at this lower price compared with paclitaxel.[18] Additionally, the ICER of paclitaxel ($380 per YLS) could be cost-effective in settings with lower per capita GDPs or lower cost-effectiveness thresholds. For example, in Zimbabwe (per capita GDP $1160 compared with Kenya GDP $1820), paclitaxel would still be cost-effective at the 50% per capita GDP threshold if non-chemotherapy costs were similar to or lower than those in Kenya.

Our analysis has several limitations. First, no data directly compared paclitaxel and PLD in LMICs; since this direct comparison was not included in the study by Krown and colleagues, we used risk ratios from US-based trials to inform adjusted Kenya-specific inputs.[6,9] Second, clinical trial-based data on PFS represent an aggregate of complete, partial, or stable response. Data are uncertain regarding relapse rates given the small sample size of limited published data, which could impact life expectancy and budget impact estimates. However, cost-effectiveness conclusions did not change when we examined a wide range of relapse rates and varied assumptions in PFS (appendix 2 p 19). Third, we did not include quality of life in this cost-effectiveness analysis given absence of consistent data comparable across different chemotherapy regimens. Although we accounted for chemotherapy drug prices, administration costs, and adverse events, we did not incorporate the operational costs of implementing new chemotherapy regimens, such as training, labour, or scale-up costs. Specifically, in countries with higher labour costs, chemotherapy and adverse event costs might be higher than these estimates; we varied these costs in sensitivity analysis to account for this uncertainty (appendix 2 p 20). We did not include second-line chemotherapy in this analysis due to lack of data on frequency and outcomes. Better estimates of relapse rates, outcomes of second-line chemotherapy, and quality of life could be incorporated in future cost-effectiveness analyses. No micro-costing or time-in-motion studies were available for Kaposi sarcoma treatment in sub-Saharan Africa; this gap should be addressed. However, we found that paclitaxel would remain cost-effective at higher paclitaxel prices (up to $340 per cycle; base case $60 per cycle).

In summary, we find that both paclitaxel and PLD for advanced AIDS-associated Kaposi sarcoma would substantially increase life expectancy in Kenya compared with bleomycin–vincristine; paclitaxel is affordable and the most cost-effective strategy for treatment of advanced Kaposi sarcoma at current costs. These long-term projections extend the clinical trial evidence of improved short-term survival with these regimens.[6] Our conclusions are based on data from Kenya but remain robust over a wide range of population characteristics, suggesting that paclitaxel would be cost-effective in other LMICs. Although PLD has been reported to have a similar efficacy to paclitaxel,[9] it would be cost-effective only if its current price is reduced by 44%. Paclitaxel should become the standard of care for people living with HIV with advanced Kaposi sarcoma in Kenya and similar LMICs. Advocacy to reduce the price of PLD is warranted, as this treatment could decrease Kaposi sarcoma-related mortality even further and reduce global disparities in cancer treatment.

Contributors

EEF and EPH did the conceptualisation, data curation, formal analysis, funding acquisition, investigation, project administration, resource provision, and supervision. NCM did the conceptualisation, data curation, formal analysis, investigation, project administration, and visualisation. AS was responsible for data curation and resource provision. KPR was responsible for investigation, resource provision, and supervision. PPP and MEHF did the formal analysis, methodology, and visualisation. NB curated the data. IVB was responsible for supervision. KAF was responsible for funding acquisition and supervision. All authors contributed to writing, reviewing, and editing the manuscript. EEF, NCM, MEHF, and EPH verified

the data, and had access to the raw data (eg, model inputs), and EEF and EPH had final responsibility for the decision to submit the manuscript.

Declaration of interests

EEF is the Section Editor for Global Health & Equity for the *British Journal of Dermatology*. EPH has royalties from UpToDate. All other authors declare no competing interests.

Data sharing

No new data were collected for this study. All data used as model inputs are publicly available and can be accessed from the sources cited in the manuscript and in appendix 2.

Acknowledgments

This work was supported by the US National Institutes of Health under the following grant numbers: R37AI058736 (KAF); K23AI136579 (EEF); U54CA190153 (EEF, AS, JNM, HB, and ML-O); U01AI069911 (AS); R01AI093269 (KPR); K01HL123349 (EPH); K24AI141036 (IVB); and U54CA254571 and P30AI027763 (JNM), as well as the Jerome and Celia Reich Endowed Scholar Award (EPH) and Weissman Family MGH Research Scholar Award (IVB). The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official views of the NIH or the Massachusetts General Hospital Executive Committee on Research. We would like to thank Stephen Resch; Isaac Ravi Brenner; Kieran Fitzmaurice; Nora Mulroy; Acadia Thielking; Nattanicha Wattananimitgul; the International epidemiology Databases to Evaluate AIDS East Africa Team, including Raphael Koima, Elyne Rotich, Celestine Lagat, and Linda Chemtai; and the CEPAC—International team for their support in the preparation of this analysis.

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