

# Evaluating the cost-effectiveness of combination antiretroviral therapy for the prevention of mother-to-child transmission of HIV in Uganda

Andreas Kuznik,<sup>a</sup> Mohammed Lamorde,<sup>b</sup> Sabine Hermans,<sup>c</sup> Barbara Castelnuovo,<sup>b</sup> Brandon Auerbach,<sup>d</sup> Aggrey Semeere,<sup>b</sup> Joseph Sempa,<sup>b</sup> Mark Ssenono,<sup>b</sup> Fred Ssewankambo<sup>b</sup> & Yukari C Manabe<sup>b</sup>

**Objective** To model the cost-effectiveness in Uganda of combination antiretroviral therapy (ART) to prevent mother-to-child transmission of human immunodeficiency virus (HIV).

**Methods** The cost-effectiveness of ART was evaluated on the assumption that ART reduces the risk of an HIV-positive pregnant woman transmitting HIV to her baby from 40% (when the woman is left untreated) to 25.8%, 17.4% and 3.8%, respectively, when the woman is given: (i) single-dose nevirapine (at an estimated total drug cost of 0.06 United States dollars [US\$]); (ii) dual therapy with zidovudine and lamivudine for 7 weeks (at a total drug cost of US\$ 15.63); or (iii) ART for 18 months (at a total annual cost of US\$ 469.77). Lifetime ART (US\$ 6883), recommended for pregnant women with < 350 CD4+ T lymphocytes per mm<sup>3</sup>, was assumed to give the same reduction in transmission risk in each subsequent pregnancy.

**Findings** Compared with single-dose nevirapine, dual therapy and no therapy, 18 months of ART averted 5.21, 3.22 and 8.58 disability-adjusted life years (DALYs), respectively, at a cost of US\$ 46, US\$ 99 and US\$ 34 per DALY averted. The corresponding figures for lifetime ART are, respectively, 19.20, 11.87 and 31.60 DALYs averted, at a cost of US\$ 205, US\$ 354 and US\$ 172 per DALY averted.

**Conclusion** In Uganda, ART appears highly cost-effective for the prevention of mother-to-child HIV transmission, even if continued over the patients' lifetimes. Given the additional public health benefits of ART, efforts to ensure that all HIV-positive pregnant women have access to lifelong ART should be intensified.

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## Introduction

The mother-to-child transmission of human immunodeficiency virus (HIV) poses a substantial risk in sub-Saharan Africa.<sup>1</sup> There are approximately 12 million HIV-positive women of childbearing age in sub-Saharan Africa<sup>2</sup> who every year account for an estimated 1.4 million pregnancies at risk of mother-to-child transmission.<sup>3</sup> In Uganda, a country with the second highest fertility rate in the world (6.7 children per woman), approximately 91 000 infants are born annually to HIV-positive women. Only 51.6% of these women receive any intervention for the prevention of mother-to-child transmission (PMTCT), although the corresponding target coverage set by the General Assembly of the United Nations is 80%.<sup>2,4,5</sup> In 2009, mother-to-child transmission accounted for approximately 24% of the 110 000 new HIV infections that occurred in Uganda.<sup>2,4</sup>

Of the Ugandan women who received any antiretroviral drug for PMTCT in 2009, 58% received single-dose nevirapine, 25% received dual therapy with zidovudine and lamivudine and the remaining 17% received combination antiretroviral therapy (ART).<sup>4</sup> In the PMTCT guidelines that were published by the World Health Organization (WHO) in 2010, two programmatic options (A and B) are outlined. In Option B, all pregnant women found to have fewer than 350 CD4+ T-lymphocytes per mm<sup>3</sup> are offered lifelong ART from week 14 of gestation. For women with higher CD4+ cell counts, it is recommended that ART be discontinued at the end of breastfeeding.<sup>6</sup> In 2011, Uganda adopted Option B, and all

Ugandan health facilities are expected to follow this protocol once adequate resources are made available.<sup>7</sup>

No published studies have evaluated the cost-effectiveness of lifelong ART for PMTCT. In the present study, mathematical models were used to evaluate: (i) the cost-effectiveness of ART for PMTCT in Uganda relative to that of other antiretroviral strategies for PMTCT; (ii) the implications of lifelong ART for eligible women from the standpoint of health economics; and (iii) the cost-effectiveness of increasing access to ART for PMTCT.

## Methods

We developed a decision-based analytical model from the perspective of the Ugandan national health system. Four PMTCT alternatives (ART, single-dose nevirapine, dual therapy or no treatment) were evaluated at the decision point. The model included one chance event node that was populated according to estimates of the transmission risk associated with each PMTCT alternative. The only clinical outcome included in the model was mother-to-child transmission of HIV. Estimates of the disability-adjusted life years (DALYs) associated with one case of mother-to-child transmission were based on the HIV-attributable reduction in life expectancy plus standard disability weights for HIV infection and acquired immunodeficiency syndrome (AIDS).

Estimates of the treatment costs for single-dose nevirapine and dual therapy included only the costs of drug acquisition; any potential costs for physician visits or laboratory examina-

<sup>a</sup> Pfizer Inc., New York, United States of America (USA).

<sup>b</sup> Infectious Diseases Institute, College of Health Sciences, Makerere University, PO Box 22418, Kampala, Uganda.

<sup>c</sup> Department of Global Health, Academic Medical Center, Amsterdam, Netherlands.

<sup>d</sup> Harvard Medical School, Boston, USA.

Correspondence to Mohammed Lamorde (e-mail: mlamorde@idi.co.ug).

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tions were excluded. For ART, however, we included both the costs of drug acquisition and the costs associated with regular physician and laboratory follow-ups. In the comparison of ART with no treatment, we assumed that incremental resources (e.g. overhead and capital costs needed to provide extra health-care facilities and equipment) would be required to make ART available to the currently untreated populations. Based on the differences in the probability of mother-to-child transmission with each treatment alternative, we calculated the treatment-related cost offsets arising from the need to provide health-care services to fewer HIV-positive infants in the future.

Two mathematical models (1a and 1b) were explored in an initial analysis and two more (2a and 2b) were investigated in a second analysis. In Model 1a we evaluated the cost-effectiveness of an 18-month course of ART (relative to that of single-dose nevirapine or dual therapy for 7 weeks in women who already have access to drugs for PMTCT). In Model 1b we evaluated the cost-effectiveness of lifelong ART (again, relative to that of single-dose nevirapine or dual therapy, and on the assumption that all subsequent pregnancies would be treated with the same regimen). Since we modelled ART relative to other drug interventions, we assumed that no additional resources would be required to deliver ART drugs and maintenance services (i.e. to populations already accessing single-dose nevirapine or dual therapy), although we also challenged this assumption in sensitivity analyses.

The second analysis evaluated the impact of increasing ART access for HIV-positive pregnant women, either for 18 months (Model 2a) or for life (Model 2b). We compared ART with no treatment in women currently without access to any PMTCT therapies due to lack of drugs, lack of local health-care centres or lack of knowledge of HIV infection.<sup>4</sup> Annual incremental overhead and capital costs needed to overcome these barriers were applied in both models.<sup>8</sup> As the estimates of these costs were uncertain, we also conducted break-even analyses to evaluate the cost level at which ART would cease to be highly cost-effective (relative to no treatment). Selected inputs were varied in one-way sensitivity analyses and all calculations were performed using Microsoft Excel 2007 (Redmond, United States of America).

## Cost inputs

The model inputs, the assumptions that were made and the calculations that were used are described in Table 1. All costs are expressed in 2011 United States dollars (US\$). Drug costs came from the Ugandan Medical Access database (UNAIDS Drug Access Initiative).<sup>12</sup> The ART regimen investigated was a combination of zidovudine and lamivudine with either efavirenz or nevirapine.<sup>7,13</sup> In the first analysis, the total annual cost associated with ART was US\$ 328.77 per patient. In the second analysis (i.e. Models 2a and 2b), additional overhead and capital costs, estimated at US\$ 141 per patient per year, were included.<sup>8</sup> These additional costs raised the total annual cost of ART to US\$ 469.77 per patient.

The per-patient drug costs of single-dose nevirapine, dual therapy and no treatment were estimated to be US\$ 0.06, US\$ 15.63 and zero, respectively. The costs of any health-care delivery and related services for single-dose nevirapine were assumed to be the same as those for the dual therapy. As discussed above, various non-drug-related health-care costs, such as those associated with physician visits, laboratory follow-up and other medication, are included in the total cost of ART but not in the total costs of the alternative strategies (Table 1).

Cost offsets included treatment costs for the proportion of HIV-infected children reported to be receiving ART in Uganda (18%).<sup>2</sup> For each child receiving ART, the discounted lifetime cost of ART was estimated to be US\$ 3808. For each of the remaining HIV-positive children in Uganda, who are assumed to have no current access to ART, a lifetime treatment cost of US\$ 495 was estimated.<sup>11</sup> As access to ART may increase in future, the proportion of HIV-positive children receiving ART was varied from 0% to 100% in sensitivity analyses, to see how this proportion affected the apparent cost-effectiveness of ART.

## Clinical inputs

The cumulative probability of mother-to-child transmission (including transmission during breastfeeding) associated with each of the treatment strategies investigated is shown in Table 1. We assumed breastfeeding would last for 20.4 months, as this is the mean duration observed in a Ugandan study.<sup>14</sup> Without any PMTCT interven-

tion, the probability of mother-to-child transmission was estimated at 40.0%.<sup>15,16</sup> Single-dose nevirapine and dual therapy reduce this estimate to 25.8%<sup>10</sup> and 17.4%,<sup>17</sup> respectively. We used a mean mother-to-child transmission rate of 3.8% (range, 1.8–6.1%) for 12 months of ART (corresponding to the duration of ART outlined in Option B).<sup>13,18</sup> These probabilities were applied uniformly in the models.

For HIV-negative neonates, we used the statistical life expectancy at birth in Uganda (Table 1).<sup>1</sup> For HIV-positive neonates receiving ART, mean life expectancy at birth (14.23 years) was calculated from published annual survival statistics in ART-treated Ugandan children.<sup>19</sup> Untreated HIV-positive neonates were assumed to live a mean of 2 years, based on pooled mortality data from several African studies.<sup>20</sup> For women with CD4+ cell counts of < 350 cells/mm<sup>3</sup> at the time of ART initiation, life expectancy was assumed to be 19.3 years, based on survival estimates derived from an African model.<sup>21</sup> The mean Ugandan national fertility rate of 6.7 children per woman was reduced by 33%, to 4.49 children per woman, to account for the relatively lower fertility observed among HIV-positive women.<sup>22</sup> We used disability weights of 0.123 for each year lived with HIV infection and 0.505 for the last year of life with AIDS.<sup>23</sup> All costs and benefits were discounted at 3% annually.<sup>24</sup>

## Patient adherence

Sensitivity analyses were conducted to explore the impact of adherence on our 18-month estimates. We assumed that the mother-to-child transmission rate of 3.8% for 12 months of ART applied only to women who were completely adherent. The reported relationship between patient adherence and sustained viral loads of < 400 ribonucleic acid (RNA) copies per ml<sup>25</sup> of blood plasma was used to estimate the higher transmission probabilities for women with less than perfect adherence. We conservatively assumed that the probability of mother-to-child transmission for a woman on ART reverted to the value for untreated women (40%) when the woman's viral load was > 400 RNA copies per ml. We also assumed that the costs of acquiring the drugs for ART would be positively correlated with adherence levels and that the level of adherence to dual therapy would be the same as that of adherence to ART.

Table 1. **Inputs used in the models to evaluate the cost-effectiveness of combination antiretroviral therapy (ART) in Uganda, 2011**

Input	Value
<b>Cost inputs (US\$ per patient)</b>	
ART-related costs	
6 weeks of nevirapine for neonate <sup>a</sup>	11.23
Annual costs	
Drugs for ART <sup>b</sup>	204.15
Clinic personnel <sup>c</sup>	42.96
Laboratory investigation <sup>c</sup>	35.04
Other medication <sup>c</sup>	33.72
Radiology <sup>c</sup>	1.68
ART, total (excluding overhead and capital costs)	328.77
Overhead and capital costs <sup>d</sup>	141.00
Comparator regimens	
Single-dose nevirapine <sup>e</sup>	0.06
Dual therapy for 7 weeks <sup>f</sup>	15.63
Cost offsets	
Lifetime cost of ART for treated HIV-positive child <sup>g</sup>	3808
Lifetime cost of ART for untreated HIV-positive child <sup>h</sup>	495
<b>Clinical inputs</b>	
Transmission probability (%)	
ART	3.8
Dual therapy	17.4
Single-dose nevirapine	25.8
No treatment	40.0
Life expectancy at birth (years)	
Male	52.17
Female	54.33
HIV-positive neonate, treated	14.23
HIV-positive neonate, untreated	2.00
Disability weights	
HIV	0.123
AIDS	0.505
Fertility of HIV-positive women (children per woman)	4.49
Paediatric treatment rate (%)	18
Annual discount rate (%)	3

AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; US\$, United States dollar.

<sup>a</sup> The recommended 6-week course of nevirapine for the neonate, at 10 or 15 mg per day depending on birth weight, requires two or three 240-ml bottles of syrup containing 10 mg of nevirapine per ml. The assumption is that three bottles are required, each costing US\$ 3.742.

<sup>b</sup> Although either nevirapine or efavirenz is recommended in combination with zidovudine and lamivudine, we modelled the per-patient cost of zidovudine, lamivudine and the relatively more expensive efavirenz, at US\$ 16.04 per month. In addition, up to 20% of HIV-positive pregnant women may develop zidovudine-related anaemia.<sup>9</sup> For such women, the zidovudine would have to be replaced with the more expensive tenofovir and this would increase the per-patient costs of ART to an estimated US\$ 20.91 per month. The per-patient weighted mean drug cost for ART used in our analysis was therefore 80% of US\$ 16.04 plus 20% of US\$ 20.91 per month, which equals US\$ 204.15 per year.

<sup>c</sup> Based on an analysis of the non-drug costs associated with ART that was conducted at a large urban outpatient HIV clinic in Kampala, Uganda, in which annual maintenance costs per patient were found to be approximately US\$ 113.40 per year.<sup>8</sup>

<sup>d</sup> Only relevant in Models 2a and 2b. Based on Babigumira et al.<sup>8</sup>

<sup>e</sup> With 16 months of breastfeeding.<sup>10</sup>

<sup>f</sup> Based on the assumption that dual therapy with zidovudine and lamivudine is initiated in week 34 of the gestation and continued for 1 week after delivery. This results in a total of 7 weeks of therapy, at an estimated weekly cost of US\$ 2.233 per patient.

<sup>g</sup> Discounted annual cost of ART of US\$ 328.77 over 14.23 years.

<sup>h</sup> Based on Shah et al.<sup>11</sup>

## Results

### Cost-effectiveness of 18 months of ART

The results of modelling 18 months of ART are displayed in Table 2. Based on the discounted differences in life expectancy between HIV-negative children (approximately 53.25 years) and HIV-positive children who are left untreated (2 years) or given ART (14.23 years), we estimated that each child infection is associated with 23.70 DALYs. The discounted cost of ART given for a period of 18 months (Model 1a) is US\$ 482 per patient. Due to the ART-attributable reduction in mother-to-child transmission, ART is also associated with cost offsets of US\$ 240 per patient compared with single-dose nevirapine and of US\$ 148 per patient compared with dual therapy. The net total incremental cost of ART per pregnancy was estimated to be US\$ 242 relative to single-dose nevirapine and US\$ 318 relative to dual therapy. However, ART averts a mean of 5.21 DALYs relative to single-dose nevirapine [calculated as (25.8–3.8%) of 23.70 DALYs] and 3.22 DALYs relative to dual therapy. Thus, the corresponding cost of ART per DALY averted was about US\$ 46 (i.e. US\$ 242 divided by 5.21) relative to single-dose nevirapine and about US\$ 99 (i.e. US\$ 318 divided by 3.22) relative to dual therapy.

### Cost-effectiveness of lifelong ART

At the prices recorded in 2011, lifelong ART (Model 1b) would cost US\$ 4817 per patient over 19.3 years. The cost differentials for ART relative to single-dose nevirapine and dual therapy are US\$ 4817 and US\$ 4747 per patient, respectively. Since lifelong ART reduces the probability of mother-to-child transmission over a mean of 3.49 future pregnancies, the corresponding cost offsets of ART are US\$ 884 (US\$ 240 multiplied by 4.49, discounted) and US\$ 547 (US\$ 148 multiplied by 4.49, discounted), respectively. The net total incremental lifetime costs of ART are therefore US\$ 3933 per patient relative to single-dose nevirapine and US\$ 4200 per patient relative to dual therapy. The corresponding total numbers of DALYs averted by the ART-attributable PMTCT are 19.20 (5.21 multiplied by 4.49, dis-

Table 2. Results from four models used to evaluate the incremental cost-effectiveness of combination antiretroviral therapy (ART) in Uganda relative to other treatment regimens or none, 2011

Variable	Model				2a: 18-month ART, relative to NT	2b: lifetime ART, relative to NT
	1a: 18-month ART, relative to		1b: lifetime ART, relative to			
	sdNVP	DT	sdNVP	DT		
Cost difference per patient (US\$)	482	467	4817	4747	689	6883
Cost offset per patient (US\$)	240	148	884	547	395	1455
Incremental cost per patient (US\$) <sup>a</sup>	242	318	3933	4200	294	5428
DALYs averted per patient	5.21	3.22	19.20	11.87	8.58	31.60
Incremental cost per DALY averted (US\$)	46	99	205	354	34	172

DALY, disability-adjusted life year; DT, dual therapy; NT, no treatment; sdNVP, single-dose nevirapine; US\$, United States dollar.

<sup>a</sup> Calculated by subtracting the cost offset from the cost difference.

counted) and 11.87 (3.22 multiplied by 4.49, discounted), respectively. Hence, the incremental costs per DALY averted as a consequence of lifetime ART are US\$ 205 relative to single-dose nevirapine and US\$ 354 relative to dual therapy.

### Expanding ART access to untreated women

In Model 2a, the total cost of 18 months of ART was estimated to be US\$ 689 per patient (with annual costs of US\$ 204.15 for drug acquisition, US\$ 124.62 for maintenance and \$141.00 for overheads and capital). However, the estimated cost offset resulting from the ART-attributable reduction in the probability of mother-to-child transmission amounts to US\$ 395 per patient, and this results in an incremental ART cost of US\$ 294 per patient. Since, relative to no treatment, ART averts 8.58 DALYs, the net cost of ART per DALY averted is US\$ 34. Compared with no treatment, lifetime ART (Model 2b) costs approximately US\$ 6883 more per patient (\$469.77 per year over 19.3 years, discounted). However, as US\$ 1455 of that expense is offset by the reduced burden on HIV-related health care, the net incremental cost of lifetime ART is estimated to be US\$ 5428 per patient. Since lifetime ART averts 31.60 DALYs, the cost of such therapy is US\$ 172 per DALY averted.

### Sensitivity analyses

We varied selected model inputs in one-way sensitivity analyses (Fig. 1). All of the main model results proved robust to variations in the lifetime cost of treating HIV-positive infants with ART (from US\$ 638 to US\$ 8514 per patient), the lifetime health-care costs of an HIV-positive infant who does not

receive ART (from US\$ 0 to US\$ 1485 per infant), the effectiveness of ART (with the probability of mother-to-child transmission being reduced to values varying from 1.8% to 6.1%), the annual discount rate (from 0% to 6%) and the fertility rate when lifetime treatment is considered (from 4.02 to 5.03 children per woman). Increasing the paediatric treatment rates led to higher cost offsets and improved the cost-effectiveness of ART. In fact, application of a paediatric treatment rate of 100% in Model 1a or Model 2a produced net cost-savings.

Model 1b proved sensitive to the cost of ART. For example, if the hypothetical annual cost of such treatment were increased to US\$ 750 per patient, the cost of such treatment per DALY averted would increase to US\$ 837 relative to dual therapy. Model 1b also proved sensitive to assumptions made about the effectiveness of the therapies with which ART was compared. Single-dose nevirapine and dual therapy have been associated with mother-to-child transmission rates as low as 13.1% and 7.5%, respectively.<sup>26</sup> At these relatively low transmission rates, the incremental cost of ART per DALY averted increases to US\$ 547 relative to single-dose nevirapine and US\$ 1424 relative to dual therapy.

In break-even analyses, our results remained robust when the incremental overhead and capital costs were set at realistic levels. Compared with no treatment, ART appeared to avert a mean of 8.58 DALYs when given for 18 months and 31.60 DALYs when given over the patient's remaining life. If the Ugandan health service were willing to pay up to US\$ 490 (i.e. the per-capita gross domestic product [GDP] for Uganda in 2009) to avert a single DALY, the

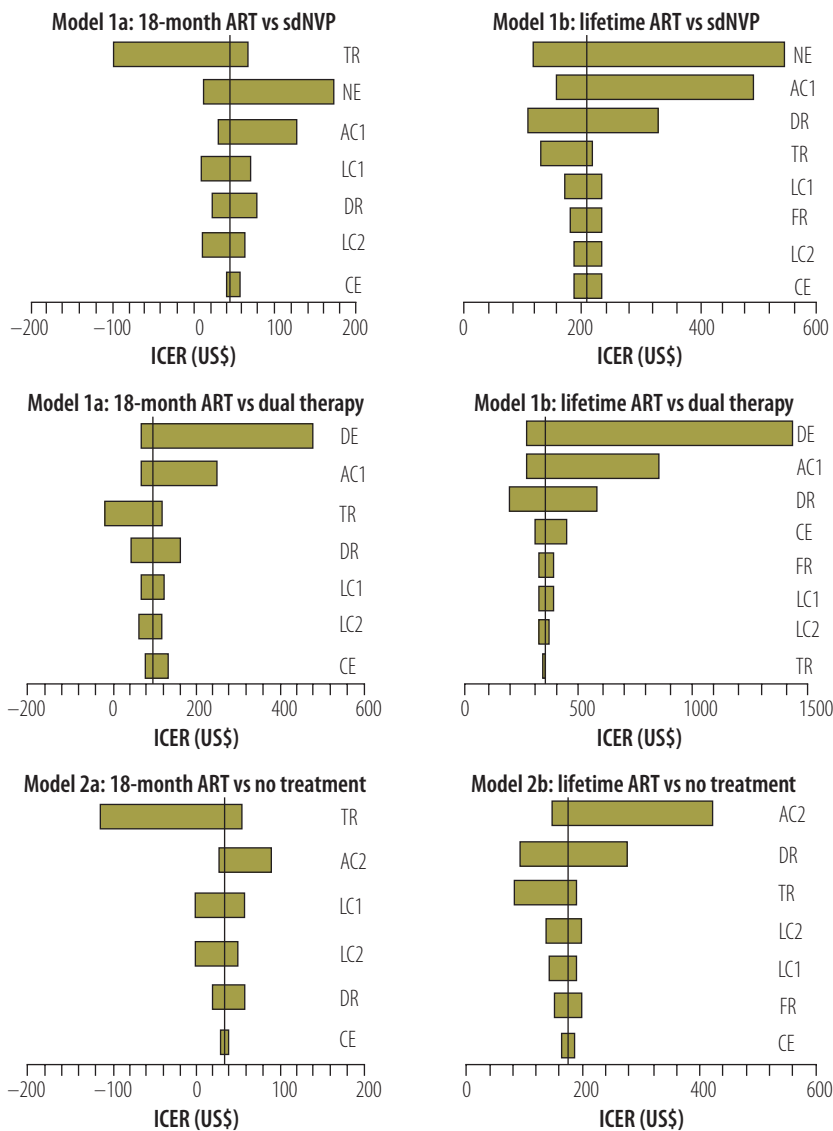
incremental per-patient costs associated with ART could rise from US\$ 294 to as much as US\$ 4204 (8.58 × US\$ 490) in the 18-month model and from US\$ 5428 to as much as US\$ 15 484 (31.60 × US\$ 490) in the lifetime model. The corresponding annual overhead and capital costs could also markedly increase, from US\$ 141 per patient up to either US\$ 2805 per patient (with 18 months of ART) or US\$ 827 (with lifetime therapy).

Finally, Fig. 2 displays the relationship between ART adherence and the incremental cost-effectiveness ratios in our 18-month model. Although there appeared to be little meaningful variability in our adherence-adjusted estimates of the incremental cost-effectiveness ratios of ART relative to no treatment or dual therapy, levels of adherence did seem to have a substantial impact on the corresponding ratios that were estimated relative to single-dose nevirapine. It was not possible to model very low levels of ART adherence but the observed trend indicates that it may not be cost-effective to use ART instead of single-dose nevirapine in populations where the level of adherence is expected to be lower than 40%.

## Discussion

This appears to be the first published study to evaluate the cost-effectiveness of lifelong ART for PMTCT. We evaluated the cost-effectiveness of antiretroviral regimens for PMTCT in the Ugandan context. Uganda's GDP in 2009 amounted to US\$ 490 per capita.<sup>27</sup> According to WHO, a health intervention in a developing country can be considered cost-effective and highly cost-effective if it costs, per DALY averted, less than three times the annual per-capita GDP

Fig. 1. Sensitivity analyses used in exploring the cost-effectiveness of combination antiretroviral therapy in Uganda, 2011



ICER, incremental cost-effectiveness ratio.  
 Note: Tornado diagrams showing the incremental ICER for combination antiretroviral therapy (ART) relative to single-dose nevirapine (sdNVP), dual therapy or no treatment, as derived from one-way sensitivity analyses of several key parameters. The parameters investigated included the annual cost of ART, with the base case value set either at US\$ 328.77 (AC1) or US\$ 469.77 (AC2) per patient and the analysis exploring values of US\$ 250–750 and US\$ 250–1000 per patient, respectively. The lifetime cost of ART for a child infected with human immunodeficiency virus (HIV), LC1, was varied between US\$ 638 and US\$ 8514, with a base case value of US\$ 3808, while the lifetime cost of care for an untreated HIV-positive child, LC2, was varied between zero and US\$ 1485 (base case: US\$ 495). The ART treatment rate in HIV-positive children (TR; base case: 18%; range: 0–100%), the effectiveness of ART (CE; base case: 3.8%; range: 1.8–6.1%), dual therapy (DE; base case: 17.4%; range: 7.5–21.0%) and sdNVP (NE; base case: 25.8%; range 13.1–38.5%), the annual discount rate (DR; base case: 3%; range: 0–6%) and the fertility rate among HIV-positive women (FR; base case: 4.49 children per woman; range: 4.02–5.03) were also explored.

and less than this product, respectively.<sup>28</sup> In terms of these thresholds, ART for 18 months appears to be a highly cost-effective strategy for PMTCT compared with either of the other regimens that are widely used for PMTCT in Uganda. Our models also indicate that ART is highly cost-effective when given over

the mother’s remaining life (although this conclusion is sensitive to the assumed effectiveness of dual therapy). Furthermore, expanding access to ART to those eligible women who are currently untreated also appears to be cost-effective. The results of our break-even analysis indicate that ART remains cost-

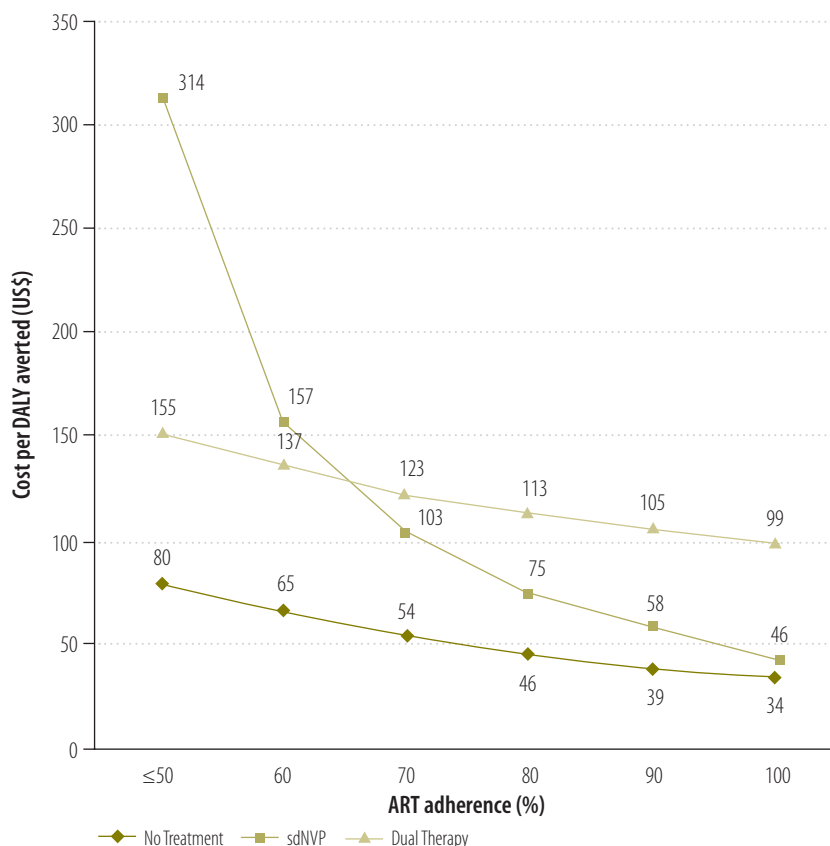
effective even with additional annual investments, to expand access, of up to US\$ 2800 per patient (US\$ 827 in the lifetime model). In sensitivity analyses, ART remains cost-effective unless adherence to the therapy falls below 40%.

Our results are similar to the results of studies in Malawi and Nigeria. In Malawi, ART given for 10 months was associated with an incremental cost per DALY averted of US\$ 35 (relative to no treatment).<sup>29</sup> In Nigeria, short-course ART initiated between weeks 14 and 24 of gestation and discontinued 6 weeks after delivery resulted in a cost per DALY averted of US\$ 113 (relative to dual therapy during pregnancy and a single dose of nevirapine at delivery).<sup>11</sup> However, our work extends these findings by evaluating the impacts of a longer duration of breastfeeding, patient adherence and lifelong treatment on the relative cost-effectiveness of ART for PMTCT.

In sub-Saharan Africa, where alternatives to breast milk are often unaffordable or unavailable, approximately half of mother-to-child HIV transmission occurs during breastfeeding.<sup>30</sup> The incorporation of a 12-month breastfeeding period is a strength of our study not seen in the earlier Malawian and Nigerian models, which only considered breastfeeding for up to 6 months and 6 weeks, respectively. The cost-effectiveness of lifelong ART also depends on the number of future childbirths per woman. Although high fertility rates are common in sub-Saharan African countries, only four such countries have currently attained the 80% target for PMTCT coverage.<sup>31</sup> Our finding that lifelong ART is highly cost-effective in Uganda may be generalizable to most countries in sub-Saharan Africa.

The programmatic implementation of Option B requires human and material resources. Given existing resource constraints, Uganda plans to transition all of its PMTCT sites to the Option B strategy in a phased manner.<sup>7</sup> At sites where this transition has not yet occurred, the Ugandan health service recommends use of the Option A strategy. In Option A, pregnant women with CD4+ cell counts >350 cells per mm<sup>3</sup> are given zidovudine daily from week 14 of gestation; zidovudine, lamivudine and single-dose nevirapine at delivery, and then dual therapy (zidovudine plus lamivudine) for the next 7 days.<sup>6,7</sup> Since Option A is less expensive than Option B, cost-effectiveness studies

Fig. 2. Relationships between the levels of adherence to combination antiretroviral therapy (ART) and the cost of such therapy per disability-adjusted life year (DALY) averted, Uganda, 2011



US\$, United States dollar.

Note: The values plotted are the modelled incremental costs of 18 months of ART, relative to single-dose nevirapine (sdNVP), dual therapy or no treatment. In the models employed, adherence at ≤50%, 60%, 70%, 80%, 90% and 100% leads to mother-to-child transmission rates of 21.9%, 18.3%, 14.7%, 11.0%, 7.4% and 3.8%, respectively.

evaluating both options should be conducted. Presently, ART is available in 109 of 122 district hospitals in Uganda. The midwives and other health-care workers who are currently providing single-dose nevirapine or dual therapy in these hospitals could be trained to initiate ART, follow up patients on ART and link patients to local and national programmes for HIV treatment and control.<sup>4,32</sup>

The present study has several limitations. Our estimates of mother-to-child transmission under each of the four strategies investigated were derived from the results of multiple trials rather than one randomized trial. Between-study differences in demographics and study design could therefore have influenced our results. We also applied a constant transmission probability to

each PMTCT strategy, but it is possible that the risk of mother-to-child transmission varies according to the clinical stage of the maternal HIV infection. Also, pregnant women in Uganda often access antenatal care only after the fifth month of their pregnancies<sup>14</sup> and ART may be less effective when initiated during the late stages of gestation. For ART, we assumed that the maternal HIV infection was always diagnosed in the first pregnancy, but some HIV-positive women already have children before their HIV infection is detected. The mean number of pregnancies after the diagnosis of HIV infection may therefore be lower than our estimate.

We were unable to incorporate ART adherence into our lifetime model because there are insufficient data available on the relationship between long-term

adherence and virological failure or, ultimately, mother-to-child transmission. As our results for 18 months of ART proved sensitive to the level of adherence, it is likely that lifelong ART would be even more sensitive to this parameter. Also, we assumed that all HIV-negative children have similar life expectancies, whereas those born to HIV-positive mothers may have relatively high mortality rates.<sup>20</sup>

Despite these limitations, our estimates of the cost-effectiveness of ART are likely to be conservative. Among HIV-positive individuals, the costs of additional health care are likely to be lower for those on ART because ART improves immune function, thereby reducing the risk of opportunistic infections.<sup>33</sup> Moreover, our models excluded the benefits of ART on maternal life expectancy.<sup>21</sup> Importantly, a recent randomized trial (HPTN052) reported a 96% reduction in horizontal HIV-1 transmission as the result of ART,<sup>34</sup> corroborating some earlier observations.<sup>35,36</sup> Consequently, the true economic value of lifelong ART includes benefits not only for the mother and child but also for any uninfected sexual partners of the mother.

## Conclusion

The measures proposed in Option B of the guidelines for PMTCT published by WHO in 2010 appear highly cost-effective in Uganda (relative to other current therapies for PMTCT) and would generate additional value if the recommended ART could reach more women. In Uganda, ART still appears to be highly cost-effective if extended over the mothers' remaining lifespans. Given that ART administered to HIV-positive pregnant women not only prevents HIV infection of the unborn child but has other transmission-mitigation benefits, efforts to ensure access to lifelong ART for all HIV-positive pregnant women should be intensified. ■

**Competing interests:** Andreas Kuznik is a full time employee of Pfizer Inc., with ownership of stock in Pfizer Inc., and his time at the Infectious Diseases Institute in Uganda was supported by the Pfizer Global Health Fellows programme.

## ملخص

## تقييم مردودية العلاج التوليفي بمضادات الفيروسات القهقرية للوقاية من انتقال فيروس العوز المناعي البشري من الأم إلى الطفل في أوغندا

التائج أدى العلاج لمدة 18 شهراً باستخدام العلاج التوليفي بمضادات الفيروسات القهقرية، بالمقارنة بنفيراين أحادي الجرعة والعلاج الثنائي وعدم العلاج، إلى تفادي 5.21 و 3.22 و 8.58 سنة من سنوات العمر المصححة باحتساب مدد العجز (DALYs)، على التوالي، بتكلفة قدرها 46 و 99 و 34 دولاراً أمريكياً لكل سنة تم تفاديها من سنوات العمر المصححة باحتساب مدد العجز. وتبلغ الأرقام المقابلة للعلاج التوليفي بمضادات الفيروسات القهقرية مدى الحياة على التوالي 19.20 و 11.87 و 31.60 سنة تم تفاديها من سنوات العمر المصححة باحتساب مدد العجز بتكلفة قدرها 205 و 354 و 172 دولاراً أمريكياً لكل سنة تم تفاديها من سنوات العمر المصححة باحتساب الاستنتاج يبدو أن مردودية العلاج التوليفي بمضادات الفيروسات القهقرية في أوغندا عالية فيما يخص الوقاية من انتقال فيروس العوز المناعي البشري من الأم إلى الطفل حتى مع استمراره مدى حياة المرضى. ونظراً لمزايا الصحة العمومية الإضافية الناتجة عن العلاج التوليفي بمضادات الفيروسات القهقرية، ينبغي تكثيف الجهود الرامية إلى ضمان حصول السيدات الحوامل الإيجابييات لفيروس العوز المناعي البشري على العلاج التوليفي بمضادات الفيروسات القهقرية مدى الحياة.

الغرض وضع نموذج لمردودية العلاج التوليفي بمضادات الفيروسات القهقرية (ART) في أوغندا بغية الوقاية من انتقال فيروس العوز المناعي البشري (HIV) من الأم إلى الطفل. الطريقة تم تقييم مردودية العلاج التوليفي بمضادات الفيروسات القهقرية على افتراض أن العلاج التوليفي بمضادات الفيروسات القهقرية يقلل من خطورة انتقال فيروس العوز المناعي البشري من السيدة الحامل الإيجابية لفيروس العوز المناعي البشري إلى رضيعها من 40٪ (عند ترك السيدة دون علاج) إلى 25.8٪ و 17.4٪ و 3.8٪، على التوالي، عند إعطاء السيدة: (1) نفيراين أحادي الجرعة (بتكلفة دواء إجمالية قدرها 0.06 دولار أمريكي) أو (2) العلاج الثنائي باستعمال زيدوفودين ولايفودين لمدة سبعة أسابيع (بتكلفة دواء إجمالية قدرها 15.63 دولاراً أمريكياً) أو (3) العلاج التوليفي بمضادات الفيروسات القهقرية لمدة 18 شهراً (بتكلفة سنوية إجمالية قدرها 469.77 دولاراً أمريكياً). وافترض الحصول على نسبة الانخفاض ذاته فيما يتعلق بخطورة الانتقال في كل حمل تال عن طريق العلاج التوليفي بمضادات الفيروسات القهقرية مدى الحياة (بتكلفة 6883 دولاراً أمريكياً) الموصى به للسيدات الحوامل اللاتي تقل لديهن الخلايا اللمفاوية التائية CD4+ عن 350 خلية لكل ميليمتر مكعب.

## الغرض

## الغرض تقييم مردودية العلاج التوليفي بمضادات الفيروسات القهقرية للوقاية من انتقال فيروس العوز المناعي البشري من الأم إلى الطفل في أوغندا

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## Résumé

## Évaluation du rapport coût-efficacité du traitement antirétroviral combiné pour la prévention de la transmission du VIH de la mère à l'enfant en Ouganda

Objectif Modéliser le coût-efficacité en Ouganda du traitement antirétroviral (TAR) combiné afin de prévenir la transmission de la mère à l'enfant du virus de l'immunodéficience humaine (VIH).

Méthodes Le rapport coût-efficacité du TAR a été évalué sur la base de l'hypothèse que le TAR réduit le risque qu'une femme enceinte séropositive transmette le VIH à son bébé de 40% (quand la femme n'est pas traitée) à 25,8%, 17,4% et 3,8%, respectivement, lorsque la femme reçoit: (i) une dose unique de névirapine (pour un coût médicamenteux total estimé à 0,06 dollar américain [\$]); (ii) une bithérapie de zidovudine et lamivudine pendant 7 semaines (pour un coût médicamenteux total de 15,63 \$), ou (iii) un TAR pendant 18 mois

(pour un coût annuel total de 469,77 \$). On a supposé que le TAR à vie (6 883 \$), recommandé pour les femmes enceintes avec moins de 350 lymphocytes T CD4+ par mm<sup>3</sup>, offrait la même réduction du risque de transmission pour chaque grossesse ultérieure.

Résultats Comparé avec une dose unique de névirapine, une bithérapie et aucune thérapie, un TAR de 18 mois évite 5,21, 3,22 et 8,58 années de vie corrigées de l'incapacité (AVCI), respectivement, pour un coût de 46 \$, 99 \$ et 34 \$ par AVCI évitée. Les chiffres correspondants pour un TAR à vie sont, respectivement, 19,20, 11,87 et 31,60 AVCI évitées, pour un coût de 205 \$, 354 \$ et 172 \$ par AVCI évitée.

**Conclusion** En Ouganda, le TAR semble offrir un très bon rapport coût-efficacité pour la prévention de la transmission du VIH de la mère à l'enfant, même si elle se poursuit tout au long de la vie des patients. Compte tenu des avantages supplémentaires en termes de santé

publique du TAR, les efforts visant à assurer que toutes les femmes enceintes séropositives aient accès au TAR tout au long de leur vie doivent être intensifiés.

## Резюме

### Оценка экономической эффективности комбинированной антиретровирусной терапии в профилактике передачи ВИЧ от матери к ребенку в Уганде

**Цель** Выполнить моделирование экономической эффективности комбинированной антиретровирусной терапии (АРТ) в профилактике передачи вируса иммунодефицита человека (ВИЧ) от матери к ребенку в Уганде.

**Методы** Экономическая эффективность АРТ была оценена на основе предположения, что АРТ снижает риск передачи ВИЧ ребенку от ВИЧ-положительных беременных женщин с 40% (когда женщина остается без лечения) до 25,8%, 17,4% и 3,8%, соответственно, когда женщина принимает: (i) одну дозу невирапина (ориентировочная общая стоимость препарата составляет 0,06 долл. США), (ii) двухкомпонентной терапии зидовудином и ламивудином в течение 7 недель (общая стоимость препаратов 15,63 долл. США), или (iii) АРТ в течение 18 месяцев (общая годовая стоимость 469,77 долл. США). Предполагалось, что АРТ в течение всей жизни (6 883 долл. США), рекомендованная беременным женщинам с <350 CD4+ Т-лимфоцитов на мм<sup>3</sup>, обеспечивает одинаковое снижение риска передачи ВИЧ при каждой последующей беременности.

**Результаты** По сравнению с однократной дозой невирапина, двухкомпонентной терапией и отсутствием терапии, 18-месячная АРТ предотвращает потерю 5,21, 3,22 и 8,58 лет жизни с поправкой на инвалидность (DALY), соответственно, а цена одного предотвращенного года составляет 46 долл. США, 99 долл. США и 34 долл. США, соответственно. Аналогичные показатели для АРТ в течение всей жизни составляют, соответственно, 19,20, 11,87 и 31,60 предотвращенных лет жизни с поправкой на инвалидность, при цене одного предотвращенного года 205 долл. США, 354 долл. США и 172 долл. США, соответственно.

**Вывод** В Уганде АРТ представляется весьма экономически эффективным методом профилактики передачи ВИЧ от матери к ребенку даже при осуществлении терапии в течение всей жизни пациента. Принимая во внимание дополнительные преимущества для общественного здравоохранения от АРТ, следует интенсифицировать усилия по обеспечению всех ВИЧ-инфицированных беременных женщин доступом к пожизненной АРТ.

## Resumen

### Evaluación de la rentabilidad de una terapia antirretrovírica de combinación para la prevención de la transmisión materno-infantil del VIH en Uganda

**Objetivo** Simular la rentabilidad de una terapia antirretrovírica de combinación para prevenir la transmisión materno-infantil del virus de la inmunodeficiencia humana (VIH) en Uganda.

**Métodos** Se evaluó la eficacia en relación con los costos de la terapia antirretrovírica suponiendo que ésta reduce el riesgo de que una mujer VIH-positiva embarazada transmita el VIH a su bebé del 40% (en mujeres que no reciben tratamiento) al 25%, 17,4% y 3,8%, respectivamente, cuando la mujer ha recibido tratamiento con: (i) una dosis única de nevirapina (con un precio total estimado del fármaco de 0,06 dólares americanos [US\$]); (ii) una terapia doble con zidovudina y lamivudina durante 7 semanas (con un coste total del fármaco de 15,63 US\$; o (iii) una terapia antirretrovírica durante 18 meses (con un coste anual de 469,77 US\$). Se ha asumido que la terapia antirretrovírica (6883 US\$) de por vida, recomendada para las mujeres embarazadas con < 350 linfocitos T CD4+ por mm<sup>3</sup>, proporciona la misma reducción del riesgo de transmisión en cada embarazo posterior.

**Resultados** Comparada con la dosis única de nevirapina, la terapia doble y la ausencia de terapia, la terapia antirretrovírica de 18 meses evitó 5,21, 3,22 y 8,58 años de vida ajustados en función de la discapacidad (AVAD), respectivamente, con un coste de 46 US\$, 99 US\$ y 34 US\$ por AVAD evitado. Las cifras correspondientes para la terapia antirretrovírica de por vida son, respectivamente, 19,29, 11,87 y 31,60 AVAD evitados, con un coste de 205 US\$, 354 US\$ y 172 US\$ por AVAD evitado.

**Conclusión** En Uganda, la terapia antirretrovírica presenta una alta rentabilidad para la prevención de la transmisión materno-infantil del VIH, incluso cuando se mantiene a lo largo de la vida de los pacientes. Dados los beneficios adicionales para la salud pública de la terapia antirretrovírica, se deberían intensificar los esfuerzos para asegurar que todas las mujeres VIH-positivas embarazadas tienen acceso a una terapia antirretrovírica de por vida.

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