# Cost effectiveness of single-dose nevirapine regimen for mothers and babies to decrease vertical HIV-1 transmission in sub-Saharan Africa

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## Summary

**Background** Identification of economical interventions to decrease HIV-1 transmission to children is an urgent public-health priority in sub-Saharan Africa. We assessed the cost effectiveness of the HIVNET 012 nevirapine regimen.

**Methods** We assessed cost effectiveness in a hypothetical cohort of 20 000 pregnant women in sub-Saharan Africa. Our main outcome measures were programme cost, paediatric HIV-1 cases averted, cost per case averted, and cost per disability-adjusted life-year (DALY). We compared HIVNET 012 with other short-course antiretroviral regimens. We also compared two implementation strategies: counselling and HIV-1 testing before treatment (targeted treatment), or nevirapine for all pregnant women (universal treatment, no counselling and testing). We did univariate and multivariate sensitivity analyses.

**Findings** For universal treatment with 30% HIV-1 seroprevalence, the HIVNET 012 regimen would avert 603 cases of HIV-1 in babies, cost US$83 333, and generate 15 862 DALYs. The associated cost-effectiveness ratios were $138 per case averted or $5.25 per DALY. At 15% seroprevalence, the universal treatment option would cost $83 333 and avert 302 cases at $276 per case averted or $10.51 per DALY. For targeted treatment at 30% seroprevalence, HIVNET 012 would cost $141 922 and avert 476 cases at $298 per case averted or $11.29 per DALY. With seroprevalence higher than 3·0% for universal and 4·5% for targeted treatment, the HIVNET 012 regimen was likely to be as cost effective as other public-health interventions. The cost effectiveness of HIVNET 012 was robust under a wide range of parameters in the sensitivity analysis.

**Interpretation** The HIVNET 012 regimen can be highly cost-effective in high seroprevalence settings. In lower seroprevalence areas, when multidose regimens are not cost effective, nevirapine therapy could have a major public-health impact at a reasonable cost.

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## Introduction

600 000 babies worldwide were infected with HIV-1 through mother-to-child transmission in 1997—about 1600 children daily. 3 million children have been infected since the beginning of the pandemic, and 90% of these were born in Africa.[1] In Harare, Zimbabwe, for example, a third of pregnant women are HIV-1-positive and mortality among children doubled between 1990 and 1996.[1] The annual incidence of childhood HIV-1 in Africa, 530 000, is similar to that of other major fatal childhood diseases. Diarrhoeal diseases accounted for 800 000 deaths and measles for 551 000 deaths in African children in 1995.[2] Identification of interventions to decrease the continuing high risk of perinatal HIV-1 transmission that are effective, deliverable, and cost-effective is, therefore, an urgent public-health priority.

The AIDS Clinical Trials Group (ACTG) protocol 076, in which zidovudine is given to women early in pregnancy, during delivery, and to babies for the first 6 weeks of life, showed that mother-to-child transmission of HIV-1 could be decreased by about two-thirds in more-developed countries.[3] However, many women in less-developed countries do not present for antenatal care in time to receive the ACTG 076 regimen. In addition, this long course of treatment costs more than US$200 per mother-baby pair for drugs alone, taking into account the 75% reduction in zidovudine prices announced by Glaxo Wellcome.[4] This cost is high for countries with annual health expenditure per person of $2–40, and may not be as cost-effective as alternative uses of HIV-1-prevention funds.[5]

In the past 2 years, important progress has been made in the prevention of mother-to-child transmission of HIV-1, with the announcement of the results of two trials of short-course regimens of antiretroviral drugs. The Centers for Disease Control and Prevention sponsored zidovudine trial reported 50% efficacy in a non-breastfeeding population in Thailand.[6] 37% efficacy was reported in a breastfeeding population in Côte d'Ivoire at 6 months postpartum.[7] That regimen consisted of 300 mg zidovudine twice daily starting at 36 weeks' gestation and every 3 h during labour until delivery.[6] The UNAIDS-sponsored PETRA trials[8] in sub-Saharan Africa reported a preliminary efficacy rate of 51% for 300 mg zidovudine and 150 mg lamivudine twice daily from 38 weeks' gestation until delivery (PETRA-A regimen). An additional 200 mg zidovudine was provided every 3 h during labour. The twice-daily zidovudine and lamivudine regimen was resumed for 1 week postpartum

| Parameters | Base-case estimate | Range of input | Data sources |
|---|---|---|---|
| **Epidemiological** | | | |
| Intervention efficacy (relative percentage reduction in transmission) | 47·0% | 20·0%–63·7%* | HIVNET 012 |
| HIV-1 seroprevalence in pregnant women | 30% | 5%–30% | Refs 12, 34, 36 |
| Background transmission rate: perinatal and early postnatal (control group) | 25·1% | 17% | HIVNET 012 |
| Percentage of women who breastfeed | 100% | .. | Refs 11, 12, 34 |
| Late postnatal breastfeeding transmission (after age 15 weeks) | 7·4% | 0–10·0% | Refs 14–16 |
| Breastfeeding transmission for babies who would have been HIV-1 positive at birth without nevirapine | 14·8% | .. | Assumption |
| Rate of progression of paediatric HIV-1 to AIDS | 25%, 80%, 100% | .. | Refs 18,19 |
| Rate of progression to death | AIDS at 12 months,60 months, and 120 months—AIDS to death: 12 months | – | |
| Average life expectancy at birth | 44 years | 56 years | Ref 20 |
| **Economic** | | | |
| Cost of nevirapine treatment per woman | $4.00 | $3.00–$6.00 | Johns Hopkins University Hospital Pharmacy, 1999 |
| Cost of voluntary counselling and testing per woman (targeted treatment only) | $7.30 | $5–$18.50 | HIVNET 012, refs 21, 30 |
| Cost per woman for registration, explanation, informed consent (universal treatment only) | $0.42 | .. | HIVNET 012 |
| Proportion of costs judged external to mother-to-child transmission | 0 | 30% | Assumption |
| Discounted lifetime cost of treating HIV-1-positive child | 0 | 0–$281 | Refs 28, 30, 32 |

*95% CI.

Table 1: **Estimated base-case values and ranges for model input parameters**

for the mother and given to the baby as 5 mg/kg zidovudine and 2 mg/kg lamivudine in syrup form every 12 h for 1 week. Efficacy was 37% in a regimen of zidovudine and lamivudine equivalent to the intrapartum and postpartum parts of PETRA-A (PETRA-B regimen). Because the Thai and the PETRA regimens begin late, at 36–38 weeks' gestation or at labour, they are more feasible and less expensive than the ACTG 076 regimen.

Results of a third short-course regimen, the HIVNET 012 trial in Kampala, Uganda, were announced in July, 1999. The nevirapine (a non-nucleoside reverse-transcriptase inhibitor) regimen consisted of a single 200 mg oral dose given to women at onset of labour and a 2 mg/kg dose given to neonates within 72 h of birth. The mothers in the control group received 600 mg zidovudine orally at onset of labour and 300 mg every 3 h until delivery, and neonates received 4 mg/kg zidovudine orally twice daily for 7 days after birth. 313 women were included in each treatment group. Compared with zidovudine, nevirapine decreased transmission of HIV-1 by 47·0% at age 14–16 weeks.[8] The regimen was well-tolerated. Because the HIVNET 012 regimen consists of only one dose to mothers and one to neonates, it is less expensive than the other regimens and potentially more cost effective.

We assessed the cost effectiveness of the HIVNET 012 regimen for sub-Saharan Africa for targeted treatment given only to HIV-1-positive mothers (counselling and HIV-1 testing offered before treatment) and for universal treatment, in which nevirapine would be given to all pregnant women, irrespective of HIV-1 status (no counselling or testing). In addition, we compared the cost effectiveness of the HIVNET 012 regimen with that of the other short-course antiretroviral interventions.

## Methods

### *Study model*

The model compared the costs, outcomes, and cost effectiveness of five short-course antiretroviral-based strategies aimed at decreasing mother-to-child transmission of HIV-1 with no intervention. The five regimens were HIVNET 012 (targeted), HIVNET 012 (universal), PETRA-A, PETRA-B, and Thai (targeted). Based on input data reflecting realities in sub-Saharan Africa, we calculated programme cost and cost effectiveness for a hypothetical annual cohort of 20 000 pregnant women who present to a clinic for prevention of mother-to-child transmission. We did the analysis from the point of view of a public-sector health-care payer. It is assumed that this payer pays all costs for voluntary counselling and testing and for the treatment itself. Our outcomes were: net cost to the public-sector payer; paediatric HIV-1 cases averted; cost per HIV-1 case averted; and cost per disability-adjusted life year (DALY). Details of the model structure are published elsewhere.[9] We did univariate and multivariate sensitivity analyses.

DALYs are a common measure of health-programme outcomes. DALYs gained from an intervention are the sum of the years of life saved, weighted to reflect quality of life and the socioeconomic value of each life-year. Future costs and benefits are discounted at 3% per year.[5]

### *Input parameters (table 1)*

For each parameter we displayed base-case values. The reported 47·0% relative decrease in transmission at age 14–16 weeks in the first parameter is the difference between 25·1% HIV-1-positive babies in the zidovudine group of HIVNET 012 compared with 13·1% in the nevirapine group, based on Kaplan-Meier survival analysis. If the zidovudine was effective, the efficacy of nevirapine would be even greater compared with placebo. 47·0% may therefore underestimate the true efficacy of nevirapine. The 95% CI values of 20·0% and 63·7% are included in the sensitivity analyses.

HIV-1 seroprevalence rates of 15–30% and higher (parameter two) are found in many urban areas of sub-Saharan Africa.[10] A range of 5–30% is included in the sensitivity analyses to test cost-effectiveness in lower seroprevalence settings.

| | Universal treatment | | Targeted treatment | |
|---|---|---|---|---|
| | 15% HIV-1 seroprevalence | 30% HIV-1 seroprevalence | 15% HIV-1 seroprevalence | 30% HIV-1 seroprevalence |
| Programme cost per 20 000 women (US$)* | 83 333 | 83 333 | 124 488 | 141 922 |
| HIV-1 cases averted | 302 | 603 | 246 | 476 |
| DALYs saved | 7931 | 15 862 | 6491 | 12 572 |
| Cost per HIV-1 case averted (US$) | 276 | 138 | 506 | 298 |
| Cost per DALY (US$) | 10.51 | 5.25 | 19.18 | 11.29 |

*20 000 who receive nevirapine (universal treatment) or 20 000 who start voluntary counselling and testing (targeted treatment).

Table 2: **Cost effectiveness of HIVNET 012**

| | HIVNET 012 universal | HIVNET 012 targeted | PETRA-A | PETRA-B | Thai |
|---|---|---|---|---|---|
| **Net programme costs (US$)** | 83 333 | 141 922 | 876 879 | 289 444 | 340 892 |
| HIV-1 cases averted | 603 | 476 | 315 | 229 | 309 |
| DALYs saved | 15 862 | 12 572 | 8326 | 6041 | 8163 |
| Cost per HIV-1 case averted (US$) | 138 | 298 | 2781 | 1265 | 1109 |
| Cost per DALY (US$) | 5.25 | 11.29 | 105.31 | 47.92 | 41.76 |

Table 3: **Cost-effectiveness of HIVNET 012, PETRA, and Thai regimens at 30% HIV-1 seroprevalence**

The HIVNET 012 trial reported a perinatal and early postnatal transmission rate of 25·1% (parameter three) in the zidovudine group (95% CI 19·5–30·8). The sensitivity analysis includes a lower background transmission rate of 17%. This rate was the average found in the PETRA trial settings, which included sites in Tanzania, Uganda, and South Africa.[8]

Almost all women in the low-income countries of sub-Saharan Africa breastfeed their babies for the first 6 months, and most do so for 12 months or longer.[11,12] As a simplifying assumption, we rounded the proportion of babies with a high exposure to breastmilk to 100% (parameter four). We also discuss how the nevirapine results affects the value of a substitute feeding programme.

Estimates of the risk of HIV-1 transmission during breastfeeding are based on studies comparing breastfeeding women with non-breastfeeding women. The mean risk associated with any breastfeeding, including short duration, has been estimated at 14·8%.[13] Most risk is in the first 2–3 months[14,15] and may be concentrated in the first month (G Gray unpublished data). Nevirapine therapy averts some cases of perinatal transmission, which increases the proportion of babies at risk of transmission via breastmilk. Late postnatal risk, from 2·5 months to 24·0 months, has been calculated in one meta-analysis at 7·4% (parameter five) of babies uninfected at 2·5 months.[16] Since the results for HIVNET 012 pertain to children aged 14–16 weeks, and mean breastfeeding duration is less than 24·0 months, 7·4% may overestimate the incremental risk of breastmilk transmission. Use of this estimate is therefore conservative because it is likely to be biased in favour of making the intervention seem less cost effective than it actually is. The sensitivity analysis includes a range of zero (no breastfeeding) to 10%.

The estimate of 14·8% (parameter six) is an assumption based on the possibility that babies who would have become infected in the absence of treatment are at higher risk than those who would not have become infected in any case. The value of this parameter is set at double the rate for those who would not have been HIV-1 infected in the absence of nevirapine. There are no data on transmission rates during breastfeeding by mothers who had been on antiviral therapy. For women who would have transmitted infection in the absence of antiretroviral treatment, breastfeeding-associated transmission rates may be higher than 7·4% because of a physiological tendency to transmit[17] and because a rebound effect might raise viral loads after treatment is stopped to loads higher than they would have been in the absence of treatment. On the other hand, the antiretroviral therapy itself may have some residual benefit in the breastfeeding period, so our approach was conservative.

The model used a disease-progression scenario in which 25% of infected children progress to AIDS by age 12 months; 80% by 60 months; and 100% at 120 months (parameter seven).[18] Children were assumed to live for an average of 12 months after progression to AIDS.[19]

As measured by DALYs, the base-case calculation used a life expectancy of 44 years (parameter eight). This is the average life expectancy for men and women for the 18 countries of east Africa designated by the Population Reference Bureau. The five countries of southern Africa have an average life expectancy of 56 years, and we explore the effect of using this higher number in the sensitivity analysis.[20]

The combined cost of a 200 mg tablet of nevirapine for mothers and a 2 mg/kg suspension dose for babies was US$4·00 (parameter nine) based on the wholesale list price of nevirapine at the Johns Hopkins Hospital Pharmacy in Baltimore, MD, USA. Dependent on local circumstances, costs of transportation, storage, and possible spoilage or expiration is likely to increase the cost per treatment delivered. On the other hand, bulk purchase discounts may lower the unit price. We varied drug costs from $3.00 to $6.00 in the sensitivity analyses to account for these possibilities.

A study of the cost of antiviral regimens for prevention of HIV-1 vertical transmission in South Africa estimated the cost of voluntary counselling and testing to be $7.30 per mother (parameter ten).[21] This cost is higher than some other relevant estimates, such as $4.00 derived from values from a project in Zambia,[9] $5.00 from the Dominican Republic[22] and our own estimate of $5.02 as the variable cost of voluntary counselling and testing derived from data from the HIVNET 012 trial site in Kampala, Uganda. However, this estimate is substantially lower than other estimates of $13.39[23] and $18.50[24] per indivdual calculated for two different free-standing clinics that used voluntary counselling and testing in Kampala. Because the drug is self-administered at the onset of labour, the HIVNET 012 regimen is likely to be made available through facilities capable of providing perinatal services. The Mulago Hospital, for example, site of the HIVNET 012 trial serves more than 20 000 women per year. Since women come to the hospital for these services in any case, it is reasonable to believe that costs per individual for voluntary counselling and testing would be lower in such settings there than in free-standing clinics that provide such services located in sexually-transmitted-disease or family-planning clinics. In the sensitivity analyses, we recalculated cost effectiveness with low and high estimates of $5.00 and $18.50, respectively.

Counselling and testing have been shown to increase condom use and other safe-sex practices in many African countries[25,26] and elsewhere.[27] Since the benefits of voluntary counselling and testing extend to prevention of horizontal transmission, a proportion of its costs could similarly be ascribed to this benefit. For parameter 11, we used the conservative (biased towards lower cost effectiveness) estimate of zero external effects. We used 30% externality in a sensitivity analysis.

Data to precisely measure the lifetime costs of treating HIV-1-positive children (parameter 12) are not available, since a proper calculation would require a full account of lifetime costs for HIV-1-negative babies. Data on costs of paediatric HIV/AIDS care are scarce and may differ substantially from estimates derived from those for adult care. For the base-case analysis, we therefore used the conservative approach of setting HIV-1 treatment costs at zero. The sensitivity analyses used the best available data to explore the effect of deducting net medical care costs from the numerator of the cost-effectiveness ratio.

Our calculation of the magnitude of overall medical costs averted was as follows: a study estimated $72.00 as the cost of care for HIV-1-negative children in South Africa aged 0–12 months, followed by $8.30 per year in subsequent years.[28] Until age 20 years, this estimate yields a discounted cost of $139.00, or 29% of the estimated $642.00 calculated as the cost of caring for an HIV-1-infected child in a district clinic in South Africa.[29] Deduction of this 29% to account for health-care costs in negative children from the more conservative $396.00 estimate used by Mansergh and colleagues[30] yields $281.00. This value was used in the sensitivity analyses.

## Results

Results of the cost-effectiveness calculation for a cohort of 20 000 women for universal treatment at 15% and 30% HIV-1 seroprevalence, and targeted treatment at 15% and at 30% seroprevalence are shown in table 2. All these results use the base-case input values in table 1.

| | Universal treatment | | Targeted treatment | |
|---|---|---|---|---|
| | Cost per DALY at 15% seroprevalence | Cost per DALY at 30% seroprevalence | Cost per DALY at 15% seroprevalence | Cost per DALY at 30% seroprevalence |
| **Base case*** | $10.51 | $5.25 | $19.18 | $11.29 |
| **Treatment efficacy (US$)** | | | | |
| Low (20%) | $24.69 | $12.35 | $45.07 | $26.53 |
| High (63·7%) | $7.72 | $3.86 | $14.08 | $8.29 |
| **Background transmission rate (17%)** | $15.51 | $7.76 | $28.32 | $16.67 |
| **Late postnatal breastfeeding transmission (after age 15 weeks)** | | | | |
| Low (0) | $8.95 | $4.48 | $16.34 | $9.62 |
| High (10%) | $11.19 | $5.60 | $20.43 | $12.02 |
| **Cost of voluntary counselling and testing** | | | | |
| Low ($5·00) | NA | NA | $14.55 | $8.27 |
| High ($18·50) | NA | NA | $50.31 | $26.37 |
| **Proportion of voluntary counselling and testing cost external to mother-to-child transmission (30% seroprevalence)** | NA | NA | $10.17 | £6.30 |
| **Cost of nevirapine per mother-baby pair ($4·00)** | | | | |
| Low ($3·00) | $7.99 | $3.99 | $18.80 | $10.91 |
| High ($6·00) | $15.55 | $7.78 | $19.93 | $12.04 |
| **Average life expectancy (years)** | | | | |
| Low (37) | $11.71 | $5.85 | $12.36 | $12.57 |
| High (56) | $9.44 | $4.72 | $17.24 | $10.15 |
| **Sensitivity analyses** | | | | |
| HIV/AIDS medical costs per child ($281) | Saving of $2300 | Saving of $87 700 | Saving of $8.54 | Saving of $0.65 |
| Low prevalence scenario (5% seroprevalence) | $31.52 | $46.32 | .. | .. |
| Low efficacy (20%) and high-cost of voluntary counselling and testing ($18.50) | NA | NA | $107.60 | $55.92 |

*See table 2.

Table 4: **Results of sensitivity analysis**

Programme costs ranged from $83 333 for universal treatment to $141 922 for targeted treatment with 30% HIV-1 seroprevalence. The least favourable scenario, targeted treatment at a seroprevalence of 15%, produced a programme cost of $124 488.

The nevirapine programme would avert from 603 paediatric HIV-1 cases (universal treatment at 30% seroprevalence) to 246 cases (targeted treatment at 15% seroprevalence). For each degree of seroprevalence, the universal treatment scenario would avert more cases than targeted treatment because attrition, which can occur at any stage of the voluntary counselling and testing process, (eg, between initial test and return for results) is eliminated.

Universal treatment at 30% seroprevalence generated the most health benefit, with 15 862 DALYs saved. Targeted treatment at 15% seroprevalence was the least effective, generating 6491 DALYs.

Cost per DALY and cost per case averted represent the cost-effectiveness ratios in which programme cost constitutes the numerator and DALYs or HIV-1 cases averted constitute the denominator. The two measures were given for comparisons with other studies that may have used only one measure. At $5.25 per DALY, universal treatment with 30% seroprevalence was the most cost-effective intervention, followed by universal treatment at 15% seroprevalence (cost per DALY of $10.51). Targeted treatment at 15% seroprevalence is the least cost-effective at $19.18 per DALY.

The cost-effectiveness outcomes for the nevirapine regimen (targeted and universal), PETRA-A and PETRA-B, and the Thai regimen are shown in table 3. This side-by-side comparison incorporated identical inputs for all five strategies except for drug costs and efficacy, since these depend on the regimens. Given the base-case value for the input parameters in table 1, the nevirapine regimen, especially the universal treatment option ($5.25 per DALY) was the most cost-effective by a wide margin. The next most cost-effective was PETRA-B at $1103.00 per case averted or $41.76 per DALY. PETRA-A was the least cost-effective at $2781.00 per case averted and $105.37 per DALY.

Comparison of HIVNET 012 with the other antiretroviral regimens was hindered by differences in trial designs. HIVNET 012 was the only trial in this analysis that measured early postnatal risk (up to age 14–16 weeks), at more than one time period after birth and is the only one with a potentially active control group. Therefore, it was impossible to precisely compare these regimens. We did, however, assess the conservative assumption that the other antiretroviral regimens would have early postnatal benefit similar to their observed perinatal benefit (as seen for nevirapine in HIVNET 012) without adjustment for the possibility that the zidovudine control of HIVNET 012 was effective and generated an underestimate of true nevirapine efficacy. HIVNET 012 retained the most favourable cost-effectiveness ratio. For example, PETRA-B had an estimated cost effectiveness of $18.35 per DALY compared with no therapy, versus $47.92 per DALY under base-case assumptions. These two results were inferior to the base case for the HIVNET 012 cost-effectiveness ratio of $11.29 (targeted treatment).

No incremental cost-effectiveness ratios are shown because the universal treatment option for the HIVNET

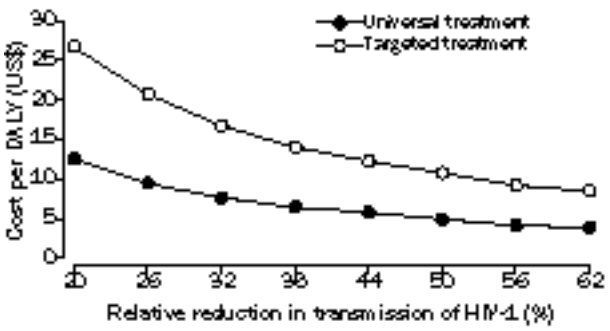


Figure 1: **Sensitivity analysis of cost per DALY for HIVNET 012 as function of efficacy (30% seroprevalence)**

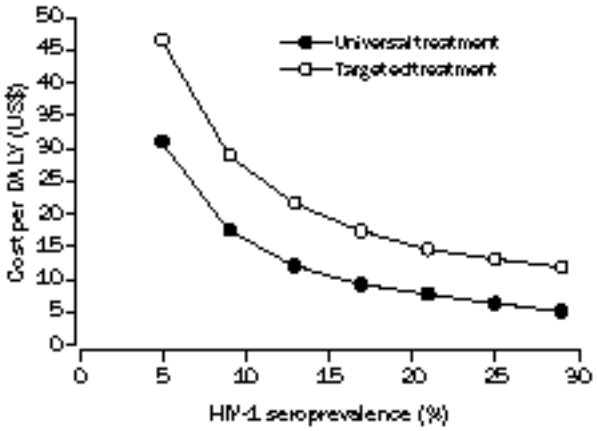


Figure 2: **Sensitivity analysis of cost per DALY for HIVNET 012 as function of HIV-1 seroprevalence**

012 regimen was more effective and less costly than all other regimens. The targeted treatment option for the HIVNET 012 regimen was more effective and less costly than the other regimens if the universal treatment option was excluded.

Since there was substantial uncertainty in estimates of the value of key inputs and because the actual values can be different in different settings, we did sensitivity analyses to find out how sensitive the basic findings were to changes in the value of key inputs (table 4). The HIVNET 012 intervention retained a cost-effectiveness ratio lower than $50 per DALY in all one-variable sensitivity analyses, with the exception of voluntary counselling and testing at 15% seroprevalence in the targeted treatment option ($50.31 per DALY).

If treatment efficacy was at the low end of the 95% CI (20%), the cost per DALY would range from $12.35 (universal treatment, 30% seroprevalence, figure 1) to $45.07 (targeted treatment, 15% seroprevalence). At the high end of the 95% CI (63.7%), the cost per DALY would range from $3.86 to $14.08 at 30% seroprevalence for universal and 15% for targeted treatment, respectively.

Other variables with substantial impact on estimated cost per DALY gained were HIV-1 background transmission rate and the proportion of voluntary counselling and testing costs external to prevention of mother-to-child transmission. Decreasing background transmission rates from 25·1% to 17·0% increased the cost per DALY from $19.18 (base case) to $28.32 in the targeted treatment option at 15% seroprevalence. The assumption that 30% of costs for voluntary counselling and testing are external to mother-to-child transmission decreased the cost per DALY (higher cost-effectiveness) by nearly half, from $19.18 to $10.17.

Variations in the cost of nevirapine also had a substantial effect in the universal treatment option, in which drug costs dominate total programme outlays. As regimen costs increased by 50% from the base-case value of $4.00 to $6.00, the cost per DALY increased by a similar magnitude, from $10.51 per DALY to $15.55 per DALY at 15% seroprevalence. Because costs of voluntary counselling and testing dominate total programme costs in the targeted treatment option, (especially with low seroprevalence), the effect of increased cost of nevirapine is slight.

Net medical-cost savings significantly affected cost-effectiveness outcomes. If net medical-cost savings were $281 per HIV-1 case averted, rather than zero as assumed in the base case, the HIVNET 012 regimen would generate net savings to the public-sector payer in all four scenarios. Variations in late postnatal breastfeeding transmission rates had little influence on cost effectiveness, and because future years of life saved are discounted, differences in average life expectancy also had only a slight effect on cost-effectiveness outcomes.

We also explored cost effectiveness with only 5% seroprevalence. Costs per DALY would be $31.52 in the universal and $46.32 in the targeted treatment options (figure 2). The universal treatment option remained more cost-effective across the entire range of relevant seroprevalences.

Finally, we assessed the effect of simultaneous occurrence of less favourable values for two key input parameters, treatment efficacy and cost of voluntary counselling and testing. In this unfavourable scenario, targeted treatment assumed costs per DALY of $107.60 at 15% and $55.92 at 30% seroprevalence.

Since the HIVNET 012 regimen seems likely to be cost-effective under a wide range of settings in sub-Saharan Africa, we calculated thresholds for various inputs beyond which it would be uneconomical. $50 per DALY was set as the highest permissible cost-effectiveness ratio. Efficacy, cost of voluntary counselling and testing, HIV-1 seroprevalence, and background transmission rate exerted the greatest influence on cost effectiveness (table 5) and the HIVNET 012 regimen remained cost effective, even if voluntary counselling and testing services were at the high end of current cost estimates. In an unfavourable scenario that included low estimates for background transmission rates and efficacy, the HIVNET 012 regimen would retain cost effectiveness at seroprevalence as low as 10·7% under the universal treatment option and 22·0% under the targeted treatment option.

## Discussion

The HIVNET 012 regimen costs between $5 and $55 per DALY under almost all plausible scenarios, with base-case estimates of between $5.25 and $19.18 per DALY. $50 per DALY can be taken as a threshold below which public-health interventions are cost effective in

| | Universal treatment | | Targeted treatment | |
|---|---|---|---|---|
| | Cost per DALY at 15% seroprevalence | Cost per DALY at 30% seroprevalence | Cost per DALY at 15% seroprevalence | Cost per DALY at 30% seroprevalence |
| Efficacy | 9·9% | 4·9% | 18·0% | 10·6% |
| Cost of voluntary counselling and testing | NA | NA | $18.56 | $36.21 |
| Prevalence | 3·0% | 3·0% | 4·5% | 4·5% |
| Background transmission rate | 5·3% | 2·7% | 9·6% | 5·7% |
| Multivariate analysis | | | | |
| Background transmission rate | 17·0% | .. | 20·0% | .. |
| Efficacy | 20·0% | .. | 22·0% | .. |
| Prevalence | 10·7% | .. | .. | .. |

Table 5: **Threshold analysis**

low-income countries.[5,31] For example, immunisation against poliomyelitis plus diphtheria-pertussis-tetanus costs $20 per DALY in areas with high mortality and $40 per DALY in low-mortality areas; and the cost effectiveness of screening and referral for acute respiratory infection has a range of $20–50 per DALY.[31] Therefore, the HIVNET 012 protocol is likely to be cost effective as targeted and universal treatment in much of sub-Saharan Africa. With the assumption of base-case values for key inputs, the nevirapine regimen exceeded the threshold of $50 per DALY only at about 4·5% seroprevalence for the targeted treatment option, and about 3·0% HIV-1 seroprevalence for the universal option. The intervention is probably, therefore, cost effective in a wide range of other circumstances, if HIV-1 seroprevalence is assumed to be 15–30%, as in much of sub-Saharan Africa.

Since the cost of the medication is low, cost-effectiveness results are especially sensitive to the remaining major cost component, voluntary counselling and testing. In settings in which HIV-1 seroprevalence is substantially lower than 15% and cost of voluntary counselling and testing is higher than $18.50 per individual, the nevirapine intervention may be uneconomical compared with other public-health investments ($50.0 per DALY at 15% seroprevalence and $18.50 for voluntary counselling and testing). However, three considerations suggest that the cost of counselling and testing need not hinder efficient implementation of the HIVNET 012 protocol, even in relatively low seroprevalence settings. First, because the single-dose regimen of nevirapine for mothers and neonates is simple, inexpensive, and is taken at onset of labour, the universal treatment option may be appropriate in many areas if long-term safety of the HIVNET 012 regimen is established. In addition, the base-case cost-effectiveness estimates assume that all of the benefits of counselling and testing in a programme to prevent mother-to-child transmission accrue to this type of prevention and not to prevention of adult-to-adult transmission. As this assumption is relaxed, the proportion of cost of voluntary counselling and testing that can be attributed to prevention of mother-to-child transmission declines. Finally, several studies have shown that costs of voluntary counselling and testing can be lower than $10 per individual in low-income countries.[22,32] With the availability of low-cost rapid tests at $2.80 per unit and double ELISA tests costing $2.80,[33] this target should be attainable in most of sub-Saharan Africa and elsewhere in the developing world.

Several considerations may limit the possible public-health impact of this intervention. First, it applies only to women who deliver at clinics and hospitals equipped to provide nevirapine therapy. In sub-Saharan Africa such facilities may be available to less than half of the population. For example in Uganda, only 35%[34] and in Zambia only 51% of women deliver at such facilities.[12] Although cost-effectiveness is unrelated to programme scope, ultimate public-health impact clearly is related. Second, this assessment does not take into account the possible increase in viral resistance resulting from short-course antiretroviral therapy. We are not aware of any data that would currently allow an assessment of the likelihood of increased resistance, but potential increased resistance could limit the use of this therapy for subsequent pregnancies. Third, beyond the need for obtaining meaningful informed consent, the universal treatment option may raise ethical concerns since it involves the distribution of antiretroviral drugs to uninfected women. In areas where the financial and human resources are available to provide voluntary counselling and testing, targeted treatment may be the preferred option, especially because counselling and testing may be a cost-effective HIV-1 prevention strategy in its own right.[35]

Finally, although the HIVNET 012 regimen is likely to be cost-effective compared with the full range of accepted public-health interventions in sub-Saharan Africa, it may not be as cost-effective as prevention of horizontal HIV-1 transmission in some settings. For example, information, condoms, and treatment of sexually transmitted diseases for prostitutes was shown to cost $8–12 per case averted in Nairobi; control of symptomatic sexually transmitted diseases in Tanzania cost a reported $234 per case averted; and a safe blood-supply programme in Uganda cost $172 per case averted.[36,37] In areas where these types of programmes have not yet been implemented, a programme based on the HIVNET 012 protocol may not be among the options with the highest incremental cost-effectiveness ratios.

Although we focused our analysis on antiretroviral therapy, a comprehensive intervention for mother-to-child transmission must also take into account substitute feeding to prevent postnatal HIV-1 transmission. The HIVNET 012 documentation of nevirapine efficacy up to age 14–16 weeks, through the period when most HIV-1 transmission associated with breastfeeding occurs, may change the preferred feeding strategy. Previous analyses suggest that the optimum feeding approach when antiretroviral drugs are administered perinatally is substitute feeding, in almost all circumstances in less-developed countries.[28,38,39] However, if nevirapine suppresses HIV-1 breastfeeding transmission risk by 50% for 14–16 weeks, HIV-1 transmission may fall to lower than the risk of non-HIV-1 mortality from substitute feeding. Based on our previous analyses, for example, the optimum feeding strategy is likely to change in rural Tanzania from substitute feeding to short-term breastfeeding. The optimum strategy depends on local mortality rates among babies, among other factors. If breastfeeding is optimum for health outcomes, it is also preferred economically because it is less expensive than a substitute feeding programme.

Single-dose nevirapine administered to mothers and neonates in the intrapartum period and soon after birth represents a deliverable and cost-effective regimen for prevention of mother-to-child transmission of HIV-1 in sub-Saharan Africa, especially under the universal treatment scenario. Our data suggest that this regimen is more cost effective than the multidose regimens used in the Thai and PETRA trials. In areas with high seroprevalence, more lives could be saved for a given investment in mother-to-child transmission. These results also imply that in lower seroprevalence areas where multidose regimens are not routinely used, or able to be used, nevirapine therapy could have an important public-health impact at a reasonable cost. If the HIVNET 012 results are confirmed in future trials or are improved on with multidrug single-dose regimens, the basis for wide implementation of antiviral drug-based control programmes for mother-to-child transmissions will have been greatly strengthened.

*Contributors*
Elliot Marseille was the principal analyst and author. James G Khan assisted inthe analytical design and execution. Francis Mmiro, Laura Guay, Philllipa Musoke, Mary Glenn Fowler, and J Brooks Jackson assisted in research and contributed to the writing of the paper.

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