**Cost-effectiveness of first-line antiretroviral therapy for**

**HIV-infected African children less than three years of age:**

**Supplemental Appendix**

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*et al.*

**INTRODUCTION**

This appendix is included to provide methodologic details to supplement the description of the methods in the manuscript text, as well as additional model output and results.

**METHODS**

**Model structure**

We have previously described in detail the structure of the CEPAC-Pediatric natural history model, reflecting HIV disease progression in the absence of ART (Ciaranello *et al, PLoS ONE,* 2013).[1](#_ENREF_1) Here, we provide additional detail about the impact of ART in the CEPAC-Pediatric model. Full details of model structure, data sources, and procedures for initiating new collaborative projects are also available on the CEPAC website, at [**http://web2.research.partners.org/cepac/model.html**](http://web2.research.partners.org/cepac/model.html)**.**

Infants enter the CEPAC-Pediatric model following HIV infection *in utero*, during delivery, or during breastfeeding, and are simulated until death. The model tracks true CD4%/CD4 and HIV RNA level, although clinical decisions are made based on observed information, such as symptomatic illness or CD4%/CD4 or RNA levels measured according to specified laboratory monitoring strategies. In each month, children can remain in care or be lost to follow-up; if they are lost to follow-up, they are assumed to stop ART, and to return to care if a severe opportunistic infection (OI) occurs.

We establish criteria by which children are modeled to initiate first-line ART, including age, observed CD4% or CD4 count, and/or development of opportunistic infections. For each ART regimen, we specify an “efficacy,” defined as the probability of suppressing HIV RNA to <400 copies/mL (c/mL), and the time point by which this occurs (usually 24 or 28 weeks). Each regimen also confers monthly medication costs, as well as gains in CD4% or CD4 count for children with suppressed HIV RNA. Children who initially suppress HIV RNA at 24 or 48 weeks face a monthly risk of virologic failure thereafter (“late failure”). Following virologic failure, HIV RNA slowly rises to a “set point” that is determined as a function of HIV RNA level at birth. For this analysis, we do not model a state of sustained, low-level viremia (RNA between 400 and 5,000 copies/mL without further increase in RNA over time). After virologic failure, there is a 12-month delay until CD4% or CD4 count begins to decline at pre-ART rates, leading to increased monthly risks of opportunistic infections and death, until the next effective ART regimen (if available) is initiated. For children who fail ART, we assign clinical criteria (number and type of opportunistic infections), immunologic criteria (decline in CD4% or CD4 count), or virologic criteria (increase in HIV RNA) by which this failure is detected, as well as the type and frequency of monitoring and confirmatory testing. After observed failure, patients can be switched to the next available line of therapy. We can also incorporate a reduction in mortality and opportunistic infection risks for children on ART, independent of CD4 level and HIV RNA suppression, as observed in adults; this parameter was used for model calibration (see below).[2](#_ENREF_2)

For each simulated infant, the model tracks clinical events, changes in CD4% or CD4 count, and the amount of time spent in each health state. After an individual simulated patient has died, the next infant enters the model. Large cohorts (1 million-10 million patients) are simulated in order to generate model outcomes that are stable to within 0.005 life-years (base-case) or 0.05 life-years (sensitivity analyses). Once the entire cohort has been simulated, summary statistics are tallied, including number and type of clinical events, the proportion alive each month, health care costs in each month, and life expectancy (mean for the cohort).

**Model input data**

Data used as input parameters for the CEPAC-Pediatric model are described in the main manuscript, and selected data inputs are shown in Manuscript Table 1. Appendix Table A includes all model input parameters.

The base-case analyses used data from P1060. We then repeated all analyses using RNA suppression and CD4 changes on suppressive ART from the PENPACT-1 trial (Table 1).[3](#_ENREF_3) PENPACT-1 included older children (median age, 6.5 years) and a range of medications; for this analysis, we limited data to children <3 years of age at trial entry treated with nevirapine or lopinavir/ritonavir. In contrast to P1060, PENPACT-1 found non-significantly higher rates of RNA suppression at 24 weeks with first-line nevirapine (77%) compared to first-line lopinavir/ritonavir (72%).

**Model calibration**

*Natural history model calibration*

We first calibrated our model to fit observed data for children in the absence of ART. This is described in Ciaranello *et al*, *PLoS ONE*, 2013.[1](#_ENREF_1) In brief, we first internally validated the CEPAC-Pediatric model to assess the accuracy of model structure. We did this by using input data from the IeDEA East Africa region, and ensuring that model-projected survival and OI rates matched the data used as inputs.[4](#_ENREF_4) We next calibrated the model to pooled survival rates from >1,300 children with *in utero* or intrapartum HIV infection in 12 PMTCT studies, pooled by the UNAIDS Child Survival Group.[5](#_ENREF_5),[6](#_ENREF_6) This involved increasing the rates of HIV-related mortality to account for survivor biases and differences in treatment availability for children in the IeDEA cohort compared to children in the pooled UNAIDS analysis.[1](#_ENREF_1)

*On-ART model calibration*

We next calibrated our model to fit observed data for children treated with ART. We had two types of calibration targets: mortality and OI rates, and rates of switching from first-line to second-line ART.

1. Calibration to observed OI and mortality rates

In the P1060 trial, observed event rates were as follows over 72 weeks of follow-up: WHO Stage 3: 9.30/100PY, WHO Stage 4: 0.73/100PY, tuberculosis: 5.60/100PY, and mortality: 3.29/100PY. In adults, a reduction in risks of OIs and death has been reported for patients on ART, regardless of whether ART is suppressive and in addition to the reduction in risk conferred by improvements in CD4 count alone, although data remain equivocal.[2](#_ENREF_2) We used adult data on this "ART effect" for simulated subjects after the age of 13. In the absence of data on a similar ART effect in children, we used this parameter to calibrate the model for children <13 years of age to fit observed OI and mortality rates in the P1060 trial. The model includes a relative risk reduction in OI incidence and in mortality >30 days after OI diagnosis (“chronic mortality”) for children on ART, relative to children at the same CD4%/CD4 level not on ART. We separately varied the relative reduction in monthly OI risks and the relative reduction in monthly “chronic” mortality risks for children on ART, from 0-100%. Our goal was to identify a multiplier for mortality and a multiplier for OI risk that could be used in all analyses; in order to increase the comparability of all model results, we did not seek to identify different multipliers for children presenting at different ages, or for different first-line ART regimens, for example.

We first attempted to match the mortality rates observed in the P1060 trial (3.29/100PY). We conducted multiple model runs for a cohort of children presenting to care at age 12 months. We used the *first-line nevirapine* strategy for these calibration analyses, in order to be conservative with respect to mortality (model-projected mortality was slightly higher with *first-line nevirapine* than with *first-line lopinavir/ritonavir*; we anticipated that the *first-line lopinavir/ritonavir* results using the calibrated multipliers would thus be closer to P1060 results). We evaluated model-projected average mortality rates over the first 2 years of observation (from 12 through 35 months of age) and over the first 4 years of observation (from 12 through 59 months). The best fit to the P1060-observed mortality rate was found with relative risk reductions of 85-95% (Appendix Table B; highlighted in yellow).

Holding the relative risk reduction in mortality at 90% (the midpoint of this range), we next compared model-generated OI rates using these multipliers to P1060-observed rates of WHO stage 3, WHO stage 4, and tuberculosis events. These were found to match most closely when the relative reduction in OI risk was 85%. (Appendix Table C, middle columns). Results are also shown in Appendix Table C for a range of OI and mortality risk reduction values, for comparison.

Finally, we compared the life expectancies projected to result from relative reductions in OI risk of 85-95% and relative reductions in mortality risk of 90-95% (Appendix Table C, right column). There are no empiric data to inform the life expectancy of HIV-infected African children treated with modern ART regimens. Based on projected results for adults, we felt that life expectancies in the 27-28-year range, observed with relative risk reductions of 85% and 90%, were most reasonable.[7](#_ENREF_7) We thus selected relative risk reductions of 85% for mortality and 90% for opportunistic infection as our final calibrated parameters. In sensitivity analyses, we varied these values widely from 0-100%.

2. Calibration to observed rates of switch from first-line to second-line ART

In preliminary analyses, we modeled perfect compliance with current recommendations for monitoring the effectiveness of first-line ART and for switching to second-line ART when needed. These were based on WHO 2010 and 2013 guidelines. In our initial analyses, monitoring included CD4 and RNA monitoring at 6 and 12 months after ART initiation, then every 12 months thereafter. Detection and confirmation of first-line ART failure was only possible after more than 24 weeks on ART, and was modeled as follows:

* Virologic failure: Observed RNA >5,000 copies/mL, confirmed by a second RNA test at least 1 month after the first
* Immunologic failure: Observed CD4% <10% (for children <5 years old) or CD4 count <100/µL (for children >5 years old), confirmed by a second CD4/CD4% test at least 1 month after the first
* Clinical failure: Observed new or recurring WHO Stage 4 or TB event, confirmed with a CD4/CD4% test at least 1 month after the clinical event.

In clinical practice, there may be both delays in detection of failure of first-line ART and intentional time lags between observation of failure and switching to second-line ART (related to attempts to improve adherence, concerns about toxicity of second-line ART, or lack of available second-line ART in appropriate formulations for age). This results in a wide range of reported rates of switching to second-line ART in the published literature (Appendix Table D).[3](#_ENREF_3),[8-15](#_ENREF_8)

For our final base-case analyses, we sought to model switching strategies that were based on current guidelines, but that also seemed realistic to clinicians practicing in resource-limited settings and led to rates of switching to second-line ART that were within published ranges. We created three scenarios to encompass the range of published values: 1) a switch to second-line immediately after confirmation of first-line ART failure as described above (as in our initial analyses); 2) a scenario in which patients and providers deliberately waited 6 months between confirmation of failure and switch to second-line ART (for example, reflecting a delay to availability of second-line formulations, or an attempt at an adherence intervention prior to switching); and 3) a scenario without RNA monitoring, in which patients switched 6 months after clinical or CD4-based detection and confirmation of first-line ART failure (Appendix Table E). Based on these results, we chose for our final base-case analysis the second scenario, which included a deliberate 6-month delay between confirmation of failure and switch to second-line ART.

**Sensitivity analyses**

The model accounts for first-order uncertainty (between-patient variability) through the microsimulation of large cohorts of patients. Following the guidance of the International Society for Pharmacoeconomics and Outcomes Research, we examine the impact of second-order uncertainty (uncertainty in data parameters and assumptions) through wide-ranging univariate and multivariate sensitivity analyses on all model input parameters and assumptions.[16](#_ENREF_16) In addition to the sensitivity analyses described in the main manuscript, we also examined variations in many treatment strategies, at the request of the WHO Maternal-Child Health HIV Guidelines Committee.[17](#_ENREF_17),[18](#_ENREF_18)

Parameters and strategies varied in sensitivity analyses included:

* HIV disease progression: rate of CD4%/CD4 decline, OI risks, and HIV-related mortality risks were varied from 0.5 to 2.0x the base-case values alone and in combination
* Loss to follow-up rates: 0, 0.2, 0.4, or 0.8% per month. These were varied equally for all ART regimens (the impact of tolerability differences between regimens was reflected in rates of late virologic failure, rather than in differential rates of loss to follow-up).
* ART initiation:
  + WHO 2010 guidelines: ART initiation in all children <24 months of age; ART initiation in children 24-35 months of age with CD4 <25% or WHO Stage 3/4 disease[19](#_ENREF_19)
* ART monitoring and switching:
  + CD4 monitoring: none; every 6, 12, or 24 months; and every 6 months only before initiation of ART (with only RNA monitoring thereafter)
  + RNA monitoring: none; every 6, 12, or 24 months
  + Clinic visits: every 3, 6, or 12 months
  + ART switching policies: 0, 6, and 12-month delay between detection of failure and initiation of second-line ART; require both observed clinical or virologic failure AND CD4 ≤10% or ≤100 cells/µL
* ART-related clinical outcomes:
  + Time horizon for initial RNA suppression: 24, 48 weeks
  + First-line ART efficacy (suppression to RNA <400 copies/mL at 24 or 48 weeks): use of the clinical and virologic outcomes from the subgroup of children enrolling before 3 years of age and treated with nevirapine or lopinavir/ritonavir in the PENPACT-1 trial
  + Risk of “late” virologic failure (after initial RNA suppression to <400 copies/mL at 24 or 48 weeks): 0.46%/month (0.5 x base case), 3.6%/month (4 x base case), varied both separately and together for each first- and second-line regimen
  + Efficacy of second-line lopinavir/ritonavir-based ART, second-line NNRTI-based ART, or both (RNA suppression to <400 copies/mL at 24 or 48 weeks): range from 10-80%
  + CD4-independent impact of ART on OI and “chronic” mortality risk: Calibrated risk reductions (see above) applied from ages 0-5, 0-13, and lifelong; risk reductions of 0-100%
  + In scenarios without HIV RNA monitoring, assume that remaining on a failing first-line nevirapine leads to accumulation of drug resistance, with lower efficacy of second-line PI (40, 50, 60%)
* ART availability:
  + One line of ART only
  + Identical second-line ART regimen in both *first-line lopinavir/ritonavir* and *first-line nevirapine* (two total lines of ART); costs and efficacy based on darunavir/ritonavir (DRV/r) as an example, although this is not widely available nor approved for young children
  + Equal third-line ART in both strategies, again based on darunavir/ritonavir (*first-line lopinavir/ritonavir*/second-line NNRTI/third-line darunavir/ritonavir; *first-line nevirapine*/second-line LPV/r/third-line darunavir/ritonavir)
  + Darunavir/ritonavir is available for second-line ART, but only following *first-line lopinavir/ritonavir* (comparing *first-line nevirapine*/second-line lopinavir/ritonavir to *first-line lopinavir/ritonavir*/second-line darunavir/ritonavir)
  + Darunavir/ritonavir is available, and NNRTIs are not used following PI failure (comparing *first-line nevirapine*/second-line lopinavir/ritonavir/third-line darunavir/ritonavir to *first-line lopinavir/ritonavir*/second-line darunavir/ritonavir).
  + Delay switching in children <3 years of age failing first-line LPV/r until they are able to take efavirenz. In *first-line lopinavir/ritonavir:* children who fail first-line lopinavir/ritonavir before age 3 years remain on this failing regimen, and switch to efavirenz when they reach 3 years of age (those failing after age 3 switch to efavirenz immediately)
* Costs:
  + All ART costs halved, doubled (separately and together for each regimen)
  + All clinical care costs halved, doubled
* **Discount rate (annual): 0% and 3% (base case), 5%, 8%**

**RESULTS**

Results of the base-case analysis and key sensitivity analyses are shown in the main manuscript. Here, we highlight a few key findings in addition to those reported in the main manuscript. All other sensitivity analyses listed in the Appendix Methods above did not lead to changes in policy conclusions, except where noted in the manuscript: *first-line lopinavir/ritonavir* remained more effective and less expensive than *first-line nevirapine* (results available from authors on request).

*ART-related reduction in OI and mortality risk.* When ART led to no relative reduction in opportunistic infection and mortality risks at any age (compared to children or adults with the same CD4%/CD4 count not on ART), life expectancies for both ART strategies were substantially lower than in the base case (undiscounted LE: 10.9-11.7 years; Appendix Table A)*. First-line lopinavir/ritonavir* became both more effective and more expensive than *first-line NVP*, yet remained very cost-effective in both countries. At intermediate values of this CD4-independent effect of ART, and when this risk varied with age throughout childhood, adolescence, and adulthood, policy conclusions were unchanged from the base case. While policy conclusions did not change when these risks were varied with age, newly emerging data from long-term follow-up of adolescents will better inform the lifetime projections for HIV-infected children.[20](#_ENREF_20)

*Comparisons between South Africa and Cote d’Ivoire healthcare costs.* There were two key differences in analyses using Côte d’Ivoire costs, compared to the base case analyses using costs from South Africa (Manuscript Figure 1, Appendix Figure A, Appendix Table G). First, pediatric ART (with either regimen) was very cost-effective, but was never cost-saving, even in the short-term, using Côte d’Ivoire costs. Second, the time required for *first-line lopinavir/ritonavir* to become cost-saving compared to *first-line nevirapine* was much longer using Côte d’Ivoire costs (26.4 years; Figure A, closed arrow) than using South Africa costs (8.7 years; Manuscript Figure 1, closed arrow). Both results occur because clinical care costs are much lower in Côte d’Ivoire than in South Africa, but medication costs are similar. The care costs saved by averting opportunistic infections and mortality with ART compared to no ART do not offset the costs of the ART medications themselves. The care costs saved by averting opportunistic infections and mortality with more effective lopinavir/ritonavir-based ART take much longer in Côte d’Ivoire than in South Africa to offset the higher medication costs of lopinavir/ritonavir compared to nevirapine.

*Patient outcomes over time*. The proportion of the modeled cohort that remains on first-line ART, has switched to second-line ART, has become lost to follow-up, or has died at each month of the simulation is shown in Appendix Figure B.

**Appendix Table A. Model input parameters (including those shown in Manuscript Table 1)**

|  |  |  |
| --- | --- | --- |
| **I. Natural History Clinical Inputs** | **Value** | **Sources** |
| CD4% at presentation to care, by age |  |  |
| 6 months | 25% | [21](#_ENREF_21) |
| 12 months | 22% |
| 24 and 36 months | 19% |
| Rate of CD4%/ CD4 decline a | Monthly Risk (%) | [4](#_ENREF_4),[22](#_ENREF_22) |
| <3 months of age (CD4%) | 4.0% |
| 3-59 months of age (CD4%) | 0.5% |
| ≥60 months of age (CD4 cells/µL, range by HIV RNA) | 3.0-6.4 |
| Risk of clinical events (range by CD4%) a | Monthly Risk (%) |  |
| <6 months of age |  |  |
| WHO Stage 3 event (except tuberculosis) | 5.2-7.8 | [4](#_ENREF_4),[22](#_ENREF_22) |
| WHO Stage 4 event (except tuberculosis) | 1.6-3.5 |
| Tuberculosis (any body site) | 0.5-1.1 |
| 6-59 months of age |  |  |
| WHO Stage 3 event (except tuberculosis) | 3.3-11.6 | [4](#_ENREF_4),[22](#_ENREF_22) |
| WHO Stage 4 event (except tuberculosis) | 1.4-6.4 |
| Tuberculosis (any body site) | 0.8-3.8 |
| ≥60 months of age |  |  |
| Mild fungal infection | 1.8-3.1 | [4](#_ENREF_4),[22](#_ENREF_22) |
| Visceral bacterial infection | 0.04-0.71 |
| WHO Stage 3 or 4 visceral disease | 0.03-1.4 |
| WHO Stage 3 or 4 mucocutaneous disease | 0.03-2.3 |
| Other WHO Stage 3 or 4 disease | 0.02-0.73 |
| Other severe disease | 0.19-1.7 |
| Other mild disease | 2.4 |
| Tuberculosis (any body site) | 0.03-1.7 |
| Risk of death within 30 days of clinical event a | 30-day risk (%) |  |
| 0-59 months of age |  |  |
| After WHO Stage 3 or 4 event | 13.5 | [4](#_ENREF_4),[22](#_ENREF_22) |
| After TB event | 11.1 |
| ≥60 months of age |  |  |
| Mild fungal infection | 0.5 | [4](#_ENREF_4),[22](#_ENREF_22) |
| Visceral bacterial infection | 2.9 |
| WHO Stage 3 or 4 visceral disease | 9.2 |
| WHO Stage 3 or 4 mucocutaneous disease | 2.4 |
| Other WHO Stage 3 or 4 disease | 20.0 |
| Other severe disease | 6.7 |
| Other mild disease | 0.4 |
| Tuberculosis (any body site) | 1.8 |
| Risk of HIV-related death (range by age, CD4%/CD4, and history of prior opportunistic disease) a | Monthly risk (%)  0.1-40.8 | [23](#_ENREF_23) |

**Appendix Table A, continued. Model input parameters (including those shown in Manuscript**

**Table 1)**

|  |  |  |  |
| --- | --- | --- | --- |
| **I. Natural History Clinical Inputs, continued** | **Value** | | **Sources** |
| Risk of non AIDS-related mortality (range by age in yearly intervals, sex, country) | Monthly risk (%) | | [23](#_ENREF_23) |
| <12 months of age | 0.41-0.49 | |
| 12-60 months of age | 0.05 | |
| 5-13 years of age | 0.01 | |
| 13-18 years of age | 0.01 | |
| >18 years of age | 0.01-0.10 | |
| Loss to follow-up prior to ART initiation | 0.2 (sensitivity analysis: 0-0.8) | | [24](#_ENREF_24),[25](#_ENREF_25) |
| **II. ART Clinical Inputs** | **Value** | | **Sources** |
| ART efficacy: HIV RNA <400c/mL at 24 weeks [48 weeks] on ART b | P1060 | PENPACT-1 | Derived from  [3](#_ENREF_3),[26](#_ENREF_26),[27](#_ENREF_27) |
| *First-line nevirapine* strategy |  |  |
| Nevirapine (in first-line ART) | 75% [72%] | 77% [73%] |
| Lopinavir/ritonavir (in second-line ART) | 75% [70%] | 81% [70%] |
| (Sensitivity analysis: 10-80%) | |
| *First-line lopinavir/ritonavir* strategy |  |  |
| Lopinavir/ritonavir (in first-line ART) | 91% [86%] | 72% [72%] |
| Nevirapine (in second-line ART) | 75% [71%] | 74% [66%] |
| (Sensitivity analysis: 10-80%) | |
| DRV-based regimen (sensitivity analysis) | 95% (assumption) | |
| CD4% increase on suppressive ART (first 6 months, after 6 months): children <60 months of age | Monthly increase | |  |
| 1st or 2nd line NNRTI regimen | 2.2%, 0.7% | | Derived from  [3](#_ENREF_3),[26](#_ENREF_26),[27](#_ENREF_27) |
| 1st or 2nd line PI regimen | 1.9%, 0.4% | |
| 2nd or 3rd line DRV-based regimen (sensitivity analysis) | 1.9%, 0.4% (assumption) | |
| CD4 increase on suppressive ART (first 6 months, after 6 months): any regimen, children ≥60 months of age | 67.3, 3.4 cells/µL | | [28](#_ENREF_28) |
| Probability of virologic failure after initial suppression c | Monthly risk | |  |
| Any regimen | 0.91%  (Sensitivity analysis: 0.5-3.6%) | | Derived from  [3](#_ENREF_3),[26](#_ENREF_26),[27](#_ENREF_27) |
| Reduction in event risk for patients on ART | Relative risk reduction (%) d  (sensitivity analysis: 0-100) | |  |
| Risk of opportunistic infection (age 0-13) | 85 | | [2](#_ENREF_2) |
| Risk of opportunistic infection (age 13+) | 32 | |
| Mortality risk (age 0-13) | 90 | |
| Mortality risk (age 13+, range by CD4) | 55-96% | |
| Loss to follow-up after ART initiation | 0.2 (sensitivity analysis: 0-0.8) | | [24](#_ENREF_24),[25](#_ENREF_25) |

**Appendix Table A, continued. Model input parameters (including those shown in Manuscript**

**Table 1)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **III. Cost Inputs** e | **Cost ( 2012 USD)** | | **Sources** | |
| Opportunistic infection care (per event; range by type of OI) | |  |  | |
| South Africa (<60 months of age) | $1,420-2,490 | | [29](#_ENREF_29) | |
| Côte d’Ivoire (<60 months of age) | $120-420 | | [30](#_ENREF_30) | |
| South Africa (≥60 months of age) | $310-1,070 | | [22](#_ENREF_22) | |
| Côte d’Ivoire (≥60 months of age) | $60-420 | | [30](#_ENREF_30) | |
| Routine care (per month, range by CD4) f |  | |  | |
| South Africa (<60 months of age) | $25-205 | | [22](#_ENREF_22),[31](#_ENREF_31) | |
| Côte d’Ivoire (<60 months of age) | $30-40 | | [30](#_ENREF_30),[32](#_ENREF_32) | |
| South Africa (≥60 months of age) | $25-205 | | [22](#_ENREF_22),[31](#_ENREF_31) | |
| Côte d’Ivoire (≥60 months of age) | $30-40 | | [30](#_ENREF_30),[32](#_ENREF_32) | |
| Care in the last month of life |  | |  | |
| South Africa | $800 | | [22](#_ENREF_22),[31](#_ENREF_31) | |
| Côte d’Ivoire | $65 | | [30](#_ENREF_30),[32](#_ENREF_32) | |
| Antiretroviral regimen costs (per month, range by age/weight) g | | |  | |
| Lopinavir/ritonavir (liquid: age <3 years (base-case) or <5 years (sensitivity analyses) | $17-27  (Sensitivity analysis: ↑1-15x) | | | [33](#_ENREF_33),[34](#_ENREF_34) |
| Lopinavir/ritonavir (pediatric or adult tablets) | $13-29 | | |
| Nevirapine (pediatric or adult tablets) | $3-8 | | |
| Nevirapine/zidovudine/lamivudine (pediatric or adult tablets) | $6-8 | | |
| Abacavir/lamivudine (pediatric or adult tablets) | $8-18 | | |
| Zidovudine/lamivudine (pediatric or adult tablets) | $4-9 | | |
| Efavirenz (pediatric or adult tablets, age ≥3 years) | $3-7 | | |
| Darunavir/ritonavir/abacavir/lamivudine  (in sensitivity analyses only) | $36-$92 | | |

**WHO**: World Health Organization. **TB**: tuberculosis.

a. In sensitivity analyses, all HIV-related event risks were varied from 0.5-2.0 x base-case values, due to lack of empiric data suggesting other ranges to examine. WHO Stage 4, Stage 4, and TB events were defined according to WHO classifications for HIV disease staging in children.

b. ART efficacy: probability of suppressing HIV RNA to <400 copies/mL by 24 weeks (in base-case analysis) or 48 weeks (in sensitivity analysis) after initiation of ART.[3](#_ENREF_3),[26](#_ENREF_26),[27](#_ENREF_27) Due to small numbers of children and similar suppression rates on second-line ART in the P1060 trial (second-line NNRTI: n=9, 24-week suppression = 75%; second-line PI: n=48, 24-week suppression = 74%), we assigned a suppression rate of 75% to both second-line regimens.

c. The monthly risk of virologic failure for those who initially suppress on ART was calculated from the difference in suppression risks at the earliest (24 or 48 weeks, depending on modeled scenario) and latest observed time point in the P1060 and PENPACT-1 trials.

d. Compared to children not on ART with similar CD4 (see text)

e. In sensitivity analyses, all costs were varied from 0.5-2.0 times the costs shown.

f. Routine clinical care costs include CD4 and viral load monitoring, according to the modeled scenario.

g. Monthly ART drug doses were calculated for children ages 0-13 years old based on the WHO weight-based dosing recommendations. Daily doses were then multiplied by unit drug costs from the May 2012 Clinton Health Access Initiative (CHAI) ARV price list to determine monthly ART costs by age and weight. All children were assumed to receive liquid/syrup drug formulations until age 3 years for lopinavir/ritonavir (5 years in sensitivity analyses), and until age 6 months for all other medications, for which dispersible tablets are available. After these ages, children were assumed to transition to pediatric or adult tablet formulations based on weight-based dosing recommendations. Fixed dose combinations were assumed to be used where available.[34](#_ENREF_34) In the absence of data on DRV/r costs for children, we assumed third-line ART would have costs equal to twice first-line LPV/r-based regimen costs.

**Appendix Table B: Calibration of the CD4-independent impact of ART: Identification of multipliers producing closest fit to observed mortality for children presenting to care at 12 months of age, treated with the *first-line nevirapine* strategy**

|  |  |  |
| --- | --- | --- |
| **Relative risk reduction (for mortality; OI risk)** a | **Rate/100PY (2-year average)** | **Rate/100PY (4-year average)** |
| P1060: observed mortality rate (comparator; median follow-up: 72-weeks) | 3.29 | |
| 100%, 100% | 2.57 | 1.87 |
| 95%, 95% | 3.38 | 2.62 |
| 90%, 95% | 3.98 | 3.02 |
| 95%, 90% | 4.04 | 3.23 |
| 90%, 90% | 4.67 | 3.65 |
| 85%, 90% | 5.34 | 4.25 |
| 90%, 75% | 6.62 | 5.40 |
| 75%, 85% | 7.28 | 5.54 |
| 75%, 75% | 8.59 | 6.74 |
| 50%, 85% | 10.56 | 7.73 |
| 90%, 50% | 9.66 | 8.13 |
| 25%, 85% | 13.82 | 9.87 |
| 90%, 25% | 12.54 | 10.71 |
| 50%, 50% | 15.25 | 11.76 |
| 0%, 85% | 17.14 | 12.04 |
| 90%, 0% | 15.24 | 13.19 |
| 25%, 25% | 21.59 | 16.52 |
| 0%, 0% | 27.72 | 21.07 |

Yellow highlighting indicates model projections that best fit mortality data from the P1060 trial (please see text).

a. Compared to children not on ART with similar CD4 (see text).

**Appendix Table C: Projected mortality and opportunistic infection rates, reflecting a range of values for the CD4-independent impact of ART on mortality and OI risk a**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Mortality**  **rate/100PY b** | **WHO3**  **Rate/100PY** | **WHO4**  **Rate/100PY** | **TB Rate/100PY** | **Model-projected life expectancy (undiscounted, years)** |
| **P1060 Trial** | **3.29** | **9.30** | **0.73** | **5.60** | **n/a** |
| **Best-fitting model results**  Reduction in OI risk of 85%, reduction in mortality risk of 90% (applied to ages 0-13) c | | | | |  |
| CEPAC – *first-line NVP* | 4.25 | 10.11 | 4.74 | 2.66 | 27.61 |
| CEPAC – *first-line LPV/r* | 3.98 | 9.45 | 4.36 | 2.41 | 28.79 |
| **Range of model results: lower bound of event risks**  Reduction in OI risk of 95%, reduction in mortality risk of 95% (applied lifelong) c | | | | |  |
| CEPAC – *first-line NVP* | 2.62 | 5.15 | 2.43 | 1.35 | 40.39 |
| CEPAC – *first-line LPV/r* | 2.51 | 4.90 | 2.29 | 1.26 | 41.09 |
| **Range of model results: upper bound of event risks**  No reduction in OI risk or mortality risk (applied lifelong) c | | | | |  |
| CEPAC – *first-line NVP* | 21.07 | 45.34 | 20.29 | 11.41 | 10.90 |
| CEPAC – *first-line LPV/r* | 19.68 | 44.01 | 19.40 | 10.77 | 11.64 |

a. Results are shown for a cohort of children presenting to care at 12 months of age.

b. P1060 mortality rates were observed over a median duration of follow-up of 72 weeks. Model-projected rates were calculated over 4 years of follow-up, to generate more stable estimates.

c. Compared to children not on ART with similar CD4 (see text). Except where noted, values derived from adults were applied after age 13 (Appendix Table A).[2](#_ENREF_2)

**Appendix Table D: Published rates of switching from first- to second-line pediatric ART**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study Name** | **Study Location** | **Study Size** | **Study years** | **Median Age** | **ART Regimen** | **Switches to Second-line** |
| Sauvageot et al, Pediatrics 2010[8](#_ENREF_8) | Africa and Asia | 3,936 | 2002-2008 | 2.6 years  (1.7-3.7) | d4T/3TC/NVP: 39.7%  d4T/3TC/EFV: 1.3%  AZT/3TC/NVP: 49.8%  AZT/3TC/EFV: 0.7%  Other: 8.5% | * 33 patients (0.8%) switched to second-line ART after median time of 27.3 months * Probability of remaining on first-line regimen after 24 months of ART was 0.99. Values were not significantly different when stratified by age at initiation. |
| EPPICC[9](#_ENREF_9) | 13 European countries  (9 cohorts) | 437 | 1996-2008 | 3.7 months | 3-drug NNRTI based: 24%  4-drug NNRTI based: 14%  Boosted PI with two NRTIs: 15%  Unboosted PI with 2-3 NRTIs:  38%  PI and NNRTI with/out NRTI or 3 NRTIs: 8% | * 18% (77/437) switched to second-line ART after median f/u of 5.9 years * 84% (41/49 with information available) switched due to treatment failure * 4 drug NNRTI or boosted PI regimens were slower to switch |
| PENPACT-1[3](#_ENREF_3) | North America, South America, Europe | 263 | 2002-2005 | 3.5 years | LPV/r based: 25%  NFV based: 24%  RTV or FPVr/r: 1%  EFV-based: 31%  NVP-based: 19% | * 188 children (71%) were still on first-line ART after median 5 years of follow up (23% switch at 5y) * 60/263 switched to second-line (28 PI group, 32 NNRTI group) * 15/263 discontinued ART after first-line ART |
| Prendergast et al, AIDS 2008[10](#_ENREF_10) | South Africa | 63 | 2003-2005 | 26 days | ZDV/3TC/NFV/NVP | * 10/63 (16%) infants started second-line ART within 1 year * 5/10 due to concurrent TB treatment * 4/10 due to virological failure * 1/10 both |
| CHIPS  (Walker et al, AIDS 2004)[11](#_ENREF_11) | UK and Ireland | 265 | 1996-2003 | 4.2 years | 108/265 (41%) PI containing regimen  126/265 (48%) NNRTI containing regimen  2/265 (1%) both PI and NNRTI containing regimen  29/265 (11%) ABC and other NRTIs  7 children started LPV/r  28 started a four-drug regimen | * 6 months post ART, 197/265 (87%) still on initial ART regimen with 99% still considered to be on first-line ART (1% switch at 6m) |

**Appendix Table D: Published rates of switching from first-line to second-line pediatric ART, continued**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study Name** | **Study Location** | **Study Size** | **Study years** | **Median Age** | **ART Regimen** | **Switches to Second-line** |
| Davies et al, JAIDS 2011[12](#_ENREF_12) | South Africa | 5,485 | 1999-2008 | 42 months | d4T and 3TC based: 89%  NVP as 3rd drug: 5%  EFV as 3rd drug: 55%  LPV/r as 3rd drug: 33%  RTV as 3rd drug: 7% | * Probability of failure (second elevated value > 1,000 copies/mL) by 36 months: 19.3% * Of those with virologic failure, 59% had never been virologically suppressed. After >1 year of follow-up post failure, 38% were switched to second-line. * Probability of switching to second-line by 3 years after ART initiation for all children = 6.2%. * Median time to switch from failure = 5.7 months * A PI-based initial regimen was negatively associated with switching. |
| Bacha et al, BMC ID 2012[13](#_ENREF_13" \o "Bacha, 2012 #4095) | Ethiopia | 1,186 | 2005-2011 | 6.22 years | d4T/3TC/NVP: 32.7%  d4T/3TC/EFV: 8.9%  AZT/3TC/NVP: 25.3%  AZT/3TC/EFV: 30.4% | * 14.1% of children had evidence of first-line failure * 5.9% clinical failure only * 6.7% immunologic failure only * 1.5% had immunologic and clinical failure * Of those with failure, 14.4% were identified as having failed first-line ART and switched to second-line. * Mean time of fail detection: 19.7 months * Mean time to switch: 24 months |
| ARROW[14](#_ENREF_14) | Uganda and Zimbabwe | 1,206 | 2007-2008 | 5.9 years (clinical monitoring)  6.0 years (routine lab monitoring) | Group A: NNRTI/3TC/ABC (n=397)  Group B: NNRTI/3TC/ABC/AZT for 36 weeks, then stop AZT (n=404)  Group C: NNRTI/3TC/ABC/AZT for 36 weeks, then stop NNRTI (n=405) | * Clinical Monitoring: 28 children (5%) switched to second-line after median 4 years (median time to switch = 2.8 years) * Routine Lab Monitoring (no viral load monitoring): 35 children (6%) switched to second-line after median 4 years (median time to switch = 2.2 years) |
| CHER[15](#_ENREF_15) | South Africa | 377 | 2005-2007 | 7.4 weeks | LPV/r + AZT + 3TC | * 7 children (1.9%) switch to second-line over 5 years – with viral load monitoring |

**Abbreviations**: **d4T**: stavudine, **3TC**: lamivudine, **NVP**: nevirapine, **EFV**: efavirenz, **AZT**: zidovudine, **NNRTI**: non-nucleoside reverse transcriptase inhibitor, **ART**: antiretroviral therapy, **PI**: protease inhibitor (boosted: combined with low-dose ritonavir), **NRTI**: nucleoside reverse transcriptase inhibitor, **LPV/r**: lopinavir/ritonavir, **NFV**: nelfinavir, **RTV**: ritonavir, **FPV**: fosamprenavir, **TB**: tuberculosis, **ABC**: abacavir.

**Appendix Table E: Modeled proportion of cohort on second-line ART at key time points a**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Years Post ART Initiation** | **Switch immediately after confirmation of failure** | | **Wait 6 months after failure confirmation to switch** | | **No RNA monitoring; switch 6 months after confirmation of failure (comparison)** | |
| *First-line NVP* | *First-line LPV/r* | *First-line NVP* | *First-line LPV/r* | *First-line NVP* | *First-line LPV/r* |
| 6 Months | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% |
| 12 Months | 22.80 % | 8.40% | 0.01% | 0.01% | 0.00% | 0.00% |
| 24 Months | 22.84% | 9.46% | 21.23% | 7.89% | 4.33% | 1.93% |
| 36 Months | 28.24% | 16.83% | 21.59% | 9.22% | 6.32% | 2.61% |
| 48 Months | 32.76% | 23.02% | 26.86% | 16.33% | 10.07% | 3.96% |
| 60 Months | 37.16% | 28.86% | 32.36% | 23.46% | 14.15% | 5.64% |

**NVP**: nevirapine; **LPV/r**: lopinavir/ritonavir; **ART**: antiretroviral therapy; **LE**: life expectancy (years)

a. Results are shown for a cohort of children presenting to care at 12 months of age. Proportions are of the original presenting cohort; children who die or are lost to follow-up are included in the denominator of each calculation. When limited to children in care and on ART, proportions on second-line ART will be higher than those shown here.

**Appendix Table F. Sensitivity analysis results (including results from Manuscript Table 3)**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **ART Strategy** | **Undiscounted LE (Years)** | | **Discounted**  **LE (Years)** | | **Discounted Lifetime Costs ($US 2012)** | | | | **Incremental cost-effectiveness ratio ($/years life saved)** | |
| **A. South Africa** | | | | | | | | | | |
| **Presenting Age = 6 months** | | | | | | | | | | |
| *No ART* | 2.50 | | 2.23 | | 8,520 | | | |  | |
| *First-line LPV/r* | 27.45 | | 16.31 | | 20,620 | | | | 860 | |
| *First-line NVP* | 26.29 | | 15.81 | | 21,960 | | | | Dominateda | |
| **Presenting Age = 12 months (base-case, as reported in main manuscript)** | | | | | | | | | | |
| *No ART* | 2.83 | | 2.52 | | 10,290 | | | |  | |
| *First-line LPV/r* | 28.79 | | 17.11 | | 21,950 | | | | 800 | |
| *First-line NVP* | 27.61 | | 16.59 | | 23,370 | | | | Dominated | |
| **Presenting Age = 24 months** | | | | | | | | | | |
| *No ART* | 3.54 | | 3.09 | | 12,650 | | | |  | |
| *First-line LPV/r* | 28.71 | | 17.10 | | 22,590 | | | | 710 | |
| *First-line NVP* | 27.52 | | 16.59 | | 24,060 | | | | Dominated | |
| **Presenting Age = 35 months** | | | | | | | | | | |
| *No ART* | 4.71 | | 4.03 | | 14,420 | | | |  | |
| *First-line LPV/r* | 29.46 | | 17.60 | | 23,240 | | | | 650 | |
| *First-line NVP* | 28.36 | | 17.11 | | 24,790 | | | | Dominated | |
| **One line of ART available** | | | | | | | | | | |
| *No ART* | 2.83 | | 2.52 | | 10,290 | |  | | | |
| *First-line NVP* | 22.42 | | 14.57 | | 24,890 | | 1,210 | | | |
| *First-line LPV/r* | 23.84 | | 15.31 | | 26,490 | | 2,190 | | | |
| **Stop second-line ART at failure** | | | | | | | | | | |
| *No ART* | 2.83 | | 2.52 | | 10,290 | |  | | | |
| *First-line NVP* | 23.76 | | 15.03 | | 17,360 | | 565 | | | |
| *First-line LPV/r* | 25.18 | | 15.74 | | 17,760 | | 570 | | | |
| **Require CD4 confirmation ( ≤10% or ≤100 cells/µL) of observed first-line ART failure** | | | | | | | | | | |
| *No ART* | | 2.83 | | 2.52 | | 10,290 | |  | | |
| *First-line NVP* | | 27.23 | | 16.35 | | 23,850 | | Weakly dominatedb | | |
| *First-line LPV/r* | | 28.64 | | 16.95 | | 24,040 | | 950 | | |
| **No HIV RNA monitoring available** | | | | | | | | | | |
| *No ART* | 2.83 | | 2.53 | | 10,300 | |  | | | |
| *First-line LPV/r* | 28.69 | | 16.96 | | 22,240 | | 830 | | | |
| *First-line NVP* | 27.09 | | 16.25 | | 22,760 | | Dominated | | | |
| **Third line ART = DRV/r for both strategies** | | | | | | | | | | |
| *No ART* | 2.83 | | 2.52 | | 10,290 | |  | | | |
| *First-line LPV/r* | 32.90 | | 18.32 | | 25,520 | | 960 | | | |
| *First-line NVP* | 31.83 | | 17.92 | | 25,670 | | Dominated | | | |
| **No CD4 or viral load monitoring** | | | | | | | | | | |
| *No ART* | | 2.83 | | 2.52 | | 10,280 | | | |  |
| *First-line LPV/r* | | 26.78 | | 16.26 | | 24,620 | | | | 1,040 |
| *First-line NVP* | | 25.51 | | 15.65 | | 25,490 | | | | Dominated |

**Appendix Table F. Sensitivity analysis results, continued**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **ART Strategy (ordered by cost)** | **Undiscounted LE (Years)** | | | **Discounted**  **LE (Years)** | | | **Discounted Lifetime Costs ($US 2012)** | | | | | **Incremental cost-effectiveness ratio ($/years life saved)** |
| **A. South Africa, continued.** | | | | | | | | | | | | |
| **Second-line ART = DRV/r for both strategies** | | | | | | | | | | | | |
| *No ART* | | | 2.83 | | | 2.52 | | | 10,290 | |  | |
| *First-line NVP* | | | 29.02 | | | 17.12 | | | 28,040 | | 1,220 | |
| *First-line LPV/r* | | | 30.07 | | | 17.56 | | | 28,680 | | 1,470 | |
| **DRV/r follows LPV/r in *first-line LPV/r* (no change to *first-line NVP*)** | | | | | | | | | | | | |
| *No ART* | | | 2.83 | | | 2.52 | | | 10,290 | |  | |
| *First-line NVP* | | | 27.61 | | | 16.59 | | | 23,370 | | 930 | |
| *First-line LPV/r* | | | 30.07 | | | 17.56 | | | 28,680 | | 5,460 | |
| **DRV/r follows LPV/r in both strategies (NNRTIs not used in second-line after *first-line LPV/r*)** | | | | | | | | | | | | |
| *No ART* | | | 2.83 | | | 2.52 | | | 10,290 | |  | |
| *First-line NVP* | | | 31.83 | | | 17.92 | | | 25,670 | | 1,000 | |
| *First-line LPV/r* | | | 30.07 | | | 17.56 | | | 28,680 | | Dominated | |
| **PENPACT-1 ART efficacies** | | | | | | | | | | | | |
| *No ART* | | 2.83 | | | 2.52 | | | 10,290 | |  | | |
| *First-line LPV/r* | | 29.28 | | | 16.96 | | | 22,240 | | Weakly dominated | | |
| *First-line NVP* | | 30.42 | | | 17.39 | | | 22,370 | | 810 | | |
| **Second-line NNRTI efficacy = 40%** | | | | | | | | | | | | |
| *No ART* | | 2.83 | | | 2.52 | | | 10,290 | |  | | |
| *First-line LPV/r* | | 26.51 | | | 16.26 | | | 23,010 | | 930 | | |
| *First-line NVP* | | 27.61 | | | 16.59 | | | 23,370 | | 1,110 | | |
| **1.7x late failure for first-line LPV/r (1.5%/month: *first-line NVP* becomes more effective)** e | | | | | | | | | | | | |
| *No ART* | | 2.83 | | | 2.52 | | | 10,290 | |  | | |
| *First-line LPV/r* | | 27.12 | | | 16.58 | | | 22,050 | | 840 | | |
| *First-line NVP* | | 27.61 | | | 16.59 | | | 23,370 | | 185,090 | | |
| **2.1x late failure for first-line LPV/r (1.9%/month: *first-line NVP* more effective and cost-effective)** e | | | | | | | | | | | | |
| *No ART* | | 2.83 | | | 2.52 | | | 10,290 | |  | | |
| *First-line LPV/r* | | 26.60 | | | 16.38 | | | 22,070 | | 850 | | |
| *First-line NVP* | | 27.61 | | | 16.59 | | | 23,370 | | 6,310 | | |
| **4.5x cost of liquid LPV/r ($80-105 per month for children <3 years of age)** | | | | | | | | | | | | |
| *No ART* | | 2.83 | | | 2.52 | | | 10,290 | |  | | |
| *First-line NVP* | | 28.77 | | | 16.59 | | | 23,480 | | Weakly dominated | | |
| *First-line LPV/r* | | 27.58 | | | 17.10 | | | 23,510 | | 910 | | |
| **15.0x cost of liquid LPV/r ($260-330 per month for children <3 years of age)** | | | | | | | | | | | | |
| *No ART* | | 2.83 | | | 2.52 | | | 10,290 | |  | | |
| *First-line NVP* | | 27.58 | | | 16.58 | | | 23,780 | | 960 | | |
| *First-line LPV/r* | | 28.79 | | | 17.09 | | | 28,170 | | 8,640 | | |
| **Liquid LPV/r used until age 5** | | | | | | | | | | | | |
| *No ART* | | 2.83 | | | 2.52 | | | 10,290 | |  | | |
| *First-line LPV/r* | | 28.77 | | | 17.09 | | | 22,730 | | 850 | | |
| *First-line NVP* | | 27.59 | | | 16.60 | | | 23,440 | | Dominated | | |

**Appendix Table F. Sensitivity analysis results, continued**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **ART Strategy (ordered by cost)** | **Undiscounted LE (Years)** | | | **Discounted**  **LE (Years)** | | **Discounted Lifetime Costs ($US 2012)** | | | | | **Incremental cost-effectiveness ratio ($/years life saved)** |
| **A. South Africa, continued.** | | | | | | | | | | | |
| **Intermediate additional impact of ART (relative risk reductions: 50% for OI, 50% for mortality, applied lifelong)**c | | | | | | | | | | | |
| *No ART* | | | 2.83 | 2.52 | | | | 10,290 |  | | |
| *First-line LPV/r* | | | 19.83 | 12.27 | | | | 16,810 | 670 | | |
| *First-line NVP* | | | 18.71 | 11.69 | | | | 17,190 | Dominated | | |
| **Additional impact of ART applied only to ages 0-13** | | | | | | | | | | | |
| *No ART* | | 2.83 | | | 2.52 | | 10,290 | | |  | |
| *First-line LPV/r* | | 23.09 | | | 15.08 | | 17,970 | | | 610 | |
| *First-line NVP* | | 22.13 | | | 14.63 | | 18,950 | | | Dominated | |
| **No CD4-independent impact of ART (relative risk reductions: 0% for OI, 0% for mortality, applied lifelong)**c | | | | | | | | | | | |
| *No ART* | | 2.83 | | | 2.52 | | 10,290 | | |  | |
| *First-line NVP* | | 10.91 | | | 7.44 | | 12,250 | | | 400 | |
| *First-line LPV/r* | | 11.67 | | | 7.89 | | 12,430 | | | 420 | |
| **Discount rate: 5% per year** | | | | | | | | | | | |
| ***No ART*** | | **2.83** | | | **2.36** | | **9,660** | | |  | |
| ***First-line LPV/r*** | | **28.79** | | | **13.16** | | **16,100** | | | **600** | |
| ***First-line NVP*** | | **27.61** | | | **12.85** | | **17,100** | | | **Dominated** | |
| **Discount rate: 8% per year** | | | | | | | | | | | |
| ***No ART*** | | **2.83** | | | **2.17** | | **8,910** | | |  | |
| ***First-line LPV/r*** | | **28.79** | | | **9.70** | | **11,400** | | | **330** | |
| ***First-line NVP*** | | **27.61** | | | **9.52** | | **11,960** | | | **Dominated** | |
| **B. Cote d’Ivoire healthcare costs d** | | | | | | | | | | | |
| **Presenting Age = 6 months** | | | | | | | | | | | |
| *No ART* | 2.49 | | | 2.24 | | 1,600 | | | | |  |
| *First-line LPV/r* | 27.46 | | | 16.31 | | 14,360 | | | | | 910 |
| *First-line NVP* | 26.30 | | | 15.80 | | 14,710 | | | | | Dominated |
| **Presenting Age = 12 months** | | | | | | | | | | | |
| *No ART* | 2.83 | | | 2.52 | | 1,820 | | | | |  |
| *First-line LPV/r* | 28.79 | | | 17.11 | | 15,120 | | | | | 910 |
| *First-line NVP* | 27.62 | | | 16.58 | | 15,480 | | | | | Dominated |
| **Presenting Age = 24 months** | | | | | | | | | | | |
| *No ART* | 3.55 | | | 3.09 | | 2,180 | | | | |  |
| *First-line LPV/r* | 28.74 | | | 17.10 | | 15,170 | | | | | 930 |
| *First-line NVP* | 27.53 | | | 16.60 | | 15,570 | | | | | Dominated |
| **Presenting Age = 35 months** | | | | | | | | | | | |
| *No ART* | 4.71 | | | 4.03 | | 2,680 | | | | |  |
| *First-line LPV/r* | 29.48 | | | 17.60 | | 15,720 | | | | | 960 |
| *First-line NVP* | 28.36 | | | 17.14 | | 16,200 | | | | | Dominated |

**Appendix Table F. Sensitivity analysis results, continued**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **ART Strategy (ordered by cost)** | **Undiscounted LE (Years)** | | **Discounted**  **LE (Years)** | | **Discounted Lifetime Costs ($US 2012)** | | | **Incremental cost-effectiveness ratio ($/years life saved)** | |
| **B. Cote d’Ivoire healthcare costs, continued** | | | | | | | | | |
| **One line of ART available** | | | | | | | | | |
| *No ART* | 2.83 | | 2.52 | | 1,820 | | |  | |
| *First-line NVP* | 22.40 | | 14.59 | | 12,410 | | | 880 | |
| *First-line LPV/r* | 23.86 | | 15.29 | | 16,030 | | | 5,130 | |
| **Stop second-line ART at failure** | | | | | | | | | |
| *No ART* | 2.83 | | 2.52 | | 1,820 | | |  | |
| *First-line NVP* | 23.73 | | 15.05 | | 12,420 | | | 850 | |
| *First-line LPV/r* | 25.21 | | 15.77 | | 13,480 | | | 1,480 | |
| **Require CD4 confirmation ( ≤10% or ≤100 cells/µL) of observed first-line ART failure** | | | | | | | | | |
| *No ART* | | 2.83 | | 2.52 | | 1,820 |  | | |
| *First-line NVP* | | 27.23 | | 16.36 | | 14,900 | 950 | | |
| *First-line LPV/r* | | 28.63 | | 16.95 | | 16,240 | 2,280 | | |
| **No HIV RNA monitoring available** | | | | | | | | | |
| *No ART* | 2.84 | | 2.52 | | 1,820 | | |  | |
| *First-line NVP* | 27.11 | | 16.25 | | 13,340 | | | 840 | |
| *First-line LPV/r* | 28.69 | | 16.96 | | 14,330 | | | 1,390 | |
| **Third-line ART = DRV/r for both strategies** | | | | | | | | | |
| *No ART* | 2.83 | | 2.52 | | 1,820 | | |  | |
| *First-line NVP* | 31.77 | | 17.94 | | 20,580 | | | 1,220 | |
| *First-line LPV/r* | 32.88 | | 18.35 | | 21,130 | | | 1,330 | |
| **No CD4 or viral load monitoring** | | | | | | | | | |
| *No ART* | | 2.83 | | 2.53 | | 1,820 |  | | |
| *First-line NVP* | | 25.50 | | 15.66 | | 12,190 | 790 | | |
| *First-line LPV/r* | | 26.79 | | 16.25 | | 13,150 | 1,600 | | |
| **Second-line ART = DRV/r for both strategies** | | | | | | | | | |
| *No ART* | | 2.83 | | 2.52 | | 1,820 | | |  |
| *First-line NVP* | | 28.99 | | 17.15 | | 21,450 | | | 1,340 |
| *First-line LPV/r* | | 30.09 | | 17.55 | | 22,780 | | | 3,250 |
| **DRV/r follows LPV/r in *first-line LPV/r* (no change to *first-line NVP*)** | | | | | | | | | |
| *No ART* | | 2.83 | | 2.52 | | 1,820 |  | | |
| *First-line NVP* | | 27.62 | | 16.58 | | 15,480 | 970 | | |
| *First-line LPV/r* | | 30.09 | | 17.55 | | 22,780 | 7,470 | | |
| **DRV/r follows LPV/r in both strategies (NNRTIs not used in second-line after *first-line LPV/r*)** | | | | | | | | | |
| *No ART* | | 2.83 | | 2.52 | | 1,820 |  | | |
| *First-line NVP* | | 31.77 | | 17.94 | | 20,580 | 1,220 | | |
| *First-line LPV/r* | | 30.09 | | 17.55 | | 22,780 | Dominated | | |
| **PENPACT ART efficacies** | | | | | | | | | |
| *No ART* | 2.83 | | 2.52 | | 1,820 | | |  | |
| *First-line LPV/r* | 29.24 | | 16.95 | | 15,000 | | | 910 | |
| *First-line NVP* | 30.33 | | 17.37 | | 16,030 | | | 2,400 | |

**Appendix Table F. Sensitivity analysis results, continued**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **ART Strategy (ordered by cost)** | **Undiscounted LE (Years)** | | **Discounted**  **LE (Years)** | | **Discounted Lifetime Costs ($US 2012)** | | | | **Incremental cost-effectiveness ratio ($/years life saved)** |
| **B. Cote d’Ivoire healthcare costs, continued** | | | | | | | | | |
| **Second-line NNRTI efficacy = 40%** | | | | | | | | | |
| *No ART* | 2.83 | | 2.52 | | 1,820 | | | |  |
| *First-line LPV/r* | 26.48 | | 16.26 | | 14,520 | | | | 930 |
| *First-line NVP* | 27.62 | | 16.58 | | 15,480 | | | | 3,010 |
| **Second-line NNRTI efficacy = 15%** | | | | | | | | | |
| *No ART* | 2.83 | | 2.52 | | 1,820 | | | |  |
| *First-line LPV/r* | 24.81 | | 15.65 | | 14,090 | | | | 940 |
| *First-line NVP* | 27.62 | | 16.58 | | 15,480 | | | | 1,500 |
| **1.7x late failure for first-line LPV/r (1.5%/month: *first-line NVP* becomes more effective) e** | | | | | | | | | |
| *No ART* | 2.83 | | 2.52 | | 1,820 | |  | | |
| *First-line LPV/r* | 27.14 | | 16.56 | | 14,260 | | 890 | | |
| *First-line NVP* | 27.62 | | 16.58 | | 15,480 | | 56,160 | | |
| **2.0x late failure for first-line LPV/r (1.8%/month: *first-line NVP* more effective and cost-effective)** e | | | | | | | | | |
| *No ART* | 2.83 | | 2.52 | | 1,820 | |  | | |
| *First-line LPV/r* | 26.71 | | 16.43 | | 14,050 | | 880 | | |
| *First-line NVP* | 27.62 | | 16.58 | | 15,480 | | 9,560 | | |
| **3.5 cost of liquid LPV/r ($65-85 per month for children <3 years of age)** | | | | | | | | | |
| *No ART* | 2.83 | | 2.52 | | 1,820 | |  | | |
| *First-line NVP* | 27.58 | | 16.58 | | 15,560 | | 980 | | |
| *First-line LPV/r* | 28.81 | | 17.10 | | 16,240 | | 1,300 | | |
| **Liquid LPV/r used until age 5** | | | | | | | | | |
| *No ART* | 2.83 | | 2.52 | | 1,820 | |  | | |
| *First-line NVP* | 27.55 | | 16.56 | | 15,530 | | Weakly dominated | | |
| *First-line LPV/r* | 28.80 | | 17.09 | | 15,910 | | 970 | | |
| **Intermediate CD4-independent impact of ART (relative risk reductions: 50% for OI, 50% for mortality, applied lifelong)**b | | | | | | | | | |
| *No ART* | | 2.83 | | 2.52 | | 1,820 | |  | |
| *First-line NVP* | | 18.67 | | 11.71 | | 11,000 | | Weakly dominated | |
| *First-line LPV/r* | | 19.79 | | 12.29 | | 11,140 | | 960 | |
| **CD4-independent impact of ART applied only to ages 0-13** | | | | | | | | | |
| *No ART* | | 2.83 | | 2.52 | | 1,820 | |  | |
| *First-line LPV/r* | | 23.13 | | 15.07 | | 13,490 | | 930 | |
| *First-line NVP* | | 22.16 | | 14.63 | | 13,500 | | Dominated | |
| **No CD4-independent impact of ART (relative risk reductions: 0% for OI, 0% for mortality, applied lifelong)**d | | | | | | | | | |
| *No ART* | 2.83 | | 2.52 | | 1,820 | | | |  |
| *First-line NVP* | 10.89 | | 7.45 | | 7,160 | | | | Weakly dominated |
| *First-line LPV/r* | 11.62 | | 7.89 | | 7,550 | | | | 1,070 |

**Appendix Table F. Sensitivity analysis results, continued**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **ART Strategy (ordered by cost)** | **Undiscounted LE (Years)** | **Discounted**  **LE (Years)** | **Discounted Lifetime Costs ($US 2012)** | **Incremental cost-effectiveness ratio ($/years life saved)** |
| **B. Cote d’Ivoire healthcare costs, continued** | | | | |
| **Discount rate: 5% per year** | | | | |
| ***No ART*** | **2.83** | **2.36** | **1,710** |  |
| ***First-line LPV/r*** | **28.79** | **13.17** | **11,810** | **930** |
| ***First-line NVP*** | **27.61** | **12.85** | **11,860** | **Dominated** |
| **Discount rate: 8% per year** | | | | |
| ***No ART*** | **2.83** | **2.17** | **1,580** |  |
| ***First-line NVP*** | **27.61** | **9.52** | **8,660** | **960** |
| ***First-line LPV/r*** | **28.79** | **9.70** | **8,850** | **1,050** |

**LE**: life expectancy. **ICER**: incremental cost-effectiveness analysis. **ART**: antiretroviral therapy. **LPV/r**: lopinavir/ritonavir. **NVP**: nevirapine. **DRV/r**:darunavir/ritonavir**.** **ART**: antiretroviral therapy. Costs are in 2012 USD. Discounting is at 3%/year unless otherwise indicated.

a. Dominated: Here, refers to a strategy that is more expensive and less effective than its alternative.

b. Weakly dominated: Here, refers to extended dominance: the incremental cost-effectiveness ratio (ICER) of the non-dominated strategy compared to the dominated strategy is less than the ICER of the dominated strategy compared to no ART, indicating that the dominated strategy is an inefficient use of healthcare resources.

c. Compared to children or adults at similar CD4% or CD4 not on ART (see text).

d. Incremental cost-effectiveness ratios (ICERs) are generally lower in sensitivity analyses for South Africa than for Côte d'Ivoire because in South Africa, the costs of HIV-related healthcare are high, relative to the costs of ART; in Côte d'Ivoire, care costs are low, relative to ART costs. Much of the difference between first-line NVP and first-line LPV/r are due to differences in drug costs, rather than differences in care costs. Sensitivity analyses that change the relative drug costs between the two strategies lead to larger cost differences in Côte d'Ivoire than they do in South Africa.

**APPENDIX TABLE G. Projected costs and survival by year after presentation to care a**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **A. South Africa costs (HIV-infected children, presenting to care at 12 months of age)** | | | | | | |
|  | **Proportion Alive** | | | **Cumulative Costs** | | |
| **Year** | **No ART** | **1st Line PI** | **1st Line NNRTI** | **No ART** | **1st Line PI** | **1st Line NNRTI** |
| 0 | 1.00 | 1.00 | 1.00 | 0 | 0 | 0 |
| 1 | 0.63 | 0.94 | 0.93 | 3,060 | 1,510 | 1,400 |
| 2 | 0.40 | 0.90 | 0.90 | 5,200 | 2,530 | 2,390 |
| 3 | 0.24 | 0.88 | 0.87 | 6,720 | 3,380 | 3,230 |
| 4 | 0.16 | 0.85 | 0.84 | 7,770 | 4,150 | 4,000 |
| 5 | 0.14 | 0.85 | 0.84 | 8,150 | 4,870 | 4,740 |
| 6 | 0.12 | 0.84 | 0.83 | 8,500 | 5,560 | 5,450 |
| 7 | 0.10 | 0.83 | 0.82 | 8,810 | 6,220 | 6,150 |
| 8 | 0.09 | 0.82 | 0.81 | 9,070 | 6,890 | 6,860 |
| 9 | 0.07 | 0.81 | 0.80 | 9,290 | 7,530 | 7,550 |
| 10 | 0.06 | 0.80 | 0.79 | 9,470 | 8,150 | 8,230 |
| 11 | 0.05 | 0.79 | 0.78 | 9,620 | 8,750 | 8,880 |
| 12 | 0.04 | 0.78 | 0.77 | 9,740 | 9,320 | 9,520 |
| 13 | 0.04 | 0.77 | 0.75 | 9,840 | 9,910 | 10,200 |
| 14 | 0.03 | 0.75 | 0.74 | 9,930 | 10,490 | 10,860 |
| 15 | 0.03 | 0.74 | 0.72 | 9,990 | 11,040 | 11,490 |
| 16 | 0.02 | 0.72 | 0.70 | 10,050 | 11,570 | 12,110 |
| 17 | 0.02 | 0.71 | 0.68 | 10,090 | 12,090 | 12,710 |
| 18 | 0.02 | 0.69 | 0.66 | 10,130 | 12,600 | 13,290 |
| 19 | 0.01 | 0.67 | 0.65 | 10,160 | 13,090 | 13,850 |
| 20 | 0.01 | 0.65 | 0.63 | 10,180 | 13,570 | 14,400 |
| 21 | 0.01 | 0.63 | 0.61 | 10,200 | 14,030 | 14,930 |
| 22 | 0.01 | 0.61 | 0.59 | 10,220 | 14,480 | 15,440 |
| 23 | 0.01 | 0.60 | 0.57 | 10,230 | 14,920 | 15,920 |
| 24 | 0.01 | 0.58 | 0.55 | 10,240 | 15,340 | 16,390 |
| 25 | 0.00 | 0.56 | 0.53 | 10,250 | 15,740 | 16,840 |
| 26 | 0.00 | 0.54 | 0.51 | 10,260 | 16,130 | 17,270 |
| 27 | 0.00 | 0.52 | 0.49 | 10,260 | 16,500 | 17,680 |
| 28 | 0.00 | 0.50 | 0.47 | 10,270 | 16,860 | 18,080 |
| 29 | 0.00 | 0.48 | 0.45 | 10,270 | 17,200 | 18,450 |
| 30 | 0.00 | 0.46 | 0.43 | 10,280 | 17,530 | 18,800 |

**APPENDIX TABLE G. Projected costs and survival by year after presentation to care**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **B. Côte d'Ivoire costs (HIV-infected children, presenting to care at 12 months of age)** | | | | | | |
| **Year** | **Proportion Alive** | | | **Cumulative Costs** | | |
| **No ART** | **1st Line PI** | **1st Line NNRTI** | **No ART** | **1st Line PI** | **1st Line NNRTI** |
| 0 | 1.00 | 1.00 | 1.00 | 0 | 0 | 0 |
| 1 | 0.63 | 0.94 | 0.93 | 600 | 1,060 | 890 |
| 2 | 0.40 | 0.90 | 0.90 | 970 | 1,910 | 1,610 |
| 3 | 0.24 | 0.88 | 0.87 | 1,210 | 2,650 | 2,280 |
| 4 | 0.16 | 0.85 | 0.84 | 1,360 | 3,340 | 2,910 |
| 5 | 0.14 | 0.85 | 0.84 | 1,440 | 4,030 | 3,550 |
| 6 | 0.12 | 0.84 | 0.83 | 1,500 | 4,680 | 4,160 |
| 7 | 0.10 | 0.83 | 0.82 | 1,560 | 5,290 | 4,750 |
| 8 | 0.09 | 0.82 | 0.81 | 1,610 | 5,900 | 5,350 |
| 9 | 0.07 | 0.81 | 0.80 | 1,650 | 6,480 | 5,930 |
| 10 | 0.06 | 0.80 | 0.79 | 1,680 | 7,030 | 6,480 |
| 11 | 0.05 | 0.79 | 0.78 | 1,700 | 7,550 | 7,010 |
| 12 | 0.04 | 0.78 | 0.77 | 1,730 | 8,040 | 7,510 |
| 13 | 0.04 | 0.77 | 0.75 | 1,740 | 8,520 | 8,020 |
| 14 | 0.03 | 0.75 | 0.74 | 1,760 | 8,970 | 8,510 |
| 15 | 0.03 | 0.74 | 0.72 | 1,770 | 9,390 | 8,970 |
| 16 | 0.02 | 0.72 | 0.70 | 1,780 | 9,780 | 9,410 |
| 17 | 0.02 | 0.70 | 0.68 | 1,790 | 10,160 | 9,820 |
| 18 | 0.02 | 0.69 | 0.66 | 1,790 | 10,510 | 10,210 |
| 19 | 0.01 | 0.67 | 0.64 | 1,800 | 10,840 | 10,580 |
| 20 | 0.01 | 0.65 | 0.62 | 1,800 | 11,160 | 10,930 |
| 21 | 0.01 | 0.63 | 0.60 | 1,800 | 11,450 | 11,260 |
| 22 | 0.01 | 0.61 | 0.58 | 1,810 | 11,720 | 11,580 |
| 23 | 0.01 | 0.59 | 0.57 | 1,810 | 11,980 | 11,870 |
| 24 | 0.01 | 0.58 | 0.55 | 1,810 | 12,220 | 12,140 |
| 25 | 0.00 | 0.56 | 0.52 | 1,810 | 12,440 | 12,400 |
| 26 | 0.00 | 0.54 | 0.50 | 1,810 | 12,660 | 12,640 |
| 27 | 0.00 | 0.52 | 0.48 | 1,810 | 12,850 | 12,870 |
| 28 | 0.00 | 0.50 | 0.47 | 1,810 | 13,040 | 13,080 |
| 29 | 0.00 | 0.48 | 0.45 | 1,820 | 13,210 | 13,280 |
| 30 | 0.00 | 0.46 | 0.43 | 1,820 | 13,370 | 13,460 |

a. These are model results that form the basis of Manuscript Figure 1 and Appendix Figure A.

**APPENDIX FIGURE LEGEND**

**Figure A. Projected survival and costs with alternative first-line pediatric ART regimens.**

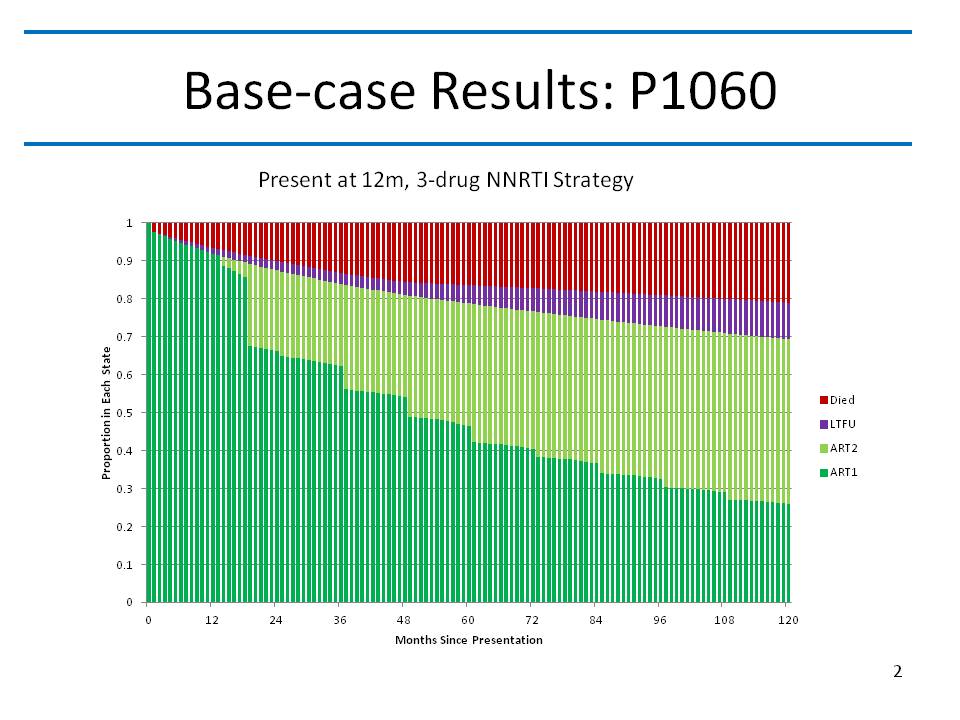
Results are shown for the sensitivity analysis using Côte d’Ivoire costs, for presenting to care at 12 months of age. The proportion of patients alive is on the left-hand vertical axis (blue lines) and the per-person cumulative costs are on the right-hand vertical axis (black lines). Survival and per-person costs are projected over 20 years (240 months) since presentation to care, shown on the horizontal axis. The *no ART* strategy is represented by solid lines, *first-line NVP* by dashed lines, and *first-line LPV/r* by dotted lines. The arrow indicates the time after presentation when *first-line LPV/r* becomes cost-saving compared to *first-line NVP:* 317 months (26.4 years; see Appendix Results text). **LPV/r**: lopinavir/ritonavir. **NVP**: nevirapine. **ART**:antiretroviral therapy.

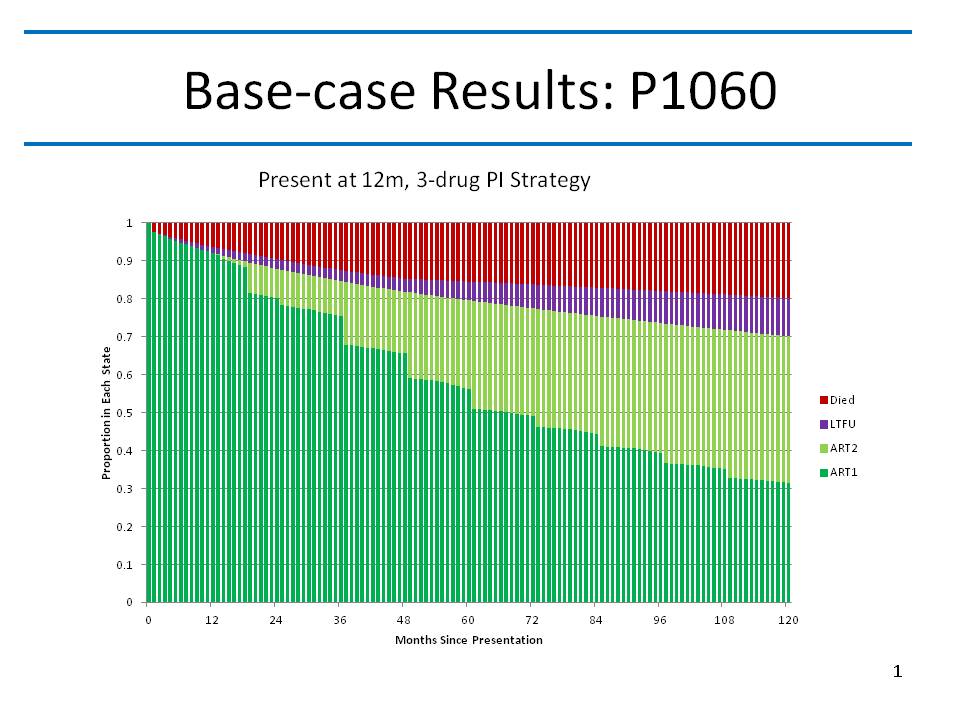
**Figure B. Patient outcomes over time.** For both modeled first-line ART regimens,the proportion of the modeled cohort that remains on first-line ART, has switched to second-line ART, has become lost to follow-up, or has died at each month of the simulation is shown in Appendix Figure B. Panel A shows results for the *first-line nevirapine* strategy, and panel B for the *first-line lopinavir/ritonavir* strategy. **LTFU**: lost to follow-up; **ART 1:** first-line ART; **ART 2**: second-line ART.

**Figure A. Projected survival and costs with alternative first-line pediatric ART regimens: Côte d'Ivoire**



**Figure B. Patient outcomes over time.**

**A.**

**B.**

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