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Modeling vertical transmission of HIV: Imperfect vaccines can be of benefit

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In the United States and other developed countries, the use of maternal HAART during pregnancy and delivery and antiretroviral treatment given to the infant during the neonatal period along with 100% formula feeding have reduced mother to child transmission (MTCT) of HIV to less than 2%.[1] However, in resource poor countries, much higher rates of MTCT (up to 35% [2][3][4]) are reported. Among the three routes for MTCT of HIV - *in utero*, *intrapartum*, and transmission through breast milk - this study concentrates on *intrapartum* and breast feeding risk which account for approximately 28% of infections.[5][6] Breastfeeding is estimated to cause about half of the 420,000 new infections in infants each year [7] and 90% of these infections occur in Africa.[8]

In some resource poor countries, including those of sub-Saharan Africa, Nevirapine (NVP) has been used as a preventive measure. One dose of NVP given to the mother during labor and delivery and one dose of NVP given to infants within 72 hours of birth has reduced MTCT of HIV from 28.2% to 15.7% measured at 12 months of age mainly by reducing *intrapartum* MTCT.[9]

In sub-Saharan African countries, bottle-feeding is not a viable alternative to breastfeeding. There is little infant formula, and even if there were more, many rural women do not have clean water to mix with it.[10] As a result, bottle-feeding and early weaning carry an increased risk for infant mortality.[11] Further, being HIV positive carries such a social stigma in these countries that few infected women want to bottle feed, essentially signaling HIV infection where breastfeeding is the norm.[10] As long as breast milk is the only safe and feasible method

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for feeding infants, HIV transmission through breastfeeding will continue and intervention at birth, by itself, will not be enough to prevent MTCT of HIV.

Resource poor countries need an intervention that is cost effective, that will substantially reduce MTCT of HIV from birth and during the lactation period, that is easy to administer, and that does not jeopardize the social status of mothers. Finding interventions that meet these social and economic needs is the key to effectively reducing MTCT of HIV in these countries.

Many researchers are now focusing on HIV vaccine development as the ultimate solution to prevention of MTCT of HIV in this unfavorable social and economic context. Other studies are underway to develop an HIV-specific monoclonal antibody (HIVAB). Once a vaccine is developed, it is anticipated that it will be used with or without NVP and HIVAB. The different combinations of interventions that include No Intervention, HIV vaccine, NVP, and HIVAB yield eight choices to consider for reducing MTCT of HIV during the *intrapartum* and breastfeeding periods. Among these eight possible interventions, HIVAB alone and NVP +HIVAB are not considered here, because of the recommendation that HIVAB be used with vaccines to give immediate and temporary protection while the vaccine generates immunity.

To best prepare for forthcoming HIV vaccines and HIVAB which may be only partially effective, public health and policy communities need a way to evaluate the effectiveness of a vaccine based strategy, and plan for its implementation even as vaccines are being developed. This study develops a tool to predict the effectiveness of a vaccine in reducing MTCT of HIV during the *intrapartum* and breastfeeding periods, given vaccine characteristics such as immunity, time to peak immunity, waning rate, boost effect, and the number of vaccine doses. MTCT *in utero* is excluded from the modeling because MTCT of HIV during the *intrapartum* and breastfeeding periods is the major current problem.

METHODS

Modeling MTCT probabilities

We measured the effectiveness of six interventions (1. No Intervention, 2. NVP only, 3. Vaccine only, 4. HIVAB+Vaccine, 5. NVP+Vaccine, 6. NVP+HIVAB+Vaccine) on reducing MTCT of HIV by using the probability for transmission by time $t=36$ months because nearly all children are weaned by then. We modeled the cumulative transmission probability $F(t)$ by specifying the hazard function, $h(t)$, noting that $F(t)$ is completely determined by $h(t)$. [12] The hazard function $h(t)$ specifies the instantaneous rate of infection at time t given that the individual has not been infected up to time t .

Base hazard functions for No Intervention and NVP Alone

The risk of transmission of HIV during the *intrapartum* period and breastfeeding period has been reported to be especially high at birth and at early ages, but to decline over time. [13] [14][15] The risk of MTCT of HIV and its rate of decline under NVP alone are expected to be different from those under No Intervention due to the effects of NVP in infants during labor and delivery and breastfeeding. [16] Thus the required features of hazard models for these two interventions include:

- 1) a high risk at birth [17]
- 2) decreasing risk as infants age.

To meet these requirements, considering the nature of MTCT of HIV, two different Weibull hazard models for No Intervention and NVP alone were assumed. A Weibull model has a hazard function given by

$$h(t) = \lambda \alpha t^{\alpha-1} \quad (1)$$

which is a declining function of time when $0 < \alpha < 1$. The two parameters in this model are usually called the scale (λ) and the shape (α) reflecting their effect on the hazard function.

To determine base hazard models for No Intervention and for NVP alone, the parameter sets, λ and α , were separately estimated using the cumulative transmission probabilities, $F(t)$, reported from several studies. For the No Intervention model, cumulative transmission probabilities from Coutoudis et al.[9] and Nduarti et al.[5] were used and for the NVP alone model, cumulative transmission probabilities from Jackson et al.[18] were used. In these breastfeeding studies, the reported overall cumulative transmission probabilities included MTCT of HIV *in utero*, *intrapartum*, and from breastfeeding, so the 7% due to *in utero* transmission [19][20] was subtracted to model transmission probability resulting from *intrapartum* and breastfeeding. For the Weibull hazard function (1), the cumulative distribution function is given by $F(t) = 1 - S(t) = 1 - \exp(-\lambda t^\alpha)$ from which we get the following linear equation in $\ln(t)$ (natural logarithm), $\ln[-\ln(1-F(t))] = \ln(\lambda) + \alpha \ln(t)$.

Here t is the age in months of a newborn, and $F(t)$ is the cumulative transmission probability at age t . Using data reporting cumulative transmission rates $F(t)$ [5][9][18], estimates for $\ln(\lambda)$ and for α were obtained using standard regression statistical routines in SAS.[21] The estimates for the NVP alone were obtained using SAS Proc Reg, while the estimates for the No Intervention parameters were obtained using SAS Proc Mixed. The latter estimates used two data sets [5][9], each with repeated measurements, necessitating the more complicated mixed model procedure. These estimates gave two base hazard functions – one for No Intervention and the other for NVP alone.

Hazard functions for Vaccine and/or HIVAB

To model the potential effect of interventions that include vaccine and/or HIVAB, the base hazards for No Intervention or NVP alone were modified by multiplicative factors which were chosen to reflect the assumed effects of vaccine and/or HIVAB. These factors, between 0 and 1, represent the proportional reduction in the hazard due to the additional intervention.

We define the term “immunity” to be $1-g$ where g is the time-varying multiplicative factor modifying the hazard. This is more intuitive than directly calculating g , since greater “immunity” corresponds to a greater reduction in transmission rates. By definition immunity must be between zero and one, with zero representing no effect and one representing no possibility of transmission. For 50% (or 0.5) immunity the hazard is halved. The reduction in incidence after 36 months (or any other time period) can be used to calculate the vaccine efficacy. Although these two measures are clearly related to each other, they are not equivalent.

A prime-boost vaccination strategy was used, in which the immunity induced by the first (priming) vaccination was further augmented by the 2nd and 3rd (boost) vaccinations. The vaccine induced immunity was assumed to increase proportional to the square root of time, reach its peak, and then to wane exponentially as a function of time. This behavior mimicked observed vaccine-induced immunogenicity for existing vaccines.[22]

An example of the immunity induced by 3 doses of vaccine (given at 0, 1, and 2 months) is illustrated in Figure 1. This curve corresponds to the following assumptions :

- 1) for the initial dose, peak immunity of 30% (=0.3) is achieved at two weeks
- 2) for the 2nd and 3rd doses, a 30% boost effect occurs after two weeks.

3) waning at 0.1% per month occurs following the each peak.

In the calculations, because the immunity is a function of time, its effect on the hazard was also time-varying.

The assumptions (Table 1) used in determining the immunity function were varied to be able to assess the sensitivity of our results. These included varying the immunity level achieved, the time to achieve peak immunity, the number of booster shots, the boost effect, and the waning rate.

Also given in Figure 1 is the assumed value for HIVAB immunity. The effect of HIVAB on the hazard was calculated as a multiplicative factor equal to 1-HIVAB immunity. The way these multiplicative effects on the base hazards was operationalized was through the calculation of four factors $g_1(t)$, $g_2(t)$, $g_3(t)$, and $g_4(t)$ corresponding to initial vaccine, 2nd dose, 3rd dose, and HIVAB. Administration of only 1 dose of HIVAB was used because of the anticipated high cost of HIVAB and the possibility of an immune response against HIVAB. Details and the precise construction of the $g_i(t)$ are given in the Appendix.

For this study we assume the population where the intervention is used is homogeneous with respect to HIV clade.

Assumptions for Vaccine and HIVAB parameter values

In order to evaluate the possible effects of each intervention that included the use of Vaccine and HIVAB, a wide range of parameter values was considered (Table 1). Vaccine parameters varied in this study included the initial immunity, the waning rate, the number of boosts, the effect of boosts, and the time to reach peak immunity. For HIVAB, the multiplicative factor $g_4(t)$ was calculated assuming 70% initial immunity and a waning rate of 50% per month (see Appendix). These assumptions for the effect of HIVAB reflect moderate initial immunity and incorporate the results from a study showing a half-life of one month. [23]

RESULTS

Parameter estimates of base hazard functions

The scale(λ) and shape(α) parameter values for the two base Weibull models were estimated as follows: $\hat{\lambda}_{No\ Intervention} = 0.151$ (95% CI: 0.052, 0.439), $\hat{\alpha}_{No\ Intervention} = 0.219$ (95% CI: 0.123, 0.316); $\hat{\lambda}_{NVP} = 0.035$ (95% CI: 0.026, 0.046), $\hat{\alpha}_{NVP} = 0.386$ (95% CI: 0.257, 0.517). The plot of the cumulative MTCT probabilities reported by studies [5],[9],[18] and cumulative MTCT probabilities calculated from the fitted Weibull model are shown in Figure 2, showing good fits for the Weibull model. Under No Intervention, the model estimated MTCT due to *intrapartum* and breast feeding transmission to be 26.2% and 28.2% at 24 and 36 months respectively. Under NVP alone, the model estimated MTCT to be 11.4% and 13.0% at 24 and 36 months respectively.

Illustration of risk reduction for Vaccine and/or HIVAB

How Vaccine and HIVAB altered the hazard rates when they were used in combination with/without NVP is shown in Figure 3. For the parameter values in Table 1, the hazard rates for all interventions were high at birth and declined over time. In Figure 3, consistent reduction in hazard rate was observed for the NVP+Vaccine intervention. The addition of HIVAB at birth further reduced the hazard rate since immune protective effects are immediately available.

Sensitivity analyses

In order to identify important vaccine factors in reducing MTCT, sensitivity analyses were done by varying the vaccine parameter values, as summarized in Table 1. The results are presented in Tables 2,3,4, and 5.

Effect of the number of Vaccine doses and initial immunity on MTCT

Table 2 shows the effect of varying the number of doses from one to three along with levels of initial immunity from 10% to 90%. The other parameter values were assumed to be the basic values listed in Table 1. The MTCT rates at 36 months showed up to 3% reduction when we changed from a 1-dose vaccine regimen to a 2-dose vaccine regimen in all interventions. The addition of a third dose at 2 months of age gave less noticeable reduction of MTCT especially as the initial immunity goes up. This can partly be explained by the high hazard rates at early age and the time needed to reach peak immunity for the vaccine.

Also in Table 2 we see the effect of varying the Initial immunity from 10% to 90% keeping the other basic vaccine parameter values fixed as listed in Table 1. For reference, recall the MTCT rate measured at 36 months of age in the No Intervention condition was 28.2% and was 13.0% in the NVP alone group. Depending on initial immunity, a 3 dose vaccine regimen alone reduced MTCT to between 10.9 and 21.9% and the addition of HIVAB to vaccine further reduced MTCT to between 4.8 and 13.8%. The addition of a 3-dose vaccine to NVP alone lowered MTCT to between 2.8 and 8.8% depending on the initial immunity. The addition of HIVAB to NVP+Vaccine intervention further reduced MTCT to between 1.6 and 6.7%. These results show that even an imperfect vaccine that generates initial immunity as low as 10% can reduce MTCT (to 8.8% when used with NVP, and to 6.7% when used with NVP and HIVAB) as long as the immunity is boosted by the second and third vaccine dose.

To facilitate interpretation of these results we have plotted 12 curves in Figure 4, which show MTCT at 36 months as a function of intervention (four sets of curves : Vaccine, HIVAB +Vaccine, NVP+Vaccine, NVP+HIVAB+Vaccine), initial immunity (horizontal axis), and number of doses (1,2,3).

Effects of other HIV Vaccine factors on MTCT

Waning rate—Table 3 shows the effect of a varying waning rate on MTCT. When the waning rate was increased from 0.01% per month to 0.5% per month, while holding other basic vaccine parameter values fixed as listed in Table 1, the increase in the 36 months MTCT was less than 1% in all interventions. These results show that the waning rate has little effect on 36 month MTCT for the waning ranges considered here.

Vaccine boost level—Table 4 shows the effect of varying vaccine boost level from 10% to 70%. Not surprisingly, a boost had the biggest effect when the initial immunity level was low. When the initial immunity was 50% in vaccine+NVP intervention, if the immunity could be boosted 50% with the subsequent doses, MTCT can still be reduced to 5.9% at 36 months of age. The addition of HIVAB to the same regimen will further reduce MTCT rate at 36 months of age to less than 4.3%.

Time to reach peak immunity—Table 5 shows the effect of varying the time to reach peak immunity from $\frac{1}{2}$ to 12 weeks and the initial immunity from 10% to 90% keeping the other basic vaccine parameter values fixed as listed in Table 1. The baseline Weibull hazard models show high risk of infection at early ages, implying that successful reduction in MTCT rates might be achieved by reducing early hazard rates. The surprising result here is that varying peak timing from 2 weeks to 12 weeks or from 2 weeks to $\frac{1}{2}$ week only changed MTCT by 0.1%~1.6% in Vaccine+NVP group and by 0.1%~0.9% in Vaccine+NVP+HIVAB group. For

example, 36 month MTCT was reduced from 7.7% to 7.5% using 3 doses of 30% initial immunity vaccine + NVP when the peak timing was reduced from 2 weeks to ½ week. The effect of varying peak timing in the Vaccine only group was more pronounced. Here, given high initial immunity ($\geq 50\%$), increasing in peak timing substantially increases MTCT rates at 36 months. This illustrates the need for other protection (NVP and HIVAB) during the first few weeks following birth. (The slight departure from monotonicity observed in Table 5 at 6 weeks peak timing is due to crossing hazard functions.)

DISCUSSION

WHO recommends exclusive breastfeeding for six months[24] since breastfeeding has been proven to reduce infant mortality and morbidity, despite increased risks of MTCT for infants born to HIV infected women.[25] In resource poor countries, breastfeeding is critical for infant survival and alternative feeding is not safe, not feasible, and culturally unacceptable. Furthermore, Kuhn et al.[26] report that abrupt cessation of breastfeeding by HIV infected women did not improve HIV-free survival among children born to HIV infected mothers and was harmful to HIV infected infants. New interventions that include extended use of NVP report reduction in rates of MTCT through breastfeeding.[27][28] However, continuing concerns regarding NVP resistance argue against this intervention.[29] An HIV vaccine, even one less than 100% effective, could be part of the best solution to preventing MTCT of HIV during the breastfeeding period in places where formula feeding is not possible. While vaccines are being developed, it is important to be able to plan interventions and make predictions of the effects of interventions that include an imperfect vaccine.

In this study we quantified the effects of HIV vaccine characteristics and HIVAB on MTCT of HIV from *intrapartum* and breastfeeding by building a flexible hazard model. The model used in this study can be modified by adding different interventions as they become available. Using this adaptable model, we evaluated different interventions that consisted of combinations of vaccine, HIVAB, and NVP therapies.

In estimating the parameters of the hazard function for No Intervention and NVP alone intervention, HIV rates reported from several long-term mother infant intervention studies[5][9][18][19][20] in Africa were used. For interventions that include the use of vaccine, the models accommodated different levels of protective immunity, waning immunity, boost effect (number and level), and timing of vaccinations and administration of HIVAB. The effects of the different intervention strategies were evaluated using the predicted cumulative transmission of HIV at 36 months of age from both *intrapartum* and breastfeeding periods.

With no HIV vaccine currently available, in order to cover the wide uncertainty in the vaccine parameters, we did extensive sensitivity analyses including extreme values of the parameters. The sensitivity analyses revealed which vaccine characteristics had the biggest effect on the results and provided the basis for recommendations for its use in combination with other therapies when it becomes available. Important vaccine characteristics in reducing MTCT of HIV during *intrapartum* and breastfeeding period were initial immunity and boost effect. One significant finding is that any HIV vaccine developed will need to induce an immune response quickly after it is administered if it is used alone. On the other hand, the waning rate was shown to have a relatively small effect on MTCT of HIV, especially when the initial immunity produced is high or boosting is well achieved.

Time to reach peak immunity had a small effect on MTCT of HIV when vaccine was used with NVP or with NVP+HIVAB.

Our model suggests that even an imperfect vaccine can greatly reduce cumulative MTCT at 36 months when used with NVP and HIVAB, as compared to single therapy interventions. In

the vaccine only intervention, the 36 months MTCT was always greater than 10% regardless of the initial immunity (10-90%) and the model shows that this is due to the very high risk of MTCT at birth. This suggests that while a vaccine is inducing protective immunity, the use of NVP or HIVAB is recommended for immediate protection at birth. Based on these results, we suggest a dual protection plan for the baby: first, treat babies with single dose of NVP with HIVAB at birth to reduce the high risk of transmission at birth, and second, vaccinate babies to provide long-term protection during the breastfeeding period. Our model showed that an intervention that uses three doses of vaccine with 30% initial immunity and 30% boost with subsequent doses (giving rise to maximum immunity less than 66% with 3 doses; see Figure 1) could reduce MTCT to 7.7% when used with NVP and to 5.9% when used with NVP and HIVAB. This latter figure drops to 4.3% using a vaccine with 50% initial immunity and 50% boost; to 3.1% with 70% initial immunity and 70% boost.

The results show how the need for the second and in particular the third dose decreases as the initial immunity goes up in all interventions. In all interventions, the additional reduction of MTCT by the third dose of vaccine was less than 1.1% when the initial immunity was 30% or higher. The general recommendation based on this research is that there is no need for the third dose of vaccine if the initial immunity is not less than 30%.

An important result from our study is that even with a highly effective vaccine, our model shows that NVP and/or HIVAB still should be used to protect the child shortly after birth until the vaccine generates full immunity. For example, a vaccine with 90% immunity induced at 2 weeks of age still had MTCT of 10.9% at 36 months (Table 2), but combining this vaccine with NVP and HIVAB drops the rate to 1.6%. This result has major public policy implications in implementing a vaccine regimen to reduce MTCT of HIV.

Depending on the socioeconomic situation of resource limited countries, different interventions can be selected using the results of this study. A useful finding that would be beneficial to health policy planners in these countries is that an inexpensive intervention that consists of two doses of HIV vaccine and NVP was more effective in reducing 36 month MTCT than the more costly intervention consisting of three dose vaccine and HIVAB regardless of initial immunity. A onetime administration of vaccine and NVP at time of birth could reduce 36 month MTCT due to *intrapartum* and breastfeeding to less than 8% as long as the immunity induced by the primary dose is not less than 50%. In places where stigma surrounding HIV infection is high, the HIV vaccination schedule can be integrated into the infant immunization schedules and the second dose of HIV vaccine can be given along with standard 2 month immunizations and this will further reduce 36 month MTCT to less than 6.8%. Such a plan will not attract unnecessary attention to the breastfeeding HIV infected mother and her baby.

This study modeled MTCT of HIV up to 3 years of life after birth but if our assumption of slow waning immunity is correct, a long-term protective effect of HIV vaccine at adolescent age is expected. Furthermore, the model developed here is flexible enough to be expanded to model the long-term effect of vaccine boost in preventing sexual transmission of HIV when these are given to children before they become adults.

Limitations

In this study, we modeled hazard functions for different interventions using Weibull based hazards for No Intervention and NVP alone. If the hazard of MTCT of HIV is not well approximated by a Weibull distribution, the estimates of MTCT probabilities for the base interventions (No Intervention and NVP alone intervention) may result in inaccurate estimates of MTCT probabilities for the interventions that use vaccine and HIVAB. However, the relative benefits of combining NVP and HIVAB with vaccine interventions will still be valid and the policy implications will still be correct. The model assumes similar waning of immunity as in

other childhood immunizations such as Hepatitis B or Cholera. If the waning rate of HIV vaccine is much higher than the values used in our sensitivity analysis, the estimates might not be reliable. However, for the waning rates that we used in this study, (which include much higher rates than observed in existing vaccines) we saw no serious effect of waning on the results. Although we made an assumption of homogeneous clade distribution in the study population, this is not a severe limitation on the applicability of the model, since we have provided extensive sensitivity analysis with wide ranges for the parameters. In the situation of a population which consists of a mixture of different clades, the model can be applied separately to each subpopulation and then the results can be combined. Similarly the model can accommodate two different vaccines with different clade effectiveness. We assumed that immunity generated by multiple doses of vaccine and HIVAB are independent and it is possible that there may be an interaction between these. We did not do sensitivity analysis on HIVAB but we believe the effect of HIVAB is short and temporary and further the assumed parameter values for HIVAB were based on best available evidence.[23]

The modeling done here should be followed by cost effectiveness analysis which will reveal how economically practical applying these interventions in resource poor countries will be.

Conclusion

In this paper, we built a model that quantified the effectiveness of different interventions that included three therapies and we performed extensive sensitivity analysis showing that the implications of the modeling are quite robust. While current vaccine research has been discouraging and a perfect vaccine might not be possible, this study shows that even a partially effective vaccine can greatly reduce the MTCT of HIV during breastfeeding period in resource poor countries. Another important implication from our model is that combination therapy should always be used regardless of the level of the immunity induced by a vaccine. These quantified results on various vaccine regimens will be a useful guideline for determining which of several different interventions to use with such a vaccine in different social and economic contexts. Currently there are numerous ongoing studies assessing the effect of the repeated doses of NVP in preventing MTCT due to breastfeeding, and the effect of administering antiretroviral therapy to the mother to reduce *in utero* and *intrapartum* MTCT. As these new interventions develop and new data become available, they can be incorporated to this adaptable model and it will be able to generate quantified results for a given intervention. However, we strongly believe the use of a vaccine in combination therapy that includes a single dose of NVP and HIVAB has the best potential to reduce MTCT and is a therapy that can be easily administered without potential consequences of drug resistance in long term antiretroviral therapy interventions while infants benefit from their mothers' breast milk.

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Appendix

Hazard Model for the One Dose Vaccine Intervention

When one vaccine dose is given to a newborn at birth the immunity is assumed to be generated proportional to the square root of time, reach a peak, and then wane exponentially at the rate R per month. (Figure 1) This immunity is written as a piecewise continuous function $f(t)$ defined on two intervals:

$$f(t) = \begin{cases} a\sqrt{t} & \text{for } 0 \leq t \leq t_{p1} \\ a\sqrt{t_{p1}}(1-R)^{t-t_{p1}} & \text{for } t > t_{p1} \end{cases}$$

where t_{p1} is the time at which the peak is reached, and $a\sqrt{t_{p1}}$ = peak immunity level.

The effect of the vaccine on the base hazard is modeled as a multiplicative factor $g_1(t)=1-f(t)$. Using an indicator function $I(\cdot)$, where $I(\text{true})=1$ and $I(\text{false})=0$, $f(t)$ can be written as a sum of two parts:

$$f(t) = a\sqrt{t} I(0 \leq t \leq t_{p1}) + a\sqrt{t_{p1}}(1-R)^{t-t_{p1}} I(t > t_{p1})$$

when it is noted that $0 \leq g_1(t) \leq 1$ and $g_1(t)=1$ corresponds to no immunity (unchanged hazard). Thus the resulting hazard function, modified for a single vaccine dose, is $h(t|1 \text{ dose vaccine}) = h(t|no \text{ vaccine}) \times g_1(t)$.

Hazard Model for the Two and Three Dose Vaccine Intervention

The immunity generated by the first (priming) vaccination is assumed to be further augmented by the 2nd and 3rd vaccinations (boosts). The immunity generated by the subsequent doses follows a similar pattern of increase, reaching its peak, and waning exponentially as a function of time. The effect on the hazards, as a function of time, is represented by multiplicative factors $g_2(t)$ and $g_3(t)$ (Appendix Table 6) and is assumed to independently modify the base hazard function. The modified Weibull Hazard models for the two dose and three dose vaccine interventions are given in Appendix Table 6.

Hazard Model for the Vaccine + HIVAB Intervention

The immunity induced by HIVAB is assumed to be highest, equal to IM_{HIVAB} , at the time of administration and to wane at the rate of R_{HIVAB} per month (Figure 1). The effect of HIVAB on the hazard is represented by a multiplicative factor

$$g_4(t) = 1 - \left[IM_{HIVAB}(1 - R_{HIVAB})^t \right].$$

Table 6

Hazard functions for the different Interventions. Weibull base hazards separately fit to available data [5][9][18][19][20] are used for the *No Intervention* and for the *NVP Alone*. Multiplicative factors ($g_1(t), g_2(t), g_3(t), g_4(t)$) (all between 0 and 1) modify the base hazards to model the combined effects of *Vaccine* and of *Vaccine + HIVAB*.

Interventions	Hazard Function
<i>No Intervention</i> or <i>NVP Alone</i>	$h(t no \text{ vaccine}) = \lambda \alpha (t^{\alpha-1})^*$
<i>Vaccine</i> or <i>Vaccine + NVP</i>	One dose: $h(t 1 \text{ dose vaccine}) = h(t no \text{ vaccine}) \times g_1(t)$ Two dose: $h(t 2 \text{ dose vaccine}) = h(t no \text{ vaccine}) \times g_1(t) \times g_2(t)$ Three dose: $h(t 3 \text{ dose vaccine}) = h(t no \text{ vaccine}) \times g_1(t) \times g_2(t) \times g_3(t)$
<i>Vaccine + HIVAB</i>	One dose:

Interventions	Hazard Function
or Vaccine + HIVAB + NVP	$h(t 1 \text{ dose vaccine} + \text{HIVAB}) = h(t \text{no vaccine}) \times g_1(t) \times g_4(t)$ Two dose: $h(t 2 \text{ dose vaccine} + \text{HIVAB}) = h(t \text{no vaccine}) \times g_1(t) \times g_2(t) \times g_4(t)$ Three dose: $h(t 3 \text{ dose vaccine} + \text{HIVAB}) = h(t \text{no vaccine}) \times g_1(t) \times g_2(t) \times g_3(t) \times g_4(t)$

$$g_1(t) = 1 - \left[I(t_1 \leq t \leq t_{p1}) \{a \sqrt{t}\} + I(t > t_{p1}) \{a \sqrt{t_{p1}}(1 - R)^{t-t_{p1}}\} \right]$$

$$g_2(t) = 1 - \left[I(t_2 \leq t \leq t_{p2}) \{b \sqrt{t} + c\} + I(t > t_{p2}) \{(b \sqrt{t_{p2}} + c) \times (1 - R)^{t-t_{p2}}\} \right]$$

$$g_3(t) = 1 - \left[I(t_3 \leq t \leq t_{p3}) \{d \sqrt{t} + e\} + I(t > t_{p3}) \{(d \sqrt{t_{p3}} + e) \times (1 - R)^{t-t_{p3}}\} \right]$$

$$g_4(t) = 1 - [IM_{HIVAB}(1 - R_{HIVAB})^t]$$

t : Age in months of a newborn

t_i : Time i^{th} vaccine dose is given ($t_1 = 0$)

t_{pi} : Time peak immunity for i^{th} dose is reached

$a \sqrt{t_{p1}}$: Initial peak immunity

$$b = \frac{(1 - a \sqrt{t_{p1}}) \times \text{Boost}}{\sqrt{t_{p2}} - \sqrt{t_2}}$$

$$c = -b \sqrt{t_2}$$

$$d = \frac{[1 - a \sqrt{t_{p1}} - (1 - a \sqrt{t_{p1}}) \times \text{Boost}] \times \text{Boost}}{\sqrt{t_{p3}} - \sqrt{t_3}}$$

$$e = -d \sqrt{t_3}$$

IM_{HIVAB} : Immunity level of HIVAB, between 0(0%) and 1(100%)

R_{HIVAB} : Waning rate of HIVAB per month

R : Waning rate of vaccine induced immunity per month

Boost : Immunity generated by boosts (10-70%)

*

The estimated values of λ and α are different for the hazard functions under *No Intervention* and *NVP Alone*.

References

- McIntyre J. Prevention of mother-to-child transmission of HIV: treatment options. *Expert Rev Anti Infect Ther* 2005;3(6):971–80. [PubMed: 16307509]
- Ryder RW, Nsa W, Hassig SE, Behets F, Rayfield M, Ekungola B, et al. Perinatal transmission of the human immunodeficiency virus type 1 to infants of seropositive women in Zaire. *N Engl J Med* 1989;320:1637–42. [PubMed: 2786145]
- Adjorilo-Johnson G, De Cock KM, Ekpini E, Vetter KM, Sibailly T, Brattegarrrd K, et al. Prospective comparisons of mother-to-child transmission of HIV-1 and HIV-2 in Abidjan, Ivory Coast. *JAMA* 1994;272:462–6. [PubMed: 8040982]
- Leroy V, Newell ML, Dabis F, Peckham C, Van de Perre P, Bulterys M, et al. International multicenter pooled analysis of late postnatal mother-to-child transmission of HIV-1 infection. Ghent international Working group on mother-to-Child Transmission of HIV. *Lancet* 1998;352:597–600. [PubMed: 9746019]
- Nduart R, John G, Mbori-Ngacha D, Richardson B, Overbaugh J, Mwatha A, et al. Effect of breastfeeding and formula feeding on transmission of HIV-1: a randomized clinical trial. *JAMA* 2000;283:1167–74. [PubMed: 10703779]

6. Dabis F, Newell ML, Fransen L, Saba J, Lepage P, Leroy V, et al. Prevention of mother-to-child transmission of HIV in developing countries: recommendations for practice. *Health Policy Plan* 2000;15(1):34–42. [PubMed: 10731233]
7. Center for Infectious Diseases. Giving Antiretroviral Drugs to Infants or Mothers Reduces Transmission of HIV Through Breast Milk. University of North Carolina at Chapel Hill School of Medicine; Jul. 2009 URL: <http://www.med.unc.edu/infdis/news/giving-antiretroviral-drugs-to-infants-or-mothers-reduces-transmission-of-hiv-through-breast-milk>
8. UNAIDS. Questions & Answers: Basic facts about the HIV epidemic and its impact. Jul. 2004 URL: http://www.cwru.edu/med/epidbio/mphp439/HIV_Mother_Child.htm
9. Coutoudis A, Rollins N. Breast-feeding and HIV transmission: the jury is still out. *J Pediatr Gastroenterol Nutr* 2003;26(4):434–442. [PubMed: 12658031]
10. UNAIDS. Questions and Answers. Mother to child transmission (MTCT) of HIV. Background Briefs. Aug. 1999 URL: http://www.unicef.org/programme/hiv/focus/mtct/mtct_ref.htm
11. Coovadia, et al. Mother-to-child transmission of HIV-1 infection during exclusive breastfeeding in the first 6 months of life: an intervention cohort study. *The Lancet* March 31;2007 369(9567)
12. Klein, John O.; Melvin, L.; Moeschberger, M. *Survival Analysis, Techniques for Censored and Truncated Data*. Springer; New York: 1997.
13. Rousseau CM, Nduati RW, Richardson BA, Steele MA, John-Stewart GC, Mbori-Ngacha DA, et al. Longitudinal analysis of human Immunodeficiency virus type 1 RNA in breast milk and of its relationship to infant infection and maternal disease. *J Infect Dis* 2003;187:741–747. [PubMed: 12599047]
14. Miotti PG, Taha TE, Kumwenda NI, Broadhead R, Mtimavalye LA, Van der Hoeven L, et al. HIV transmission through breast feeding: a study in Malawi. *JAMA* 1999;282:744–9. [PubMed: 10463709]
15. Moodley, D. The Saint Trial: Nevirapine (NVP) versus Zidovudine (ZDV) + Lamivudine (3TC) in prevention of peripartum HIV transmission; XIII International AIDS Conference; Durban, South Africa. 2000;16; 2000
16. O'Sullivan MJ, Boyer PJ, Scott GB, Parks WP, Weller S, Blum MR, et al. The pharmacokinetics and safety of Zidovudine in the third trimester of pregnancy for women infected with human immunodeficiency virus and their infants: phase I acquired immunodeficiency syndrome clinical trials group study (Protocol 082). Zidovudine Collaborative Working Group. *Am J Obstet Gynecol* 1993;158:1510–6. [PubMed: 8098905]
17. Rousseau CM, Nduati RW, Richardson BA, John-Stewart GC, Mbori-Ngacha DA, Kreiss JK, et al. Association of levels of HIV-1-infected breast milk cells and risk of mother-to-child transmission. *J Infect Dis* 2004;190(10):1880–8. [PubMed: 15499546]
18. Jackson JB, Musoke P, Fleming T, Guay LA, Bagenda D, Allen M, et al. *Intrapartum* and neonatal single-dose Nevirapine compared with Zidovudine for prevention of mother to child transmission of HIV-1 in Kampala, Uganda: 18-month follow-up of the HIVNET 012 randomized trial. *Lancet* 2003;362:859–868. [PubMed: 13678973]
19. Moodley, D.; McIntyre, J.; Team, TSS. Evaluation of safety and efficacy of two simple regimens for the prevention of mother to child transmission (MTCT) of HIV infection; Nevirapine vs. Lamivudine and Zidovudine used in a randomized clinical trial (the SAINT Study); XIII International AIDS Conference; Durban, South Africa. 2000; 2000
20. Deville J, Bryson YJ. Perinatal Transmission of HIV: Recognition and Treatment Interventions. *Curr Infect Dis Rep* 2001;3(4):388–396. [PubMed: 11470031]
21. SAS Statistical Analysis System. Ver 9.1.3. SAS Institute Inc. ®; USA:
22. Reeves, WG. *Lecture Notes on Immunology*. Blackwell Scientific Publications; 1989. © P7
23. Guay LA, Mukosa P, Hom DL, Nakabiito C, Bagenda D, Fletcher CV, et al. Phase I/II trial of HIV-1 hyperimmune globulin for the prevention of HIV-1 vertical transmission in Uganda. *AIDS* 2002;16:1391–1400. [PubMed: 12131216]
24. World Health Organization. WHI HIV and infant feeding technical consultation – consensus statement. Geneva, Switzerland: 2007. URL:statement

http://www.who.int/child_adolescent_health/documents/pdfs/who_hiv_infant_feeding_technical_consultation.pdf

25. The Breastfeeding and HIV International Transmission Study Group. Late postnatal transmission of HIV in breast-fed children: an independent patient data meta analysis. *J Infect Dis* 2004;189:2154–66. [PubMed: 15181561]
26. Kuhn L, Aldrovandi GM, Sinkala M, Kankasa C, Semrau K, Mwiya M, et al. Effects of Early, Abrupt Weaning on HIV-free Survival of Children in Zambia. *N Engl J Med* 2008;359(2):130–41. [PubMed: 18525036]
27. Kumwenda NI, Hoover DR, Mofenson LM, Thigpen MC, Kafulafula G, Li Q, et al. Extended Antiretroviral Prophylaxis to Reduce Breast-milk HIV-1 Transmission. *N Engl J Med* 2008;359.DOI: 10.1056/NEJMoa0801941
28. SWEN Study Group. Extended-dose nevirapine to 6 weeks of age for infants to prevent HIV transmission via breast feeding in Ethiopia, India, and Uganda: an analysis of three randomized controlled trials. *Lancet* 2008;372:300–313. [PubMed: 18657709]
29. Church JD, Omer SB, Guay LA, Huang W, Lidstrom H, Musoka P, et al. Analysis of Nevirapine (NVP) Resistance in Ugandan Infants Who Were HIV Infected Despite Receiving Single-Dose (SD) NVP versus SD NVP Plus Daily NVP Up to 6 weeks of Age to Prevent HIV Vertical Transmission. *J Infect Dis* 2008;198(10):1075–1082. [PubMed: 18684096]

Figure 1.

Kinetics of immunity generated by 3-dose HIV *Vaccine* and *HIVAB*. The immunity is assumed to be generated proportional to square root of time, reach its peak, and then start to wane exponentially. The immunity generated after the first (priming) vaccination is further augmented by the 2nd and 3rd vaccinations (boosts).

Figure 2.

Estimated and reported cumulative MTCT[5][9][18][19][20] probabilities of HIV from *intrapartum* and breast Milk. The estimated cumulative MTCTs were obtained by fitting Weibull hazard model to the reported cumulative MTCTs.

Note: These probabilities do not include *intrauterine* transmission probability of 7% [19], [20].

Figure 3.

Altered hazard rates by *Vaccine*(A) and *HIVAB*(B) on the *No Intervention* and the *NVP alone intervention*. Altered hazard rates were obtained by multiplying immune factors and *HIVAB* factors to the estimated base hazards rates for *No Intervention* and *NVP alone Intervention*.

Figure 4.

The cumulative MTCT rates at 36 months from *Intrapartum* and breastfeeding under different intervention scenarios plotted as a function of initial immunity. Within each scenario, 3 curves are shown (for 1,2, and 3 doses). For reference, the model-estimated cumulative MTCT rates at 36 months under *No Intervention* and *NVP* alone are 28.2% and 13.0% respectively.

Table 1

Assumptions for Vaccine and HIVAB Parameter values used in the model to predict 36 month cumulative MTCT of HIV.

Parameters	Vaccine Values (Range Used in Sensitivity Analysis)	HIVAB Values
	0, 1, 2 Months of Age	At Birth
Age given		
Doses	3 (1~3)	1
Initial peak immunity (%)	30 (10~90)	70
Waning rate (%) per month	0.1 (0.01~0.5)	50
Boosting (%)	30 (10~70)	-
Time to reach peak immunity (weeks)	2 (0.5~12)	-

Table 2

The cumulative MTCT rates at 36 months from *Intrapartum* and breastfeeding under different intervention scenarios. The model estimated cumulative MTCT rates at 36 months under *No Intervention* and *NVP* alone are 28.2% and 13.0% respectively.

Im* (%)	Vaccine (No. Doses)			HIVAB + Vaccine (No. Doses)			NVP + Vaccine (No. Doses)			NVP+HIVAB+ Vaccine (No. Doses)		
	1	2	3	1	2	3	1	2	3	1	2	3
90	11.0	10.9	10.9	4.9	4.8	4.8	2.8	2.8	2.8	1.7	1.7	1.6
70	15.1	14.7	14.5	8.6	8.1	7.9	5.2	4.9	4.8	3.8	3.5	3.4
50	19.7	18.0	17.5	12.1	11.0	10.4	7.5	6.8	6.4	5.8	5.2	4.8
30	22.9	20.9	19.9	15.4	13.4	12.3	9.7	8.4	7.7	7.9	6.6	5.9
10	26.5	23.3	21.9	18.7	15.4	13.8	12.0	9.8	8.8	9.9	7.7	6.7

Im* : Initial peak immunity assumed

Table 3

The cumulative MTCT rates at 36 months from *intrapartum* and breastfeeding for interventions that include *Vaccine*, *NVP*, and *HIVAB* when vaccine immunity waning rate is varied from 0.01% to 0.5%.

Waning Rate per Month (%)	Vaccine Initial Immunity			HIVAB + Vaccine Initial Immunity		
	90%	70%	50%	30%	10%	0%
0.01	10.7	14.4	17.4	19.8	21.8	4.7
0.05	10.8	14.4	17.4	19.9	21.9	4.7
0.10	10.9	14.5	17.5	19.9	21.9	4.8
0.50	11.5	14.9	17.8	20.1	22.1	5.4
Waning Rate per Month (%)	NVP + Vaccine Initial Immunity			NVP + HIVAB + Vaccine Initial Immunity		
	90%	70%	50%	30%	10%	0%
0.01	2.7	4.7	6.4	7.7	8.7	1.6
0.05	2.7	4.7	6.4	7.7	8.7	1.6
0.10	2.8	4.8	6.4	7.7	8.8	1.6
0.50	3.2	5.1	6.7	7.9	8.9	2.1

The cumulative MTCT rates at 36 months from *intrapartum* and breastfeeding for interventions that include *Vaccine*, *NVP*, and *HIVAB* when the vaccine boost level is varied from 10~70%.

Table 4

Amount Boosted (%)	Vaccine					HIVAB + Vaccine				
	Initial Immunity					Initial Immunity				
	90%	70%	50%	30%	10%	90%	70%	50%	30%	10%
70	10.8	14.0	16.2	17.5	18.2	4.7	7.4	9.0	9.8	9.9
50	10.8	14.2	16.7	18.6	19.8	4.8	7.6	9.6	10.9	11.7
30	10.9	14.5	17.5	19.9	21.9	4.8	7.9	10.4	12.3	13.8
10	10.9	14.9	18.5	21.7	24.7	4.9	8.3	11.4	14.2	16.8
Amount Boosted (%)	NVP + Vaccine					NVP + HIVAB + Vaccine				
	Initial Immunity					Initial Immunity				
	90%	70%	50%	30%	10%	90%	70%	50%	30%	10%
70	2.7	4.4	5.6	6.1	6.2	1.6	3.1	3.9	4.2	4.2
50	2.8	4.6	5.9	6.8	7.4	1.6	3.2	4.3	5.0	5.3
30	2.8	4.8	6.4	7.7	8.8	1.6	3.4	4.8	5.9	6.7
10	2.8	5.0	7.1	9.0	10.7	1.7	3.7	5.5	7.1	8.6

Table 5

The cumulative MTCT rates at 36 months from *intrapartum* and breastfeeding for interventions that include *Vaccine*, *NVP*, and *HIVAB* when time to reach peak immunity was varied from 0.5 ~ 12 weeks.

Peak Timing (Weeks)	Vaccine						HIVAB + Vaccine					
	Initial			Immun			Initial			Immun		
	90%	70%	50%	30%	10%	0%	90%	70%	50%	30%	10%	0%
0.5	9.0	13.1	16.4	19.3	21.6	4.1	7.3	10.0	12.0	13.6		
1	9.9	13.7	16.9	19.5	21.7	4.4	7.6	10.1	12.2	13.7		
2	10.9	14.5	17.5	19.9	21.9	4.8	7.9	10.4	12.3	13.8		
4	12.2	15.7	18.6	21.0	22.8	5.5	8.6	11.2	13.1	14.6		
6	12.8	16.0	18.5	20.6	22.3	5.8	8.6	10.9	12.8	14.1		
10	13.9	16.8	19.2	21.1	22.6	6.4	9.1	11.3	13.1	14.4		
12	14.9	17.6	19.8	21.5	23.0	7.2	9.7	11.8	13.4	14.7		
Peak Timing (Weeks)	NVP + Vaccine						NVP + HIVAB + Vaccine					
	Initial			Immun			Initial			Immun		
	90%	70%	50%	30%	10%	0%	90%	70%	50%	30%	10%	0%
0.5	2.2	4.4	6.1	7.5	8.6	1.5	3.2	4.7	5.8	6.6		
1	2.5	4.5	6.2	7.6	8.7	1.5	3.3	4.7	5.8	6.6		
2	2.8	4.8	6.4	7.7	8.8	1.6	3.4	4.8	5.9	6.7		
4	3.5	5.3	6.9	8.2	9.2	1.9	3.7	5.1	6.3	7.1		
6	3.5	5.3	6.8	8.0	9.0	2.0	3.6	5.0	6.0	6.8		
10	3.9	5.7	7.1	8.2	9.1	2.2	3.9	5.2	6.2	6.9		
12	4.4	6.0	7.4	8.5	9.3	2.6	4.1	5.4	6.4	7.1		