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Universal nevirapine upon presentation in labor to prevent mother-to-child HIV transmission in high prevalence settings

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Abstract

Objective—To assess the uptake of and adherence to nevirapine to prevent mother-to-child HIV transmission among women of unknown HIV serostatus presenting in labor. We also assessed preliminary efficacy of the approach.

Design—Women of unknown HIV serostatus presenting in labor were offered single-dose nevirapine in a prospective cohort study. Two additional contemporaneous comparison populations were also studied.

Methods—We measured uptake by counting the number of women that accepted enrollment when offered. We measured adherence with cord blood nevirapine assay. We measured preliminary efficacy with HIV DNA polymerase chain reaction of infant blood spots at 4–6 weeks of life.

Results—Of 1591 women approached in labor, 634 (40%) took up the intervention and received nevirapine, of whom 185 (29%) were HIV infected. Of 179 cord blood specimens from HIV-exposed infants that could be evaluated, 178 (99.4%) had nevirapine detected. This was higher than the 73 of 98 (74%) adherence rate observed in a comparison cohort in which women self-administered nevirapine before presenting to the labor ward ($P < 0.001$). Of 145 available infant specimens, 17 (11.7%) showed evidence of infection at 4–6 weeks, compared with 12 of 60 (20%) infants born immediately prior to study commencement whose HIV-infected mothers did not receive nevirapine ($P < 0.05$).

Conclusions—Nevirapine without HIV testing upon presentation in labor was accepted by two-fifths of women. Because therapy is directly observed, adherence is nearly perfect. Labor ward dosing to enhance nevirapine coverage should be considered as an adjunct to antenatal nevirapine administration for prevention of mother-to-child transmission of HIV.

Keywords

HIV; AIDS; perinatal; mother-to-child; nevirapine; universal; voluntary counseling and testing; directly observed therapy; adherence; Zambia

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Introduction

Despite the encouraging results of recent clinical trials, perinatally acquired HIV/AIDS remains a major public health emergency. In recognition of this fact, a United Nations General Assembly Special Session (UNGASS) on HIV/AIDS has set the ambitious goals of a 20% worldwide reduction in the number of perinatally infected children by 2005 and a 50% reduction by 2010 [1]. Given that single dose intra-partum and neonatal nevirapine (NVP) – the most effective and easily administered intervention widely available today – reduces the risk of transmission by only 41% in a breast-feeding population [2], reaching even the 20% reduction goal will involve delivering NVP or other short-course antiretroviral (ARV) regimens to at least half of the HIV-infected pregnant women in the world.

Thus, it is important that as prevention of mother-to-child transmission (PMTCT) programs are implemented, public health officials focus not only on geographic dispersion, but also on maximizing the proportion of HIV-infected women that correctly ingest a prophylactic ARV medication. Evolving evidence indicates that a number of barriers to coverage exist, even in systems where PMTCT programs are in place and performing reasonably well [3,4]. Despite the presence of a PMTCT program, all antenatal women are not always offered participation; if offered they may not accept HIV testing; if tested, they may not receive their result; if found to be seropositive, they may not accept the NVP tablet to take home for ingestion at labor onset. There is even evidence to suggest that as many as one in four women who successfully negotiate this process of being identified as HIV infected and issued a NVP tablet for self-administration at labor onset may not actually ingest their tablet [5].

In addition, there is argument in the economic literature that a program of NVP distribution without HIV testing could be considerably cheaper to administer and thus allow some health care systems to deliver a lifesaving intervention to a larger proportion of their population [6–8]. In light of the economic data, as well as the myriad programmatic barriers to delivery of test-based PMTCT interventions, we studied a novel strategy of offering NVP to women of unknown HIV serostatus, as they presented in labor.

Methods

In a concurrent protocol linked to a previously-reported clinical trial comparing NVP implementation strategies based in antenatal care [5], we approached women as they presented in labor at two high-volume delivery clinics in Lusaka, Zambia from September 2000 to May 2001. The study preceded the advent of widespread availability of NVP-based PMTCT services in the Lusaka District [4]. Women of unknown HIV serostatus and without complications that mandated transfer to the referral hospital were eligible. We did not exclude women who had not received antenatal care, but we did exclude women who had refused enrollment in the antenatal protocol [5]. After providing written informed consent, women were administered a directly-observed oral dose of 200 mg NVP by a study midwife. Infants were dosed with NVP syrup at discharge from the clinic. Women were offered HIV counseling and testing post-partum and at their subsequent postnatal visits.

We collected maternal serum in labor and fetal cord blood at delivery on all participants. Maternal HIV status was assessed with a serial rapid antibody test algorithm, previously validated in our setting, using Capillus (Cambridge Biotechnology, Galway, Ireland) and Determine (Abbott Laboratories, Abbott Park, Illinois, USA) kits [4]. A CD4+ lymphocyte count was estimated with enzyme-linked immunoassay performed on lysed whole blood (TRAx CD4; Innogenetics, Atlanta, Georgia, USA). As the study's primary aim was to measure uptake of and adherence to NVP at labor among women of unknown HIV serostatus, we did

not *require* infant diagnosis in order to participate. In those infants whose mothers wished for them to be tested for HIV post-partum, we collected blood spots at 1 day and 4–6 weeks of life. Infant HIV infection was diagnosed with HIV DNA polymerase chain reaction (PCR) of peripheral blood mononuclear cells from whole blood collected on filter paper. Each PCR specimen was subjected to at least two independent amplifications; we did not confirm the diagnosis with a second specimen. We screened for syphilis with a single, non-treponemal test (RPR Immunotrep; Omega Diagnostics, Alloa, Scotland). Cord blood NVP concentration was determined with high performance liquid chromatography (HPLC; Microsorb MV C8, 4.6 × 250 mm; 5 μm; Varian, Inc., Palo Alto, California, USA). This assay is capable of measuring concentrations in the range of 25–10 000 ng drug/ml plasma [9].

Comparison cohorts

There were two cohorts available for comparison of outcomes. The NVP-treated clinical trial cohort derives from a previously-reported, concurrent clinical trial [5] that compared two strategies for NVP delivery in antenatal care (thus differing from this labor-ward-based approach). That trial compared a 'targeted' strategy, in which women were offered HIV testing in antenatal care followed by NVP if seropositive to a 'universal' approach, in which NVP was offered to all women in the population, without HIV testing. It found that women were somewhat more willing to participate in a universal strategy than a targeted strategy (71 versus 64%; $P < 0.01$), but that adherence to the single-dose intervention (determined by cord blood HPLC assay for NVP) was considerably better with the targeted strategy, in which women knew their HIV status (74 versus 61%; $P < 0.05$) [5].

A second, untreated observational cohort was also available. This group of mother–infant pairs were approached as they came for their 4–6 week follow-up visit at the same study facilities [10]. They participated in a post-partum voluntary counselling and testing (VCT) and infant diagnosis effort that was conducted just as the larger trial [5] commenced. Thus, these participants were born just prior to the beginning of the study, and had not had the chance to receive any PMTCT intervention. Of the 222 mothers who were assessed, 60 (27%) were HIV seropositive. Of the 60 HIV-exposed babies, 12 [20%; 95% confidence interval (CI), 12–32%] were infected at 4–6 weeks of life.

All analyses were performed with SAS System release 8.01 for Windows (SAS Institute, Cary, North Carolina, USA). This study was approved by the University of Zambia Research Ethics Committee and by the University of Alabama at Birmingham Institutional Review Board.

Results

Between September 2000 and May 2001, we approached 1591 women for enrollment as they presented in labor and 634 (40%) accepted. Selected demographic and biomedical characteristics of the cohort are presented in Table 1. There was a significant discrepancy in the uptake rate between clinic 'A', where 344 of 1022 (34%) women accepted and clinic 'B' where 290 of 569 (51%) women accepted ($P < 0.001$). The women who took part did not differ from those who did not with respect to age, parity, or history of prior fetal or infant death (data not shown, available from authors).

Of the 634 participants, 185 (29%) were HIV-infected. Cord blood specimens for adherence assessment were not available from six participants (3.2%.) Of 179 HIV-infected participants who could be evaluated, 178 (99.4%) had NVP detected by HPLC. The single woman who did not have NVP in cord blood had vomited immediately after ingesting the drug and delivered 17 minutes later. We did not perform HPLC on HIV-seronegative specimens. In comparisons with either all participants in the NVP-treated clinical trial cohort (68% adherence rate), or with only those enrolled in the 'targeted' arm of that trial (74% adherence rate), the 99.4%

adherence rate observed in the labor ward strategy was significantly higher ($P < 0.001$ for both comparisons).

Of the 185 HIV-infected mothers and their infants that could be evaluated, 145 (78%) provided infant specimens at 4–6 weeks of life and 17 (11.7%) were found to be infected. This was significantly lower than the 12 of 60 (20%) transmissions observed in the observational untreated comparison group ($P < 0.05$). Women enrolled in the labor ward strategy were nearly twice as likely to deliver within 1 h of NVP ingestion compared with the treated clinical trial cohort, (13 versus 22%; $P = 0.065$). Only 6% of women in the labor ward strategy elected to be tested post-partum.

Discussion

To our knowledge, this is the first report of universal administration of NVP to women of unknown HIV status upon presentation in labor. We found the strategy to be acceptable to a substantial minority of women (40%) and to result in near perfect adherence to the intervention. Furthermore, this study validates HPLC of cord blood as an extremely sensitive measure of NVP adherence, as the drug was detectable in all but a single woman observed to have ingested it.

These data strongly suggest that universal NVP at the labor ward can result in significant reduction of MTCT. First, we observed a transmission rate that is in line with other published reports of NVP efficacy [11,12]. Second, when compared with an untreated, contemporaneous control group from the same birthing centers, we observed a 42% relative reduction in transmission risk. Unfortunately, we do not have data available on the control population to allow careful assessment of its comparability to our study cohort (e.g. CD4 cell count, viral load). However, the rate of transmission at 4–6 weeks of infant life observed in the control population was very similar to that observed in numerous other untreated cohorts [13]. Given the prevalence of HIV in our population (29%) and observed efficacy (42%), we can calculate that one would need to treat about 41 mother–infant pairs of unknown HIV status with NVP in order to prevent one infant infection (number needed to treat = 41). As single dose intra-partum and neonatal NVP prevents an infection that is essentially universally fatal, it would have to be fatally toxic in 2.4% of cases in order for its benefit to be negated by its risks.

These data make several important points. Labor ward administration of NVP to women of unknown HIV serostatus is acceptable to a substantial minority of women. It could be argued that active labor is not the best time for women to be asked to make a decision about NVP, and indeed this may explain why more than half of women declined to participate. However, the choice whether to take NVP in labor does not differ in risk–benefit complexity than myriad other decisions that women make in labor (e.g. whether to undergo cesarean delivery). A major benefit of labor-ward-based therapy is that it is directly observed, and thus adherence is considerably better than if the drug is issued to patients in antenatal care for self-administration at labor onset [5].

There are several arguments against the use of this approach in systems that can support more sophisticated services in antenatal care. First, women who for whatever reason do not deliver at an obstetric facility are unable to access the medication. Second, we noted very low rates of VCT uptake at postnatal visits. Since we cannot verify how thoroughly our study staff advocated testing at postnatal visits, we cannot state that our low subsequent VCT rates are generalizable to other settings. They are, however, clearly sub-optimal. Third, labor ward administration almost certainly results in later timing of the maternal dose compared with the dosing at the onset of labor – an effect that may work to diminish the prophylactic efficacy of NVP [14].

Thus, although universal labor-ward-based NVP may be inferior to other approaches as a primary PMTCT strategy, it still may be appropriate in two very important circumstances: (1) as an emergency or interim measure in settings where fully-fledged PMTCT services are unavailable, and (2) as an adjunctive approach to an antenatal-based program in order to reach those women who might have been missed previously or who might have failed to take their NVP as planned. In such a role, universal labor-ward-based NVP would be very likely to improve the population coverage of the drug. Indeed, even in settings in which a well-functioning antenatal PMTCT program is in place, offering NVP to all women presenting in labor, unless they have a documented negative HIV result, will be likely to save lives when background HIV seroprevalence rates are high. Although such an approach may result in double dosing of some women, the overall dose in such cases (400 mg) would not exceed the daily dose for adults on chronic NVP therapy and would be unlikely to add viral resistance concerns beyond those already extant. Given the negligible risks of single-dose NVP to HIV-uninfected women and their infants, a compelling rationale can be made for the addition of a labor ward NVP component to PMTCT programs in areas of high HIV prevalence. This component could, with high cost effectiveness, save many infant lives.

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Table 1

Characteristics of HIV-positive members of study population and comparison cohort.

Characteristic	Universal nevirapine at labor ward (n = 185)	Targeted nevirapine at antenatal care [5] (n = 121)	*P*
Mean (SD) age (years)	27 (5.5)	26.5 (4.7)	0.82
Mean (SD) education (years)	6.6 (2.9)	6.3 (2.8)	0.55
Mean (SD) weekly income (US$)	12.8 (22.0)	13.4 (23.1)	0.35
Median parity (range)	2 (1–8)	3 (1–8)	0.17
Median number of children who have died (range)[a]	0 (0–3)	0 (0–2)	0.08
Median number of years cohabitating with current partner (range)	4 (0–20)	4 (0–22)	0.86
Mean number of lifetime sexual partners (SD)	2.3 (1.6)	2.3 (1.6)	0.92
Mean body mass index at 36 weeks gestation (SD)	24.6 (3.2)	25.0 (3.3)	0.62
Median CD4+ lymphocyte estimate (cells × 10^6/l) at entry (IQR)[b]	342 (238–500)	329 (210–467)	0.27
Number with positive syphilis test at enrollment (proportion)	20 (0.11)	19 (0.15)	0.069

[a] Prior to the index pregnancy, not including stillbirths.

[b] Calculated from the enzyme-linked immune assay (TRAx CD4). IQR, inter-quartile range.