

NOVEL PACKAGING OF SINGLE INFANT DOSE NEVIRAPINE TO PREVENT HIV TRANSMISSION FROM MOTHER TO CHILD IN RESOURCE-CONSTRAINED SETTINGS

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Keywords: Mother-to-child transmission of HIV (MTCT), HIV/AIDS, antiretroviral drugs, drug delivery, nevirapine

Abstract

In order to reduce mother-to-child transmission of HIV among resource-poor populations who have little to no access to healthcare services, a novel foil pouch for packaging infant antiretroviral medications such as nevirapine has been developed by The Pratt School of Engineering at Duke University. Due to the pouch's long shelf life, mothers can receive prophylactic medications during their first or second trimester at maternal diagnosis (which has until now been impossible) enabling mothers who deliver at home to administer NVP as recommended by the World Health Organization guidelines at birth and until the first postnatal care visit. Bench testing and field acceptability testing among nurses and pharmacists in Tanzania has been completed, and twelve months of stability testing is in process. Thus far, results demonstrate that the pouch solution can successfully be administered by mothers in resource-constrained settings. In the future, clinical trials will document the pouch's impact on HIV transmission reduction in such settings.

1 Introduction

Over 90% of the 430,000 new HIV cases in children in 2008 were attributed to mother-to-child transmission even though transmission is avertable by low-cost, proven, efficacious medications such as nevirapine (NVP)[7]. The World Health Organization (WHO) recommends that infants receive a small dose of a liquid antiretroviral (ARV) such as an NVP oral suspension immediately after birth and daily for either six weeks or until one week after the breastfeeding period ends [8]. The regimen for preventing transmission during the birthing process requires that infants receive the ARVs within 72 hours of birth to be effective, and preferably within 24 hours. In Sub-Saharan Africa, many clinics possess these medications but cannot easily distribute them to the large percentage of mothers who give birth at home. For example, according to the United Nations Population Fund, 57% of all

Tanzanian women delivered at home in 2005 [4]. The only way for these infants to receive post exposure prophylaxis is for the mother to travel to a clinic immediately after birth. An HIV+ mother will often be reluctant to travel the day or two after delivering her baby. She may not have funds or means for transport to a hospital, feel too weak to travel to a clinic miles away, or fear stigmatization after explaining why she must go to a clinic after delivering a healthy baby. This leaves millions of children at risk of being infected with HIV during the birthing process.

In 2008, less than one third of infants born to HIV+ mothers received prophylactic antiretroviral drugs, while 45% of their mothers did [9]. To meet UN Millennium Development Goals and United Nations General Assembly Special Session targets of 80% coverage of antiretroviral drugs for women and infants who need them, new interventions must be investigated to increase access to ARVs, particularly for infants among resource poor populations [3]. Mothers must be given single doses of infant ARVs in advance, at maternal diagnosis, to guarantee they can prevent transmission until they can come into a hospital. Providing drugs like NVP to the mother at the first antenatal care visit will increase the number of infants who receive NVP within 72 of birth.

Normally, it is not possible to provide infant NVP many months before delivery for several reasons. Infants cannot swallow pills or tablets. Pharmacists have been packaging single doses in oral syringes, cups, and other ad hoc solutions, but these have very limited shelf lives due to moisture loss, precipitation, and perhaps preservative loss, and they are prone to contamination [1]. Furthermore, the tips of oral syringes may leak and may be a choking hazard. Manufacturers have been unwilling to release a single dose package because of the cost of development and regulatory approval and the limited market outside the developing world.

In response to this unmet need, Duke University has developed a new packaging system for liquid ARVs: a labelled, foilized, polyethylene single-dose pouch filled and sealed on site by a pharmacist that extends the life of NVP.

2 Methods and Results

2.1 Bench Testing

Two barriers were identified as limiting the shelf life of NVP, preservative loss and moisture loss. Thus, initial pouch prototypes sought to improve both variables as compared to the Exacta-Med syringe in a foil bag solution proposed by PATH, a non-profit corporation in Seattle, WA, USA. Preservatives were suspected of being absorbed by the packaging, so three storage types (syringe in an adhesive sealed bag, syringe in a heat sealed bag, and a heat sealed bag) were tested for absorption of the preservatives in NVP. The testing revealed that a syringe absorbs a significant amount of material (130-140 mg of a 0.6 ml dose). The pouch absorbed significantly less material (15 mg, $p < 0.001$) (see Fig.1).

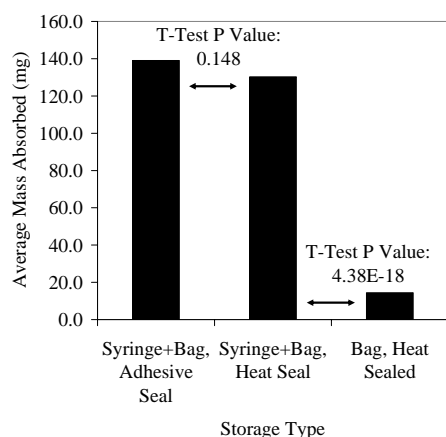


Figure 1: Preservative Absorption by Packaging Type

Three candidate materials were bench tested for moisture loss after adhesive sealing or heat sealing with a commercially available sealer. Ambient temperatures and humidities were monitored. Over a period of three weeks, the pouches showed no measurable loss in water, whereas the PATH solution lost nearly six percent of its weight (see Fig. 2).

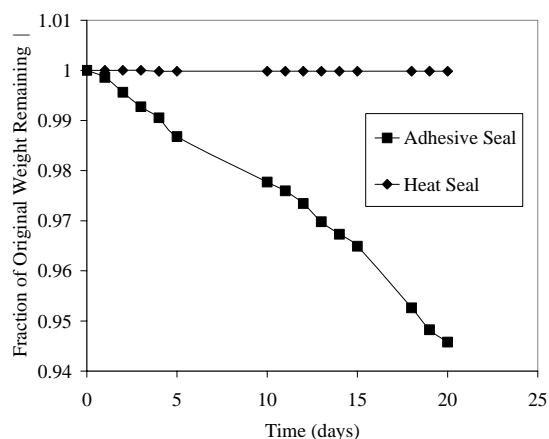


Figure 2: Water Loss For Two Sealing Methods

2.2 Field Acceptability Testing

To determine the acceptability of the foilized pouch solution among end users in Sub-Saharan Africa, a field acceptability study was conducted in northern Tanzania from June to August, 2009. Ten nurses and six pharmacists from both rural and urban hospitals were observed and interviewed. All participating nurses interviewed worked directly with HIV+ mothers in their hospital's maternity ward and were familiar with NVP and PMTCT national protocols. Nurses were provided with pouches and picture instructions explaining how to tear open the pouch and empty a placebo dose into a small cup.

Results indicated that, even in resource-constrained settings, end users could effectively administer the drug using our package by dropping the medication directly into the infant's mouth (Table 1). About half of the nurses expressed concerns about using the device, mostly relating to the HIV stigma (the risk of revealing one's status by using the pouch) and education about the pouch. For example, one nurse was worried that without proper education, a mother may squeeze the drug into a contaminated cup before giving to the infant, which may cause diarrhea. Despite these concerns, all nurses felt that with the proper education about the pouch all mothers could administer the NVP successfully at home.

Nurse Sampling	
6	Total hospitals represented
10	Total number providers interviewed
13	Total number pouches emptied

Nurse Interview Results	
90%	Thought mothers could effectively tear open pouch and drop medicine into child's mouth
100%	Thought most mothers could effectively administer drug to their infant if trained how to use the pouch by provider
50%	Had concerns about using the device to distribute NVP

Table 1: Nurse Acceptability Study Summary

The six pharmacists interviewed were given supplies and picture instructions needed to seal an empty pouch with 0.6mL of water without using electricity. Most pharmacists were able to fill and seal the pouch successfully, but some failed to adhere to the instructions perfectly, which caused a leaking seal. While pharmacists indicated they could seal the pouch, they all felt that more than simple picture instructions would be necessary. A short training session or pictures with more text would be needed.

The non-electric method was bench tested for seal strength and proved to be successful, but the amount of training necessary for seal quality to be controlled in the field is

unknown. Thus, the non-electric method would only be recommended when electricity and batteries are not available. In light of this, the preferred method is a battery operated or electric hand sealer (see section 4 below), which could seal larger batches of pouches at one time for distribution to dispensaries and clinics.

Pharmacist Sampling	
3	Total hospitals represented
6	Total number pharmacists interviewed

Pharmacist Interview Results	
1.33	Ease of method (1-very easy, 5-very difficult)
1.83	Ease of understanding instructions (1-very easy, 5-very difficult)
100%	Liked the pouch
100%	Felt that the method was safe for most medical personnel to perform
100%	Felt safe and comfortable sealing another pouch
2/3	Clinics/hospitals already had the materials needed to seal the pouch with this method
100%	Felt that picture instructions alone are not enough; training is needed

Table 2: Pharmacist Acceptability Study Summary

2.3 Stability Testing

The FDA has approved polyethylene packaging for a single dose liquid oral drug such as NVP. It also recommends that USP tests be performed on the packaging [5, 6]. Several samples of heat sealed pouches filled with a single infant dose of NVP are being assayed for twelve months of drug stability testing, initiated in October, 2009. Full stability data will not be completed until fall 2010. However, thus far, the pouch has proven to be stable for up to four months, twice as long as the PATH solution. The drug was well within acceptance criteria for biological and microbial contaminants. It is expected that the pouch will remain stable for the full twelve months.

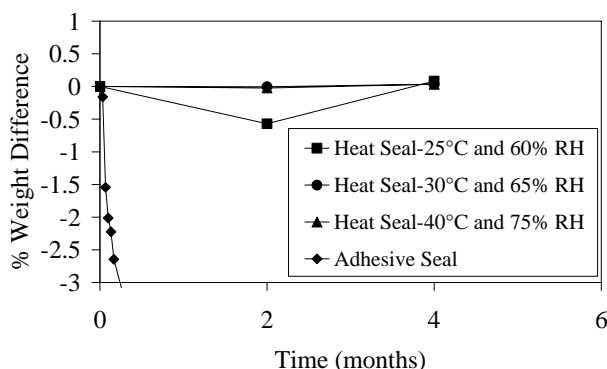


Figure 3: Moisture loss to date. The adhesive seal solution by PATH lost nearly six percent of its weight in less than two months.

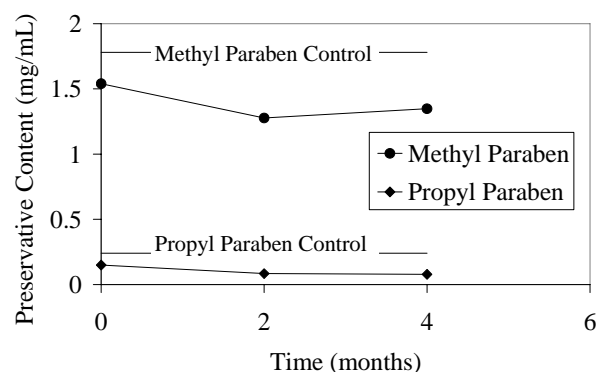


Figure 4: Preservative levels to date. Preservatives are still present and seem to be stabilizing.

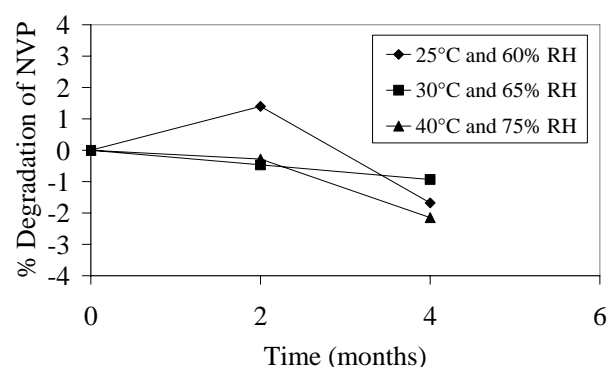


Figure 5: Drug stability in the pouch to date. The pouch preserves the NVP from degradation.

3 Conclusions and Discussion

Analysis indicates that the pouch could act as a bridge between birth and the first postnatal care visit to increase access to antiretroviral treatment among resource-constrained populations, helping to meet the targets and commitments related to antiretroviral coverage. Field acceptability study results affirm this approach as being acceptable to end users. Up to this point, stability testing has confirmed a shelf life of four months, twice that of the PATH solution.

Planning and partnerships for clinical trials which gauge the pouch's impact and ensure patient safety are crucial next steps going forward. While nevirapine was chosen as the pilot drug due to its suitability for resource-constrained settings, continued bench testing and stability testing of a variety of pediatric antiretroviral drugs and fixed dose combinations will determine the breadth of this solution within HIV treatment.

Instead of assuming that hospitals alone will distribute the medication, our pouch targets areas with minimal Prevention of Mother-To-Child Transmission (PMTCT) access, involving public and private sectors, dispensaries, and private midwife clinics because of its long shelf life. Data from a comprehensive study of rural Tanzanian populations' access to healthcare services found that over 50% more rural

Tanzanians had access to a health center or dispensary within walking distance (2-5 km) than did to a hospital [2].

There is currently no other technology allowing antiretrovirals to be provided to mothers who may deliver at home during the second trimester or earlier other than the nevirapine pouch solution. If infant ARVs could be mobilized for administration outside of a hospital setting with this pouch, it is expected that the 13% coverage gap between mothers and infants receiving ARVs for HIV prophylaxis could be narrowed without significant additional costs, making significant steps toward a generation free of HIV.

Acknowledgements

We would like to acknowledge the support of the Research in Practice Program (RIPP) and The Provost's Common Fund at Duke University. We also acknowledge the contributions of Michael Spohn, Peter Horgan, and Shannon Skinner.

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