# A Pouch May Be Prevent the Transmission of HIV from Mother to Child

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*Abstract*- **Many children become HIV+ due to mother-to-child transmission during home birth. This risk can be largely eliminated if infants ingest antiretroviral (ARV) medications immediately after birth. Unfortunately, there is currently no mechanism to provide dosed medication at a mothers first and perhaps only, antenatal care visit, months before delivery. We propose a foilized, polyethylene pouch to preserve pre-dosed ARV's. In this work we show that pharmacists can fill and seal the pouch, the pouch can preserve the medication and HIV+ mothers can empty the pouch into a simulated infant's mouth.**

**A pharmacists in Moshi Tanzania was trained and then filled and sealed 60 pouches which were tested for their effect on the medication, their mechanical strength (burst and leakage) and their volume accuracy. Under laboratory conditions, pouches from two manufacturers were filled with AZT and NVP (two common ARV's) and stored in conditions ranging from 25 ℃/60% relative humidity (RH) to 40 ℃/75% RH for twelve (AZT) or four (NVP) months. Sixty-one HIV+ mothers were asked to tear open pouches and empty the contents into plastic cups of approximately the size and shape of an infant's mouth.**

**No pharmacist sealed pouches burst or leaked (average percent weight loss maximum 0.080%). The AZT (102.2% of labeled concentration) and NVP (96.4%) in the pharmacist sealed pouches were stable. Pharmacist handling of the mediation did consume some of the sacrificial preservatives (72.4% remaining in AZT and 40.2% remaining for NVP) but not enough to affect the active ingredient. The same impurities were identified in the NVP and AZT samples sealed in Africa and the NVP and AZT samples removed from the bottles indicating that the pouches do not introduce impurities that are not already introduced from the bottle. The pharmacist filled pouches with an overall volume error of 0.13% +/- 6.6%. When the pouches were filled under laboratory conditions, there was no significant change in AZT (97.4% to 97.9%) or NVP (102.3% to 101.9%) concentrations after months of storage. All tested mothers were easily able to empty the contents of the pouch (89.8%: NVP, 89.7%, AZT) into the simulated mouth.**

**We conclude that the pouch can be sealed by pharmacists in in realistic settings, the pouch can preserve the medication for months and HIV+ mothers can open the pouch and empty its contents.**

***Keywords- PMTCT; HIV; AIDS; Anti-Retroviral Preservation; Home Birth***

## I. INTRODUCTION

Mother-to-child transmission is one of the major causes of HIV infection [1]. Transmission can happen in the womb, during birth or as a result of breast feeding. Transmission during birth can be prevented by giving the child antiretroviral therapy immediately after birth. But some children are not getting the treatment or not getting it in time. Children living in resource poor settings are at a particularly high risk: less than 33% of children born to HIV+ mothers receive prophylactic antiretroviral drugs [2]. Presumably even fewer receive treatment in the first few days of life.

The World Health Organization (WHO) recommends that infants receive a small dose of a liquid antiretroviral such as Nevirapine (NVP) oral suspension immediately after birth [3]. The infants should receive their first dose 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, e.g., 57% of all Tanzanian women delivered at home in 2005 [4]. Mothers who deliver at home will often be reluctant to travel the day or two after delivering their baby because they do not have funds or means for transport, feel too weak to travel or fear stigmatization at explaining why she must go to a clinic after delivering an apparently healthy baby.

If the mother might deliver at home and might not return to the clinic with a day or two, it is logical to provide the infant's ARVs in advance. Unfortunately, it is not possible at this time to provide infant ARV's many months before delivery for several reasons. Infants cannot swallow pills or tablets so pharmacists in resource-poor settings have been packaging single doses of liquid medication in oral syringes, cups, and other ad hoc solutions [5], but these have very limited shelf lives, and they are prone to contamination. Manufactures 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.

Thus, at this moment, there is an unmet need for a system to deliver ARVs to HIV+ pregnant mothers months before they deliver for administration to their children in the event that they deliver at home. We have previously proposed a foilized, polyethylene pouch to store the medication [7]. However, in our previous work, we only showed that the pouch can preserve NVP for up to twelve months. This is not sufficient. To be an effective solution, a local pharmacist must be able to seal the pouch, the pouch must preserve the medication, including alternative such as zidovudine (AZT) and, most importantly, mothers must be able to open the pouch and dispense its contents. In this paper we expand on our previous work by showing



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that the pouch from a second manufacturer can preserve the medication, demonstrate our previous results for a new medication, carefully examine the ability of a pharmacist in Africa to seal the pouch and measure the ability of HIV+ mothers to empty the pouch.

## II. METHODS

### *A. Pharmacists Ability to Fill and Seal*

A pharmacist at KCMC hospital in Moshi, Tanzania was given written instructions, a sealer and pouches. The pharmacist used 2 ml syringes (Becton, Dickinson and Company) and tapered dispensing tips (TT14-DHUV, Techcon Systems, Garden Grove. CA). With coaching, the pharmacist was instructed to fill as many pouches as needed to achieve accurate and complete seals. If present, medication on the outside of the syringes was removed before filling the pouch. Pouches were weighed and tested until the pharmacist felt he could complete the task.

The pharmacist then sealed ten pouches containing 0.6 ml of NVP (50 mg/5 ml oral suspension, Aurobindo Pharma, Ltd) and ten pouches containing 1.2 ml of AZT (50 mg/5 ml oral solution, Cipla, Ltd). The pouches and the bottles from which the medicine was drawn were returned to the US for chemical analysis. An additional ten pouches were filled with 0.6 ml of NVP and ten pouches with 1.2 ml of AZT and returned to the US for burst pressure and leakage testing. Finally, ten more pouches were weighed empty, filled with 0.6 ml of NVP and ten pouches with 1.2 ml of AZT by the pharmacist, then weighed again, to determine the pharmacists filling accuracy. For accuracy comparison, the pharmacist also filled ten syringes (5 NVP and 5 AZT), the vehicle currently used in the hospital to deliver the medications. The syringes were weighed empty and after filling to determine volume.

Leakage testing was performed by weighing the pouches, baking the pouches at 175 ℉ for eight hours (Lindberg Blue M Single Wall Gravity Convection Laboratory Oven) and then weighing again. Burst testing was performed by stacking ten pouches on top of blotting paper, then applying 110 pounds of force (greater than 20 psi) using a Tinius-Olsen Model 1000 Materials Testing Machine at a rate of 0.30 in/min.

The first twenty pouches were stored at room temperature for three months. We have previously described our testing methods for ARV analysis in detail [7]. Briefly, pouches were sent to Southern Testing and Research Division of Microbac Laboratories, Inc. (Wilson, NC). Flora and fauna challenges (total microbial aerobic, yeast and mold) were performed following USP61 using USP33-NF28 methodology and tested for the presence of E. Coli (USP62) following USP33-NF28 methodology. Samples were weighed prior to stability testing and again when pulled. In addition to determination of the ARV concentrations, levels of preservatives in the samples were estimated using independently prepared standards. Finally, the chromatographs were analyzed to determine if impurities were induced in the medication or extracted from the plastic.

### *B. Pouch's Ability to Store Medication*

Although we have already shown that at least one manufacturers pouch can preserve NVP, we wished to expand the application of our work by showing that the method is not sensitive to the pouch manufacturer and can be used with other anti-retrovirals, like AZT.

For testing AZT, premade foilized pouches (PAKVF4, outside polyester/ polyethylene with a 0.00035 inches thick Al foil layer and an inside linear low density polyethylene layer, 4.3 mil total thickness, Sorbent Systems, Los Angeles, CA) were used directly from the factory without further sterilization or cleaning. Pouches were filled by hand with 1.5 mL of AZT oral solution (50 mg/5 ml Cipla, Ltd) using the technique described above for the pharmacist. An identical protocol was followed for NVP with the exception that we used premade, foilized pouches from a second manufacturer (Flex-Pak, Product #210057).

Testing followed the methods described for the pharmacist except that pouches were submitted for twelve (AZT) or four (NVP) months of controlled storage and testing. Samples were stored in walk in stability chambers at 25 ℃/60% relative humidity (RH) and 40 ℃/75% RH and in a reach in chamber at 30 ℃/65% RH. Microbiological, weight change, and chemical testing were performed on the pouches as described for the pharmacist study above.

### *C. Ability of Mothers to Open Pouches and Empty Them*

Sixty-one HIV+ mothers in Ecuador were recruited when they returned for their ARV therapy. Each subject was asked to open a FlexPak pouch and empty it into a 30 mm diameter cup. This size cup closely mimics the measured 28.5 x 26.9 mm opening of an infant's mouth. The cup and a clean weigh boat were tared before the subject emptied each pouch. The weight of the liquid delivered in the cup was recorded and compared against the total weight of liquid that was originally in the pouch to determine emptying percentage. As a comparison, mothers were also asked to empty the contents of a syringe, dropper and cup, common alternatives provided in Ecuador and elsewhere. All tested devices were filled with a high-viscosity liquid to mimic NVP or a low-viscosity liquid to mimic AZT. The viscosity of the liquid was adjusted to match the run velocity of an equal sized drop of NVP or AZT placed on vertically held polyethylene.



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## III. RESULTS

### A. Pharmacists Ability to Fill and Seal Pouch

No pouches burst and the blotting paper showed no evidence of bursting or leakage during testing. The average percent weight loss during baking was 0.051% (maximum loss of 0.080%). This is far below the moisture loss indicative of a poorly sealed pouch. The AZT (102.2%) and NVP (96.4%) were stable in the pouches. Percentages indicate percent concentration as compared to the bottle-stored ARV. These levels of change are well within the USP allowed +/-10% tolerance.

There was evidence of preservative loss in all samples, as expected when the medication is handled, exposed to oxygen and exposed to light. The preservative in the AZT dropped to 72.4% of the bottle-stored AZT and the preservatives in the NVP dropped to 40.2% of the bottle-stored NVP. While these were significant drops, they are reasonable considering the performance reported previously under laboratory conditions [7] and there was clearly sufficient preservative remaining, since the levels of ARV were stable.

The same impurities were identified in the NVP and AZT samples sealed in Africa and the NVP and AZT samples removed from the bottles. All impurities were slightly increased in concentrations in the pouch (max 0.10%). Yet, all impurities were present at concentrations below 1% in all samples. This strongly suggests that the pouch and pharmacist handling does not induce impurities in the medication and neither the pharmacist nor the medication extract impurities from the pouch.

The pharmacist filled pouches with an overall volume accuracy of 0.13% +/- 6.6% and he filled syringes with an overall volume accuracy of 1.8% +/- 5.4%. There was no statistically significant difference between filling syringes and filling pouches. There was an overall tendency to overfill AZT and underfill NVP in both syringes and pouches.

### B. Ability of Pouch to Preserve Medication

The most critical function of the pouch is to preserve the active ingredient for later delivery to the infant. Figure 1 shows that the AZT concentrations remained nearly unchanged for all time points at all storage conditions. Likewise NVP was stable in the pouches from the second pouch manufacturer dropping from 102.3% to 101.9% of the bottle-labeled concentration over four months.

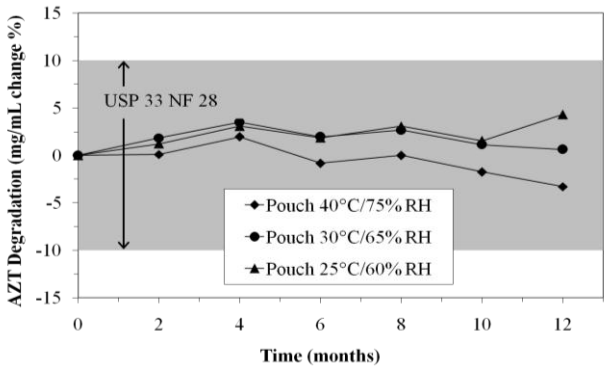


Figure 1 The percent degradation of AZT solution fell well within the USP 32 NF 27 standard even after twelve months in the pouch.

Figure 2 shows that there was a significant drop in preservative levels in the AZT due to handling. This is to be expected as the medicine is exposed to mechanical stress, light and oxygen. However, after this initial drop, the preservative levels drop at a predictable and slow rate. The concentration of AZT shows that the preservative continues to do its job of being a sacrificial oxidant. Similar findings can be reported for the NVP where the preservatives fall a maximum of 4.6% over the length of the experiment. We have previously reported more detailed results of NVP preservatives and the pouch [7].

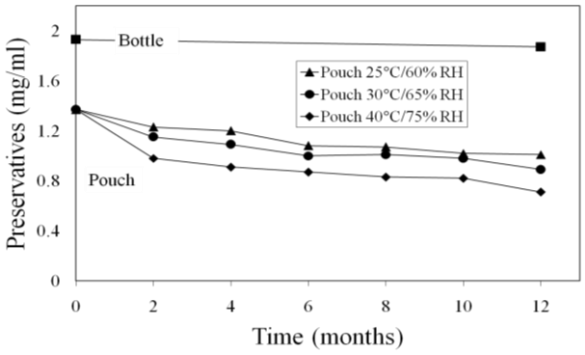


Figure 2 Preservatives act as sacrificial oxidants and their loss may limit shelf life. However, this graph shows that despite initial losses attributed to filling and sealing, the sacrificial oxidants remained in adequate quantities to preserve the medication.



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As with the pharmacist sealed pouches, the same impurities were found in all three: the freshly opened bottle, the stored bottle and the stored pouches for both AZT and NVP. Storage in the pouch did not introduce any impurities that were not already present in the original material analyzed when the bottles were first opened.

### *C. Ability of Mothers to Empty Pouch*

All 61 tested, HIV+ mothers were easily able to empty about 90% (average 89.8%: NVP, 89.7%, AZT) of the FlexPak pouch into a simulated baby's mouth. As a comparison, they were only able to empty 55.8% of a high-viscosity liquid from a tablespoon and 39.3% of a high-viscosity liquid from a cup. The mothers had difficulty with the high-viscosity liquid in the syringe and dropper probably due to the small openings of each. For the low-viscosity liquid, however, they could empty 97.2% and 99.1% of the contents for the syringe and dropper respectively.

## IV. DISCUSSION

The immediate target population for our device is HIV+ mothers who deliver at home. At this time, there is no easy way for these mothers to reduce the risk that their children will become HIV+. Our work presents the first evidence of a technique that can preserve the medication and accurately deliver it to these high risk children.

In our previous work, we showed that the pouch can preserve the medication. However, before we can begin clinical trials, we must also show that the pharmacist can fill and seal the pouch and that mothers can empty the pouch in to their children. Indeed we have shown that HIV+ mothers can empty the pouch into simulated baby mouths. Furthermore, pharmacists in Africa can fill and seal the pouch successfully. Sterile, laboratory conditions are not required. We believe that we now have sufficient evidence to justify commencing clinical trials.

However, this paper also addresses more subtle issue of the supply chain. We have shown that pouches from two manufacturers can both be used. As this pouch is intended to be introduced into the healthcare system, it is important that ministries of health have a choice of providers. Finally, we have shown that a second ARV, AZT, can be stored in the pouch. While most countries are not using AZT at this time, it may return in the future as an alternative technique.

While we have presented evidence that the provision of a dropper or syringe and a bottle of ARV, as is done in Africa for mothers who deliver in the hospital, is an effective delivery vehicle for low viscosity medications like AZT. We also have evidence that this solution may be less effective for high viscosity liquids like NVP. In addition, any comparison assumes that mothers can correctly measure using a cup, spoon or syringe, something that was not measured here.

It should be noted that our results could not be reproduced with a central sealing facility at this time. Each pharmacist must fill the required pouches for his patients. If the pouches were filled and sealed centrally, this would be considered a manufacturing step in the US and most countries. As a manufacture, the pouches size and contents of the pouch, and its labeling, would require FDA approval for each variant as protocols, medications and baby weights changed. However, when filled and sealed by a local pharmacist, the pouch is simply a pill bottle for liquid medications, dramatically lowering the cost of regulatory approval.

### Limitations

We only used one pharmacist. While this is sufficient to show that the pouch can be filled and sealed outside of the laboratory, as we claim, it is not sufficient to show that all pharmacists can accomplish the task or even most.

## V. CONCLUSION

In conclusion, we have shown evidence that the pouch can be sealed by a pharmacist, store the medication until delivery and that mothers can empty the pouch into their baby's mouth. The pouch is the only option to help prevent the transmission of HIV from mother to child for mothers at high risk of delivering at home.

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## REFERENCES

[1] WHO. PMTCT strategic vision 2010–2015: preventing mother-to-child transmission of HIV to reach the UNGASS and Millennium Development Goals. Geneva, Switzerland: WHO; 2009: 9. Available at: http://www.who.int/hiv/pub/mtct/strategic_vision.pdf.

[2] WHO, UNAIDS, UNICEF. Towards universal access: scaling up priority HIV/AIDS interventions in the health sector. Progress report 2009. Geneva, Switzerland: WHO; 2009: 112. Available at: http://www.who.int/entity/hiv/pub/tuapr_2009_en.pdf.

[3] WHO. Rapid advice: antiretroviral therapy for HIV infection in adults and adolescents. Geneva, Switzerland: WHO; 2009. Available at: http://www.who.int/hiv/pub/arv/rapid_advice_art.pdf.



DOI: 10.5963/BER0202002

[4] UNFPA (17 April 2007). "The Prime Minister of Tanzania Calls on Regional Leaders to Increase Health Spending to 15 Per Cent of National Budgets and to Strive for Achieving Health MDGs". Press release. Available at: http://www.unfpa.org/public/News/pid/308.

[5] Berman A, Brooke S. Sourcing Guide: The Nevirapine Infant-Dose Pouch for Use in Prevention of Mother-to-Child Transmission of HIV/AIDS Programs. Version 1. Seattle, Washington: PATH; 2006: 2. Available at: http://www.path.org/files/TS_NVP_sourcing_guide.pdf.

[6] FDA Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologic, May, 1999. Section III.F.1.

**[7]** RA Malkin, C Howard, A Foilized Polyethylene Pouch for the Prevention of Transmission of HIV from Mother to Child, Open Biomed Eng J, 2012, v6, 92-97.



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