Accurate Dosing of Antiretrovirals at Home Using a Foilized, Polyethylene Pouch to Prevent the Transmission of HIV From Mother to Child

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Abstract: Mother-to-child HIV transmission rates remain elevated in countries with high home birth rates. This risk can be dramatically reduced if infants receive antiretroviral (ARV) medication within 24 hours after birth. However, many barriers prevent access to these medications immediately after delivery, for example, there is currently no suitable mechanism to preserve predosed ARVs in the home during the months before birth. In response to this, students of the Duke University developed the Pratt pouch, a foilized polyethylene packet designed to preserve predosed ARVs.

This cross-sectional study presents the data from the first clinical trials of the Pratt pouch in Guayaquil, Ecuador. Fourteen HIV-positive mothers and nurses were observed using the pouch to deliver a dose of ARVs to an infant. Weight measurements, time, and notes on spillage were taken at each observation period. Successful usage was quantitatively assessed through the calculation of dosing accuracy based on the volume of liquid medication emptied from the pouch. Additionally, mothers were surveyed after a month of using the device at home to assess their perception of the accuracy, acceptability, and ease of use of the pouch. Used pouches were collected for physical analysis of tearing.

Observations of pouches delivered accurate doses (M = 101.1%, standard deviation = 8.2%) in an average time of 2.6 minutes. A total of 2869 used pouches were recovered. No seal failures or failed attempts at opening/delivering the pouches were observed or detected. Forty-three mothers were surveyed. All mothers (100%) reported that they were able to follow their physician’s treatment plan, all pouches were received in good condition and the pictorial sheets provided clear instructions.

We conclude that the Pratt pouch is a highly accurate and easy-to-use device for delivering liquid oral ARVs to infants and is appropriate for prepackaging ARVs for home use.

(Medicine 94(25):e1030)
pouches filled with a simulation liquid into a cup. The present study builds off this previous work by assessing the accuracy and feasibility of delivering ARVs to an infant in a hospital and at home via the pouch. To do so, this study aimed to observe the first human use of the pouch, measure dosing accuracy, assess user acceptability in the home through oral surveys, and analyze used pouches to investigate tearing practice.

METHODS

Prior to this study, the polyethylene pouch ("the pouch") was approved for use for the delivery of weight-based oral doses of ARVs (AZT, NVP, and 3TC) to all HIV-exposed neonates by the Coordinator of Prevention of Vertical Transmission of HIV/AIDS at Hospital Gineco-Obstettrico Enrique C. Sotomayor (HECS) in Guayaquil, Ecuador. All HIV-exposed infants born at HECS received ARVs via the Pratt pouch from June 2013 onward unless otherwise explicitly specified by a physician in the case of low birth weight or other special circumstances.

The study was split into 2 parts: hospital use—direct observation of the use of the pouch in the hospital; and home use—surveying mothers who used the pouch in their home and analysis of their returned used pouches.

All HIV+ women who had given birth at HECS and had given consent to participate were enrolled in this study. Additionally, HECS nurses or patient’s friends or relatives who administered ARVs to HIV-exposed infants in the hospital were also observed. All observed users verbally consented to observation. The number of adults consenting to observation during the study period determined the sample size. The protocol was approved by the Duke University Institutional Review Board and permission for the study was granted by the Coordinator of Prevention of Vertical Transmission of HIV/AIDS at HECS.

Pratt Pouch Filling and Sealing

A pharmacist at HECS was provided with 3 mL syringes (A3; General Laboratory Supply Inc., Pasadena, TX), syringe tips (TT14-DHUV; Techcon Systems, Garden Grove, CA), a heat sealer (TISH-105; TEW Electric Heating Equipment, Taipei, Taiwan), and pouches (3.94" × 1.38" × 0.007" polyethylene, Flex-Pak, Product #210057). The pharmacist was also provided written instructions on how to fill and seal pouches and was trained to proficiency. Each pouch was labeled with either a large (1 7/32" × 2 5/8") or small (3/4" × 1") acrylic-adhesive sticker (Gaylord, Syracuse, NY). Large labels were placed in the middle of the pouch approximately 10-mm below the tear notches (see Figure 1) in order to prevent interference with tearing. Small labels were placed at the bottom of the pouch along the pharmacist’s seal, farthest from the notches. The information on the labels was printed on a locally available color printer (Color Laser Jet CP2025; Hewlett-Packard, Palo Alto, CA) using color and words to indicate the type of medication, dosage, and expiration date. Pouches were weighed and compared to their theoretical weight (calculated based on the prescribed dose volume and medication density).

Hospital Use

Users were provided with verbal instructions on how to tear open and dispense the pouch from a supervising nurse. For each observation, one labeled, filled pouch was weighed on a portable precision balance (HCB123; Adam Equipment, Danbury, CT). Timing measurements were taken at the following intervals: from the time the subject was handed the pouch to when she began to open it, from the time the subject began tearing to when the pouch was opened, and from the time the subject began dispensing the medicine into the infant’s mouth to when the subject stopped. Notes were taken to qualitatively assess and describe the subject’s ability to identify the correct tear site, hand placement, tearing and emptying technique, and spillage. To avoid potential bias, the individuals collecting and recording these measurements were not the same individuals who provided the training for the users. Once the subject had completed delivering the dose to the infant, the complete top and bottom portion of the used pouch was then reweighed on the precision balance to compute the amount emptied from the pouch and emptying percentage. Emptying percentage was determined by subtracting the empty pouch weight from the weight of the pouch after use, divided by the weight of the medicine originally in the pouch, and subtracting this value from 100%. The percentage of the desired dose delivered was also calculated based on the volume of medicine delivered from the pouch divided by the intended dose as prescribed by the physician.

Home Use

Subjects discharged from the hospital were sent home with a month-long supply of ARVs prepackaged in labeled pouches stored in a plastic container that included a receptacle for used
pouches. Mothers were instructed in how to use the pouches to deliver dosages to their infant by a nurse and received a pictorial instruction sheet prior to discharge with the same information. At the mother’s first postnatal visit after approximately 1 month, surveys were administered orally by an HECS volunteer or doctor. All returned empty pouches from the month of use were collected.

Returned Pouch Analysis

Used pouches were analyzed for several features. The tear site was identified as the open end of the used pouch. Each pouch was noted to be either partially opened or separated into 2 pieces. For partially torn pouches, a measurement was made of the tear length remain, defined as the distance from the attached edge of the tear to the nearest edge of the pouch (Figure 1). If the tear length remain was <6 mm, the tear was considered to be “full but attached.” If the tear length remain was between 6 and 18 mm, the tear was classified as an “intentional partial tear.” If the tear length remain was >18 mm, meaning nearly the entire pouch remained unorn, the tear was classed as an “intentional small tear.” Note was also taken if the tear was “into the pouch,” that is, not between the notches (risking spillage), or if the pouch had been opened by a shearing implement such as scissors (absence of evidence of tension at the tear site under microscopic analysis). To assess whether the user’s tear site extended into the liquid contents of the pouch, the tear height was measured. The tear height was defined as the length from the bottom edge (edge parallel to notches) of the pouch to the minimum point of the tear site and was measured (Figure 1).

RESULTS

All consenting participants completed the study. There were no recorded adverse events, either severe or mild.

Hospital Use

A total of 14 users were observed opening a pouch and delivering a dose of ARVs to the mouth of a newborn, including 4 HIV+ mothers and 10 nurses. All 4 of the mothers were first-time users of the pouch. One nurse had one previous, unobserved use of the device. One observed nurse’s data was not included in calculated averages due to technical difficulties with weight measurement.

The pouch was a highly accurate dosing device. Users delivered an average of 101.1% (standard deviation [SD] = 8.2%) of the desired dose, and took an average of 2 minutes and 36 seconds to tear open and deliver the full dose of medication to the infant (Table 1). Users can deliver more than the intended dose because pouches are intentionally overfilled by 10% to allow for residual medicine in the pouch. Spillage was noted in 6 users, 3 of whom spilled >2 drops of medicine. One of these 3 users used their fingers to push medicine that had spilled into the infant’s mouth. No failed attempts at opening/delivering the pouches were observed.

Home Use

A total of 43 HIV+ mothers that delivered ARVs to their infant at home via the Pratt pouch completed surveys at their 1-month hospital visit. Of these 43 surveyed users, all mothers (100.0%) reported that they were able to follow the treatment plan as prescribed by their doctor (Table 1), with 14 (32.6%) of the mothers delivering ≥2 different medications per day. All (100.0%) of the mothers reported that the pouches were received in good condition and that the provided pictorial instruction sheets provided clear directions. A total of 34 (79.0%) mothers reported having no difficulty emptying the complete dose from the pouch. The other 9 (21.0%) mothers indicated that they had problems delivering a complete dose. Out of the 43 surveyed, 38 (88.4%) mothers felt confident that they were delivering the correct dose of ARVs to their infant, 4 (9.3%) did not feel confident, and 1 (2.3%) said she did not know whether or not she was delivering the correct dose.

Surveyed mothers were asked to compare the pouch to other currently available oral suspension medication delivery methods for infants. Of the 43 mothers surveyed, 28 (65.1%) had previously delivered liquid medication to an infant via an oral syringe extracting the medication from a cup or bottle. Of these 28 mothers, 17 (60.7%) found the pouch easier to use, 19 (67.8%) found the pouch to be a faster delivery method, and 18 (64.3%) reported that the pouch was more acceptable to their baby. One mother found both methods equally easy, fast, and accepted by their infant.

Slightly less than half (46.5%) of the surveyed mothers reported that they had spilled any volume of medicine from the pouch during their month of home use. Of those that reported spillage, 13 (65.0%) categorized their spillage as “a little,” 2 (10.0%) categorized it as “a lot,” and 5 did not specify.

Pouch Analysis

A total of 2869 used pouches were collected from home use (Table 1). A total of 234 pouches were returned unopened. Unused pouches probably resulted because some mothers returned to their doctors a few days before completing the full month. To be certain that these pouches did not remain unopened due to a failed attempt, their dimensions were measured and compared to an unperturbed filled pouch. The pouches were also observed for any evidence of tension applied to any part of the unopened material. None of the 234 pouches that were returned unopened exhibited evidence of a failed attempt at opening.

For opened pouches, evidence of tensile force was indicated by the presence of stretching of the inner most layer of the pouch. Pouches without any tensile evidence were assumed to have been opened with a shearing implement, that is, scissors or a knife. Very few pouches were opened with implements. Pouches without tensile stress were seen in 178 (6.2%) of the returned pouches. In total, only 63 (2.2%) of those pouches

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**TABLE 1. Hospital and Home Use Result Summary**

|                  | Hospital Use | Home Use |
|------------------|--------------|----------|
| Total pouches    | 14           | 2869     |
| Failed tears     | 0            | 0        |
| Ability to follow treatment plan | 100%        | 100%     |
| Mean time to deliver dose | 156 s       | —        |
| Mean dosing accuracy | 101.1%     | —        |
| Median dosing accuracy | 101.0%      | —        |
| Dosing inaccuracy (>10% error) | 1           | —        |
| Dosing inaccuracy (>20% error) | 0           | —        |

Hospital use data obtained through observational measurements. Dosing accuracy was calculated by dividing the volume of medicine delivered from the pouch by the intended dose as prescribed the physician. Home use data obtained from patient survey and returned pouch analysis. Dashes indicate data not collected from home uses.
opened with implements were cut to make the opening of the pouch smaller.

Note was taken for each pouch that had a tear with a tear height below the notches (8.5 mm from the bottom of the pouch). This kind of tear below the notches was noted in 386 (13.5%) pouches. However, only 79 (2.8%) of these pouches were torn >0.5 mm below the notches, suggesting that users had little to no difficulty in tearing without spillage.

DISCUSSION

Primary Analysis

This study presents the first human use of the Pratt pouch and the first home use. We conclude that the Pratt pouch as a highly accurate method to deliver liquid oral ARVs to infants. The demand for improved delivery methods for liquid AZT has been exhibited in a previous study demonstrating the high prevalence of major dosing inaccuracies by caregivers using cups and syringes in the developing world. In 2014, Howard et al found that 49.7% of subjects using a cup and 47.8% of subjects using a syringe to measure a dose of liquid AZT made an error of at least 20% deviation from the reference dose. Included in these values were the 28.4% of subjects using a cup and 27.9% of subjects using a syringe who made errors of at least 40%. These results highlight the need to address caregiver dosing accuracy. In contrast, the Pratt pouch bypasses the need for caregivers to measure out the medication themselves by prepackaging individual doses. We have shown here that this results in higher delivery accuracy and virtually eliminates the potential for dosing errors >20% provided that the user does not spill the contents of the pouch.

The observed accuracy results from several carefully coordinated steps. Pharmacists are instructed to overfill the pouch by 10% to account for residual medicine in the pouch. In other words, we anticipate that mothers can deliver 90% of the pouches contents to their child. However, there was a slight tendency by pharmacists to fill the pouches beyond the 10% (M = 103.7%, SD = 3.1% of the intended weight). This was compensated by a slight tendency of users to deliver less than our predictions (M = 86.5%, SD = 5.8% of the liquid medication contained in each pouch).

Furthermore, at an average of 2.5 minutes, the total dosing time is highly reasonable, and no subjects were observed to have difficulties tearing open the pouch. The ease in which the Pratt pouch allows for accurate dosing is highly advantageous in settings wherein resource and literacy limitations prevent mothers and caregivers from learning how to dose liquid medications in a cup or syringe.

A critical component of this study was to investigate the feasibility of home usage of the pouch. In one application, the Pratt pouch would be distributed months before delivery to an HIV+ mother who will likely give birth at home. We have previously shown that the Pratt pouch can preserve the medication for up to 1 year. This mother would be able to store the medication packaged in the pouch in her home until she gives birth to her child. At that point, the mother would refer to a pictorial instruction sheet on how to use the device to deliver medication to her newborn. We have shown that mothers can follow the instructions indicated on a pictorial sheet and confidently deliver doses to their child. Furthermore, most mothers reported positive home use experiences and were able to successfully deliver medication to their child without difficulty. Based on these results, we predict that the Pratt pouch will be a feasible ARV delivery device in this target population.

Before the introduction of the Pratt pouch, mothers who gave birth at HCES were sent home with a urine specimen collection cup filled with a month supply of medication and an oral syringe. This method raised concerns of poor medication adherence, especially in the cases in which mothers needed to keep track of ≥2 medications for their infant. There was also a risk of contamination, spillage, and spoilage of the medication. In contrast, all mothers who used the Pratt pouch in the home reported that they were able to follow their treatment plan and most preferred our device over the previous cup and syringe method. This supports the pouch as a feasible method for mothers to keep track of their child’s medication regimen.

In the future, regimens could be further simplified by customizing pouch labels to indicate when that particular dose should be taken (ie, “Day 1: Morning”) or to color code the device to its intended use. Alternatively, a low-cost custom box similar to a multicompartment pillbox could be designed to designate which pouches to take each day.

Furthermore, the success of the Pratt pouch at HECS supports the feasibility of a hospital or clinic adopting the device for prepackaging ARVs. The pharmacist trained onsite was able to successfully fill, seal, and label pouches according to protocol, and these pouches were observed to be in good condition with no reported seal failures. Although the workload of the pharmacist was not investigated in this study, future studies may further quantify pharmacist performance.

Secondary Analysis

Unmonitored home usage provides less opportunity for precise analysis. However, examination of the pouches returned from home gives some insight into the mothers’ month of use. Overall, the pouches returned from the home revealed good tearing practice by the majority of users. Most of the pouches were torn into 2 complete pieces between the notches, which is the recommended tearing method. We also found that only a small portion of the pouches exhibited tears below the notches, and those that did were within a millimeter of the intended tear site. In other words, users had little to no difficulty in tearing open the pouch at home without spilling medication in the process.

We therefore believe that the use of an implement does not necessarily indicate difficulties with opening the pouch or that the opening of the pouch is too large. Other possible explanations include a familiarity with using scissors to open other types of packaging in the home or the possibility that other users in the home who had not been trained chose to use an implement. This issue is not trivial: The use of an unsanitary tool could cause contamination of the liquid contents. In the future, mothers should be discouraged from using implements to open the pouch.

Limitations

The small sample size of observed users limits its generalizability. Further studies including a larger sample size of HIV+ mothers should be conducted to confirm the observational results.

Furthermore, the use of implements highlights a weakness of this work. Mothers typically use spoons or cups to deliver medication to their children. Either tool may or may not have been thoroughly cleaned between uses. The Pratt pouch offers the possibility of improved hygiene but only when used
correctly. The recommended delivery method is for the user to tear open the pouch between its notches and pour the contents directly into the baby’s mouth. In this study, about a quarter of mothers who used the pouch in the home reported using alternate methods, such as mixing the liquid contents with milk, pouring the medicine in a spoon, pouring the medicine into a cup and then drawing it up into an oral syringe. Although these methods are not necessarily harmful, they can negate some of the benefits of the Pratt pouch. This is supported by the fact that a third of the mothers who reported using these alternate methods also reported spillage in their survey. In the future, these alternate methods should be discouraged through more extensive training in which a nurse stresses the importance of delivering the dose directly to the baby’s mouth. Furthermore, because mothers tend to be the only caregiver in the home who receives direct verbal training by a nurse, they should be encouraged to be the only person who delivers doses to the baby.

CONCLUSION

The Pratt pouch provides an accurate, feasible, and effective method for the delivery of liquid oral ARV medication to HIV-exposed infants in resource-poor settings at home and in the clinic. HIV+ mothers were observed to interact positively with the pouch and had no difficulties tearing open the pouch and delivering the liquid contents to their infant’s mouth. Also, the emptying percentage data reveals that the pouch provides a highly accurate dosing method. This is significant in resource-poor settings wherein dosing errors using cups or syringes are exceedingly common among adult caregivers. Furthermore, this data supports the Pratt pouch as an acceptable method for the delivery of ARVs in the home. Mothers reported positive, successful interactions with the pouch >1 month of home use. The returned pouch analysis suggests that, in general, mothers do not have any difficulty properly opening the device. Overall, the results from this study support the use of the Pratt pouch as an ideal delivery method for liquid oral ARVs. These results have significant implications for the use of the Pratt pouch in future clinical trials.

ACKNOWLEDGMENTS

The authors would like to acknowledge Humberto and Gabriela Mata at Fundacion VIHDA for their technical support in Ecuador as well as Sebastian Baquerizo and Gabriela Martinez-Moure for their on-the-ground technical assistance. They would also like to thank the HCES administration and employees for their cooperation and support throughout this study.

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