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Pharmacy Refill Data are Poor Predictors of Virologic Treatment Outcomes in Adolescents with HIV in Botswana

Leah Genn[1] · Jennifer Chapman[1] · Harriet Okatch[1,2] · Neil Abell[3] · Tafireyi Marukutira[4] · Ontibile Tshume[4] · Gabriel Anabwani[4,5] · Robert Gross[6] · Elizabeth D. Lowenthal[1,7]

Abstract

In adults living with HIV, pharmacy refill data are good predictors of virologic failure (VF). The utility of pharmacy refill data for predicting VF in adolescents has not been reported. We evaluated data from 291 adolescents on antiretroviral therapy. The main outcome measure was VF, defined as two consecutive HIV viral load measurements ≥ 400 copies/mL during 24-months of follow-up. Pharmacy refill non-adherence was defined as two consecutive refill adherence measurements $< 95\%$ during the same period. Fifty-three (18%) adolescents experienced VF. One hundred twenty-eight (44%) adolescents had refill non-adherence. Refill non-adherence had poor discriminative ability for indicating VF (receiver operating characteristic AUC = 0.60). Sensitivity and specificity for predicting VF was poor (60% (95% CI 46–74%) and 60% (95% CI 53–66%), respectively). The lack of a viable surrogate for VF in adolescents highlights the urgent need for more access to virologic testing and novel methods of monitoring adolescent treatment adherence.

Keywords Adherence monitoring · Africa · Resource-limited settings · Medication-possession ratio · Adolescent autonomy

Resumen

En los adultos que viven con el VIH, los datos en la farmacia sobre la renovación de recetas médicas son buenos predictores del fracaso virológico. La utilidad de los datos en la farmacia sobre la renovación de recetas médicas para predecir fracaso virológico en adolescentes no ha sido reportada. Se evaluaron los datos de 291 adolescentes en terapia antirretroviral. La principal medida de resultado fue el fracaso virológico, definida como dos medidas consecutivas de carga viral del VIH ≥ 400 copias/ml durante 24 meses de seguimiento. La no adherencia a la renovación de recetas médicas en la farmacia se definió como dos medidas consecutivas de adherencia a la renovación de recetas médicas $< 95\%$ durante el mismo período. Cincuenta y tres (18%) adolescentes tuvieron fracaso virológico. Ciento veintiocho (44%) adolescentes tuvieron no adherencia a la renovación de recetas médicas. El no-adherencia a la renovación de recetas médicas tuvo poca capacidad para indicar fracaso virológico (característica de funcionamiento del receptor AUC = 0.60). La sensibilidad y especificidad para predecir fracaso virológico fue deficiente (60% (95%: 46–74%) y 60% (95% CI 53–66%), respectivamente). La falta de un sustituto viable para el fracaso virológico en los adolescentes resalta la necesidad urgente para más acceso a las pruebas virológicas y métodos novedosos para monitorear la adherencia del tratamiento en los adolescentes.

Palabras clave Seguimiento de adherencia · África · Ámbitos con recursos limitados · Relación de posesiones médicas · La autonomía del adolescente

✉ Elizabeth D. Lowenthal
  lowenthale@email.chop.edu

Extended author information available on the last page of the article

Abbreviations

ART	Anti-retroviral therapy
AUC	Area under the curve
HIV	Human immunodeficiency virus
MEMS	Medical event monitoring system
ROC	Receiver operating characteristic
VF	Virologic failure

Introduction

Worldwide, adolescent HIV-related deaths have more than tripled since 2000, making it the second most common cause of adolescent mortality globally and the leading cause in Africa [1]. Adolescents are the only age group around the world for which AIDS deaths rose between 2001 and 2012 [2, 3]. Infants perinatally infected with HIV during the time of peak incidence in high-prevalence settings, are now reaching adolescence [4]. Many have been taking antiretroviral therapy (ART) for more than 10 years. Compared with younger children and adults, adolescents are more likely to exhibit variability in their daily activities and to experiment with risk-taking behaviors [5, 6]. Adolescents who achieved virologic suppression on antiretroviral therapy have been shown to have a more rapid time to virologic failure (VF) compared to adults [7].

Adherence is strongly associated with virologic response in a dose-dependent manner [8]. Viral load monitoring can improve counselling and clinical decision-making, but is frequently unavailable in low-resource settings [9]. Immunologic criteria are often used in lieu of viral load testing but $CD4 + T$ lymphocyte cell count (CD4 count) criteria have been shown in adults to miss nearly half of all VF cases due to the fact that immunologic decline tends to follow, instead of precede, viral load increases [10]. Substantial misclassification of ART success and failure with immunologic monitoring can happen in both directions. Because of natural variability in CD4 counts, using immunologic criteria as a sole indicator of VF can also lead to premature switches to second-line regimens [11, 12]. Multiple studies have shown that immunologic criteria have poor sensitivity and specificity in identifying VF in both adults and children [13, 14].

Researchers have increasingly turned to pharmacy refill monitoring as a low-cost, simple method of tracking adherence. Pharmacy records have been found to be more strongly associated with virologic outcomes than self-reported adherence data in adults [15]. In addition, Bisson et al. reported that pharmacy refill data were more accurate predictors of VF than CD4 count changes among adults newly starting antiretroviral treatment in Botswana [16]. This association has yet to be studied in a treatment-experienced population or among adolescents. We hypothesized that pharmacy refill would be less predictive in adolescents due to the fact that adolescents frequently have autonomy over medication-taking even when they do not obtain their own refills. This difference in control over medication taking versus obtaining refills potentially delinks the expected association between obtaining refills regularly and taking medications regularly. Given low access to viral load monitoring and the potential for

available metrics to predict VF, we sought to determine and compare the discriminative abilities of pharmacy refill measured adherence and immunological criteria for VF in adolescents.

Methods

Participants and Procedures

Three hundred primarily perinatally HIV-infected adolescents (aged 10–< 20 years) were enrolled in an observational study at the Botswana-Baylor Children's Clinical Centre of Excellence in Gaborone, Botswana beginning in October 2012. This is a large pediatric HIV treatment and referral center in the capital city, which opened in 2003. Participants had a minimum of 6 months of antiretroviral treatment experience at the time of study enrollment. Study participants obtained standard-of-care monitoring and treatment per the Botswana National HIV Treatment Guidelines, including HIV viral load testing and $CD4 + T$-lymphocyte counts every 3 months [17]. Refill adherence measurements were obtained with every medication refill with refill frequency being determined by the treatment team. In addition, adherence to treatment was monitored using microelectronic medication (MEMS) [18] caps on the adolescents' medication bottles. The adolescents and staff at the treatment site were blinded to the MEMS data to help minimize incentives to open the medication bottles when doses were not taken. Data from the first 24 months of follow-up were included in this analysis.

Definitions

Virologic Treatment Failure (VF)

VF was defined as at least two consecutive viral loads > 400 copies/mL during the 24-month follow-up period or a single viral load > 400 copies/mL if it was the last viral load obtained before an adolescent failed to follow-up for scheduled monitoring.

Refill Non-adherence

Refill non-adherence was evaluated as both a continuous variable and a dichotomous variable. The dichotomous refill non-adherence variable allows for direct comparison to the dichotomous immunologic failure variable and classifies refill non-adherence as at least two consecutive refill adherence measurements < 95% during the 24-month follow-up period. The continuous variable was calculated as the number of visits at which adherence was < 95% divided by the total number of visits, reported as a percentage.

Immunologic Failure

Immunologic failure was defined as worsening WHO immune status classification (e.g. from mild to advanced or from advanced to severe CD4 levels) at any point during 24-month follow-up [19].

Adolescent Autonomy

Adolescents' autonomy over obtaining their medications was assessed using a 3-point scale. (1 = adolescent went to the clinic and picked up medicines alone; 2 = adolescent went to the clinic and picked up medications accompanied by someone else; 3 = someone else went to the clinic and picked up the adolescent's medicines for him or her.) Adolescents' autonomy over taking their medicines was assessed using a 4-point scale. (1 = "On most days, I took my medicines by myself with nobody reminding me or watching me;" 2 = "On most days, I took my medicine by myself, but somebody reminded me to take them;" 3 = "On most days, somebody gave me my medicines when it was time for me to take them but I took them by myself;" 4 = "On most days, somebody gave me my medicines and watched me take them.") Autonomy scores at each study visit were averaged over the 24-month study follow-up period.

MEMS Adherence

Electronic medication event monitoring systems (MEMS) [18] caps were utilized with blinding of Botswana-based members of the study team to the MEMS data to minimize social desirability bias. MEMS adherence was calculated based on the number of medication cap openings divided by the number of doses prescribed, and were truncated at 100% per day (with days beginning and ending at 3AM to minimize dosing errors).

Data Analysis

Data were collected and stored using Research Electronic Data Capture (REDCap) Software [20]. Logistic regression and receiver operating characteristic (ROC) analysis assessed the associations of the two-comparator measures of refill non-adherence and immunologic failure with the outcome of VF. ROC analysis also was applied to the comparison between MEMS adherence and VF. Test characteristics were calculated to measure sensitivity and specificity of both refill non-adherence and immunologic failure as diagnostic tests for VF. The ROC curves were compared through non-parametric comparison of areas under the

curve (AUC). To further characterize differences between age and medication-taking autonomy among adolescents with and without VF, Wilcoxon rank-sum tests were performed. Pearson's correlation was used to describe the correlation between age and autonomy. All analyses were completed using STATA 14 software [21].

Results

291 adolescents were included in the analyses. Potential study participants were excluded if they left the study before completing 24 months of follow-up (N = 7) or because genotypic resistance testing indicated that they had moderate or severe resistance to their antiretroviral regimen (N = 2) that might have compromised their ability to achieve and sustain virologic suppression even with perfect adherence to their medications. Subject characteristics are summarized in Table 1. The range of ages was 10.1–19.9 years at study entry with ages skewed toward younger adolescents. Time on treatment at study entry ranged from 6 months to 11.5 years.

53 adolescents (18%) met the pre-defined criteria for VF. With the expectation that each adolescent would have a viral load result at least every 3 months, 84% of expected viral load values (n = 1957) were available for the 24 month follow-up interval. The median number of viral loads per adolescent was 7 (IQR 6–7). Those with VF were older (median age 16.1 years (IQR 14.2–17.7) versus 12.9 years (IQR 11.5–14.7) at study entry, p < 0.01) and had higher levels of autonomy over obtaining their pharmacy refills (median refill score 1.49 (IQR 1.37–1.61) versus 1.78 (IQR 1.74–1.83), p < 0.01). Older adolescents were more likely than younger adolescents to have increased autonomy over obtaining their refills (Pearson's correlation coefficient − 0.74, p < 0.01) and over taking their medicines daily (Pearson's correlation coefficient − 0.66, p < 0.01). However, there was only a moderate correlation between refill autonomy and medication-taking autonomy (Pearson's correlation coefficient 0.58, p < 0.01). Median time on treatment at entry into the study was ~ 7.5 years for both those with and without VF (p > 0.5).

128 adolescents met our definition of refill non-adherent during the 24-month study period and 32 (25.0%) of these individuals experienced VF during the same time period. Of 163 adolescents who did not meet the definition of refill non-adherence, 21 (12.9%) also experienced VF. The odds of having VF was 2.3 times higher among individuals with refill non-adherence than among those who are refill adherent (95% CI 1.2–4.1; p < 0.01).

109 adolescents had immunologic failure during the 24-month study period and 34 (31.2%) of these individuals also experienced VF during the same time period. 182

Table 1 Characteristics of study population (N = 291)

Participant characteristics	Value
Age [median (IQR)]	13.4 years (11.8–15.6)
Time on ART [median (IQR)]	7.5 years (5.3–8.8)
Sex	53% female
ART regimen	
NNRTI	147 (50.5%)
PI	144 (49.5%)
Orphan status	
Non-orphans	164 (56.4%)
Double-orphans	39 (13.4%)
Maternal orphans	32 (11.0%)
Paternal orphans	30 (10.3%)
Unknown	26 (8.9%)*
Number of pharmacy refills during study period [median (IQR)]	18 (16–20)
Number of viral loads during study period [median (IQR)]	7 (6–7)
Number (%) of adolescents with refill non-adherence	128 (44.0%)
Number (%) of adolescents with immunologic failure	109 (37.5%)
Number (%) of patients with virologic failure	53 (18.2%)

IQR interquartile range, *NNRTI* non-nucleoside reverse transcriptase inhibitors, *PI* protease inhibitors

*For some adolescents who lived with only one parent or extended relatives, the vitality status of one or both parents was not known
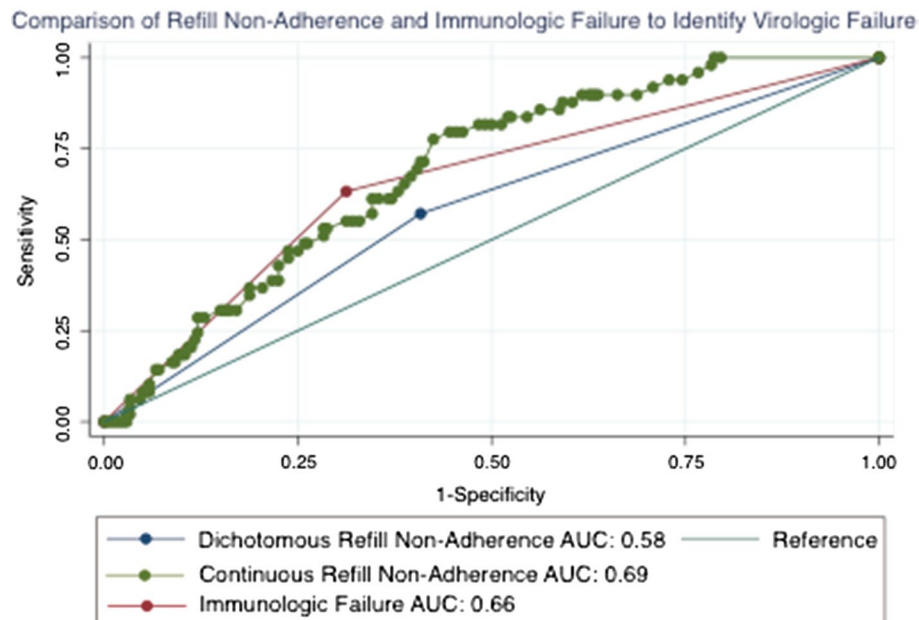

Fig. 1 ROC curve for refill non-adherence and immunologic failure when used to identify patients with virologic failure. Blue and green lines are observed dichotomous and continuous refill non-adherence values, respectively, and the red line demonstrates observed immunologic failure values. The graphs therefore represent the sensitivity graphed against the 1-specificity that would result if each observed refill non-adherence or immunologic failure were used as a diagnostic test for virologic failure. The AUC was 0.58 (95% CI 0.50–0.66) for dichotomous refill non-adherence, 0.69 (95% CI 0.61–0.76) for continuous refill non-adherence and 0.66 (95% CI 0.58–0.73) for immunologic failure. The reference line represents an AUC of 0.50, what would be expected with a measure based on flipping a coin

adolescents maintained or improved their CD4 + T-lymphocyte count and 19 (10.4%) of these individuals also experienced VF. The odds of having VF was 5.6 times higher among individuals with immunologic failure than those who did not have immunologic failure (95% CI 3.0–10.6; p < 0.001) (Fig. 1).

Table 2 Test characteristics for identification of virologic failure (N = 291)

Exposure	Sensitivity	Specificity	PPV	NPV	LR+	LR−
Dichotomous refill non-adherence	60.4% (46.0–73.6)	59.7% (53.1–66.0)	25.0% (17.8–33.4)	87.1% (81.0–91.8)	1.5 (1.2–2.0)	0.7 (0.5–0.9)
Immunologic failure	64.2% (49.8–76.9)	68.5% (62.2–74.3)	31.2% (22.7–40.8)	89.6% (84.2–93.6)	2.0 (1.6–2.7)	0.5 (0.4–0.8)

PPV positive predictive value, *NPV* negative predictive value, *LR+* positive likelihood ratio, *LR−* negative likelihood ratio

Fig. 2 Distribution of Autonomy Scores. Average autonomy of adolescents during the 24-month study follow-up period. Adolescents with an average autonomy of "1" always picked up their medications alone. Those with an average of "3" always had another person pick up the medicines for them. For the subgroup analyses described in the text, adolescents with higher averaged levels of autonomy were classified as "Group 1" and adolescents with lower averaged levels of autonomy as "Group 2"
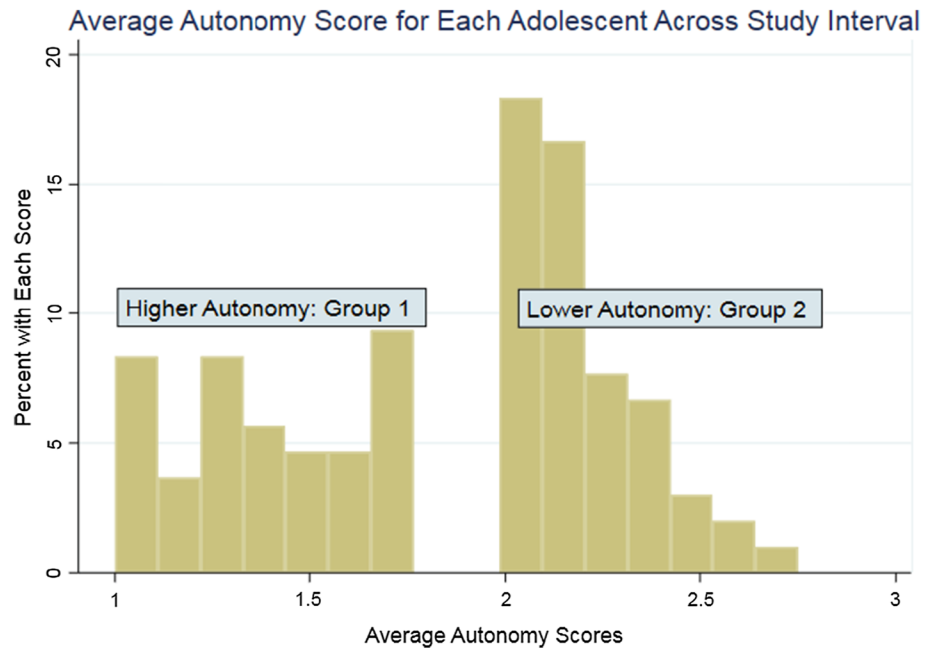
Test characteristics for refill non-adherence and immunologic failure compared to the outcome of VF are outlined in Table 2. ROC analysis resulted in an area under the curve (AUC) of 0.69 (95% CI 0.61–0.76) for the continuous refill measure and 0.58 (95% CI 0.50–0.66) for the dichotomous refill measure. The AUC for the dichotomous immunologic failure measure was 0.66 (95% CI 0.58–0.73) and did not differ significantly from that of the dichotomous refill measure (difference = 0.08; $\chi^2 = 2.71$; p = 0.10) or from that of the continuous refill measure (difference = 0.03; $\chi^2 = 0.38$; p = 0.54) (Fig. 2).

The refill adherence and VF relationship was the weakest among adolescents with the lowest average levels of autonomy ("Group 2") throughout the study period (AUC = 0.49; 95% CI 0.32–0.65). In comparison, adolescents with the highest average levels of autonomy ("Group 1") had an AUC of 0.63 (95% CI 0.50–0.76). Thus, while the relationship of refill to viral load was weak in both groups, it was particularly unhelpful among those with little autonomy over picking up their own refills.

In contrast to the low AUC's observed for the comparisons between refill adherence/virologic failure and immunologic failure/VF, the AUC for the comparison between adherence as measured by electronic monitors and VF was 0.91 (95% CI 0.86–0.96). The high AUC for the comparison between adherence as measured by electronic monitoring caps and VF demonstrates that non-adherence was responsible for most of the VF seen in these adolescents.

Discussion

These results demonstrate that both refill non-adherence and immunologic failure have low sensitivity and specificity for identifying VF in treatment-experienced adolescents. The two-comparator measures were similarly suboptimal for indicating VF in our cohort. Bisson et al. reported that pharmacy refill data reflected virologic treatment outcomes better than immunologic response to treatment and both measures were stronger in identifying VF in treatment-naïve adults than in our treatment-experienced adolescent cohort [16]. In a cohort of treatment-experienced South African adults, pharmacy refill data predicted virologic outcomes nearly as well as electronic monitoring [22]. Pharmacy refill measures have also been shown to be strongly associated with adults' virologic treatment outcomes in Brazil [23].

In some populations, pharmacy refill measures have been found to be sensitive, but not specific for detecting antiretroviral therapy non-adherence [24–27]. However, in our adolescents, sensitivity of the pharmacy refill measure was also poor.

There are several possible reasons for the difference in the strength of pharmacy refill records to predict virologic treatment outcomes in adolescents compared with adults. Perinatally HIV-infected adolescents might be more likely than adults to share pills with others in the household due to increased rates of within-family disclosure of their HIV status [28]. Adolescents may have autonomy over taking their medications, but not over obtaining their own pharmacy refills. Discordance between responsibility over medication-taking and responsibility over obtaining refills may lead to increased misclassification of good refill adherence as indicative of good medication adherence. Pharmacy refill records may be more predictive of treatment failure in an adult population because adults typically maintain autonomy over every step of the medication-acquisition and medication-taking processes. In addition, adolescents may receive a "secondary gain" from coming to the clinic for refills, not because they want their medications but because they receive emotional support or comfort from the clinic staff. Finally, during late adolescence, the majority of adolescents have yet to transition from concrete to abstract thinking [29]. This may lead them to come to the clinic simply because they are scheduled for a refill, despite not having completed their medications.

Our results therefore may not be generalizable to clinics that do not provide patients with a scheduled refill date. It is common in public clinics in Africa for pharmacy refill visits to be scheduled, however [24]. Similarly, clinics with high staff turnover and/or particularly busy staff who have little time to engage with individual patients might have fewer adolescents who come for refills when they have not completed their medications. The strength of relationships with clinic staff (or the likelihood of being scolded for not obtaining refills on the prescribed date) likely impacts behavior. Although most adolescents had viral loads drawn as scheduled every 3 months, misclassification of treatment outcomes may also have occurred for adolescents who did not get their viral loads drawn as scheduled.

Despite these limitations, this study has several major strengths. First, the Botswana-Baylor Children's Clinical Centre of Excellence is adjacent to the clinic where the Bisson, et al. study was conducted, serving similar catchment areas, and thus allowing for a more direct comparison between the adult and adolescent populations than would have been possible with two disparate settings. Frequent and consistent viral load monitoring was available throughout the 2-year follow-up. The strong association between MEMS data and viral load values demonstrated that most

VF can be directly attributed to poor adherence in our cohort.

Conclusion

Since both pharmacy refill data and CD4 counts are poor identifiers of treatment failure for treatment-experienced adolescents, there is a strong need for alternative monitoring methods or increased access to viral load tests for this vulnerable group.

Compliance with Ethical Standards

Conflict interest None of the authors have conflicts of interest related to this manuscript.

Ethical Approval All procedures were in accordance with the ethical standards of the institutional and national research committees and with the 1964 Helsinki Declaration and its later amendments and comparable ethical standards. The study was approved by the Botswana Health Research Development Committee and Institutional Review Boards at the University of Pennsylvania and Baylor College of Medicine. Written informed consent was obtained from a parent or guardian of each adolescent study participant and assent was obtained for each adolescent participant.

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Affiliations

Leah Genn[1] · Jennifer Chapman[1] · Harriet Okatch[1,2] · Neil Abell[3] · Tafireyi Marukutira[4] · Ontibile Tshume[4] · Gabriel Anabwani[4,5] · Robert Gross[6] · Elizabeth D. Lowenthal[1,7]

Leah Genn
leahgenn@gmail.com

Jennifer Chapman
chapmanj1@email.chop.edu

Harriet Okatch
okatcharriet@gmail.com

Neil Abell
nabell@fsu.edu

Tafireyi Marukutira
tcmarukutira@yahoo.com

Ontibile Tshume
otshume@baylotbotswana.org.bw

Gabriel Anabwani
ganabwani@gmail.com

Robert Gross
grossr@mail.med.upenn.edu

1   Children's Hospital of Philadelphia, Philadelphia, PA, USA

2 Masters of Public Health Program, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA

3 Department of Social Work, Florida State University, Tallahassee, FL, USA

4 Botswana-Baylor Children's Clinical Centre of Excellence, Gaborone, Botswana

5 Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA

6 Departments of Medicine and Epidemiology, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA

7 Departments of Pediatrics and Epidemiology, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA