Contribution of maternal ART and breastfeeding to 24-month survival

in HIV-exposed uninfected children:

an individual pooled analysis of African and Asian studies

Shino Arikawa, Nigel Rollins, Gonzague Jourdain, Jean Humphrey, Athena P. Kourtis, Irving Hoffman, Max Essex, Tim Farley, Hoosen M. Coovadia, Glenda Gray, Louise Kuhn, Roger Shapiro, Valériane Leroy, Robert C. Bollinger, Carolyne Onyango-Makumbi, Shahin Lockman, Carina Marquez, Tanya Doherty, François Dabis, Laurent Mandelbrot, Sophie Le Coeur, Matthieu Rolland, Pierre Joly, Marie-Louise Newell, Renaud Becquet

Nigel Rollins, MD

Department of Maternal, Newborn, Child and Adolescent Health, World Health Organization, Geneva, Switzerland

Gonzague Jourdain, MD

Institut de recherche pour le développement (IRD) UMI 174-PHPT, Marseille, France ; Faculty of Associated Medical Sciences, Chiang Mai University, Chiang Mai, Thailand ; and Department of Immunology and Infectious Diseases, Harvard T.H. Chan School of Public Health, Boston, USA

Jean Humphrey, ScD

Department of International Health, Center for Global Health, Bloomberg School of Public Health, Johns Hopkins University, USA

Athena P. Kourtis, MD

Women's Health and Fertility Branch, Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, USA; Emory University School of Medicine and Eastern Virginia Medical School, Atlanta, USA

Irving Hoffman, PA

Division of Infectious Diseases, Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, NC, USA

Max Essex, PhD

Department of Immunology and Infectious Diseases, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA

Tim Farley, PhD on behalf of the Kesho Bora study team

Sigma3 Services SÀRL, Nyon, Switzerland

Hoosen M. Coovadia, MD

Maternal Adolescent and Child Health (MatCH), University of the Witwatersrand, Johannesburg, South Africa

Glenda Gray, MD

South African Medical Research Council Tygerberg, South Africa; Perinatal HIV Research Unit, University of the Witwatersrand, Johannesburg, South Africa

Louise Kuhn, PhD

Gertrude H. Sergievsky Center, College of Physicians and Surgeons; and Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, USA

Roger Shapiro, MD

Department of Immunology and Infectious Diseases, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA

Valériane Leroy, MD

Inserm, Centre de recherche Inserm U1027, Université Paul Sabatier Toulouse 3, Toulouse, France

Robert C. Bollinger, MD

Center for Clinical Global Health Education, Johns Hopkins University, Baltimore, USA

Carolyne Onyango-Makumbi, MD

Makerere University – Johns Hopkins University Research Collaboration/MU-JHU CARE LTD, Kampala, Uganda

Shahin Lockman, MD

Department of Immunology and Infectious Diseases, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA

Carina Marquez, MD

Division of HIV, Infectious Diseases and Global Medicine, University of California, San Francisco, Zuckerberg San Francisco General Hospital, USA

Tanya Doherty, PhD

Health Systems Research Unit, South African Medical Research Council, Tygerberg, South Africa

François Dabis, MD

University of Bordeaux, Inserm, Bordeaux Population Health Research Center, team IDLIC, UMR 1219, Bordeaux, France

Laurent Mandelbrot, MD

University Paris-Diderot, Assitance Publique Hôpitaux de Paris, Paris, France

Sophie Le Coeur, MD

Institut National d'Etudes Démographiques (Ined), Paris, France; Institut de recherche pour le développement (IRD) UMI174-PHPT, Marseille, France; Faculty of Associated Medical Sciences, Chiang Mai University, Chiang Mai, Thailand ; and Department of Immunology and Infectious Diseases, Harvard T.H. Chan School of Public Health, Boston, USA

Matthieu Rolland, MSC

University of Bordeaux, Inserm, Bordeaux Population Health Research Center, team IDLIC, UMR 1219, Bordeaux, France

Pierre Joly, PhD

University of Bordeaux, Inserm, Bordeaux Population Health Research Center, team Biostatistics, UMR 1219, Bordeaux, France

Marie-Louise Newell, PhD

Institute for Developmental Science and Global Health Research Institute, Faculty of Medicine, University of Southampton, UK

Renaud Becquet, PhD

University of Bordeaux, Inserm, Bordeaux Population Health Research Center, team IDLIC, UMR 1219, Bordeaux, France

Corresponding author:

Shino Arikawa (shino.arikawa@u-bordeaux.fr), MPH

University of Bordeaux, Inserm, Bordeaux Population Health Research Center, team IDLIC, UMR 1219, F-33000 Bordeaux, France

Postal adresse : 146 Rue Léo Saignat, 33076 Bordeaux cedex France

Telephone: +33 (0)5 57 57 13 93 Fax: +33 (0)5 56 24 00 81

Summary: Pooled results from 21 studies involving over 19 thousand HIV-exposed but uninfected children show that an estimated two-thirds of infant deaths are attributable to lack of antiretroviral treatment for mothers, low birthweight, never being breastfed and mother's death.

ABSTRACT

Background

Increasing numbers of HIV-infected pregnant women receive antiretroviral therapy (ART) to prevent mother-to-child transmission (PMTCT). Studies suggested that HIV-exposed uninfected (HEU) children face higher mortality than HIV-unexposed children, but evidence mostly relates to the pre-ART era, breastfeeding of limited duration and considerable maternal mortality. Maternal ART and prolonged breastfeeding under cover of ART may improve survival, although this has not been reliably quantified.

Methods

Individual data on 19,219 HEU children from 21 PMTCT trials/cohorts undertaken 1995-2015 in Africa and Asia were pooled and the association between 24-month mortality and maternal/infant factors quantified using random-effects Cox proportional hazards models accounting for between-study heterogeneity. Adjusted attributable fractions of risks computed using the predict function in the R package "frailtypack" estimate the relative contribution of risk factors to overall mortality in HEU children.

Results

Cumulative incidence of death was 5.5% (95%CI: 5.1-5.9) by age 24 months. Low birth weight (LBW<2500g, adjusted Hazard Ratio (aHR: 2.9), no breastfeeding (aHR: 2.5) and maternal death (aHR: 11.1) were significantly associated with increased mortality. Maternal ART (aHR: 0.5) was significantly associated with lower mortality. At population level, LBW accounted for 16.2% of child deaths by 24 months, never breastfeeding for 10.8%, mother not receiving ART for 45.6%, and maternal death for 4.3%; these factors combined explained 63.6% of deaths by age 24 months.

Conclusion

Survival of HEU children could be substantially improved if public health strategies provided all mothers living with HIV with ART and supported optimal infant feeding and care for LBW neonates.

Key words: HIV-exposed uninfected, children, infants, mortality, Asia, Africa

INTRODUCTION

Antiretroviral therapy (ART) to prevent mother-to-child transmission (PMTCT) has dramatically reduced the number of HIV-infected infants(1, 2); as more women living with HIV survive and become pregnant, the number of HIV-exposed uninfected (HEU) children continues to increase(3). Several studies have shown that HEU children may experience worse health outcomes than HIV-unexposed uninfected (HUU) children in the same setting (4-10), although this has not been confirmed everywhere (11-14). Most evidence relates to the era before widespread use of ART for PMTCT or for treatment, when increased mortality in HEU children was associated with poor maternal health and lack of prolonged breastfeeding. Maternal ART for life and prolonged breastfeeding with the protection of ART could ameliorate such negative associations (15, 16), but this has not yet been reliably quantified.

By pooling available individual data on HEU children from clinical trials and observational studies, from both the pre- and post-ART era, we assessed mortality risk in HEU children in Africa and Asia and associated factors. We also estimated the relative importance of identified risk factors in mediating poor outcomes among HIV-exposed, uninfected children.

METHODS

In a recent systematic review(17), we electronically searched two bibliographic databases, PubMed and Scopus, of papers published 2004-2015 with keywords: "HIV"; "Mortality"; and "Child" or "Infant", without restrictions on type or region of study, limited to English and French. Titles and abstracts were assessed; retained articles were subject to full text reviews with identification of additional references. Additionally, we identified PMTCT trials with potential data on mortality in HEU children. Overall 29 studies were identified and their principal investigators contacted. One declined participation(18), five were unable to share data(5, 19-22) and two did not meet inclusion

criteria(23, 24), leaving 21 studies for the pooled 24 month-mortality analysis: 16 from sub-Saharan Africa(4, 8, 25-38) and five from Asia(39-42). Of these, 17 were randomized trials and 4 observational studies, conducted at different times (Supplementary file, Table 1), with varying sample sizes and follow-up durations (Table 1).

Maternal antiretroviral exposure was categorized as: (a) None; (b) single/double peripartum antiretrovirals for PMTCT; (c) 3-drug ART for PMTCT given antenatally and postnatally until cessation of breastfeeding when breastfeeding or until delivery when exclusively formula-fed; or (d) 3-drug ART for life, prescribed beyond breastfeeding cessation, as per WHO HIV treatment and prevention recommendations (43, 44). Mothers with missing information on antiretroviral use (n=44) were assumed to have followed the relevant study protocol (28, 35) and thus categorized into the single/double antiretroviral PMTCT. The final HIV status of each child was defined by study-specific criteria. In our analyses, each child contributed from birth to 24 months of age, with right-censoring in case of death, end of study follow up and loss-to-follow up. We restricted analyses to HEU children with information on breastfeeding, excluding 457 children with unknown infant feeding status. Mortality rates per 100 child-years of follow-up were estimated by maternal and child characteristics. We used Kaplan-Meier method to estimate survival curves and the log-rank test to test for differences between groups.

Associations between 24-month mortality and the following factors were assessed: residence (rural vs urban/peri-urban), sex, low birth weight (<2,500g), breastfeeding (ever/never), maternal education (none/primary vs above), maternal age at delivery (5-year categories), maternal antiretroviral exposure (fixed) and maternal vital status (time-dependent). Children known to have initiated breastfeeding, but with unknown weaning date (n=1,032) were considered to have been breastfed from birth to either six months of age as per WHO feeding guidance at the time(45), study exit date or date of mother's death, whichever occurred first. We used random-effects Cox proportional hazards models to estimate the association between 24 month-mortality and potential

risk factors, accounting for heterogeneity between studies. The final multivariable model included region (Africa vs Asia) as fixed effect and adjusted for maternal antenatal CD4 cell count (categorical) as CD4 counts and ART eligibility varied widely between studies. Data from different sites in Kesho Bora and HIVNET024 were treated separately. Missing data were included as a separate category to maintain sample size. We used a stepwise-descending approach for selection of variables in multivariable models which included variables statistically significant in univariate analyses (at P-value < 0.1, except for maternal antiretroviral exposure which was maintained in the model independent of statistical significance). In the final model, statistical significance was reached when P-value <0.05. We also analyzed the association between weaning and survival among breastfed children only (n=13,418), with breastfeeding cessation defined in a time-varying manner.

We assessed the combined effects of breastfeeding and maternal 3-drug ART (for PMTCT or for life) on mortality, classifying observation time for each HEU child into four different categories defined by child being breastfed (yes/no) and mother being on 3-drug ART (yes/no), with breastfeeding and ART variables time-dependent. When the date of ART end was unknown, ART was assumed to have continued until the weaning date or six months post-partum(45), whichever came first. The association between 24-month mortality and breastfeeding/maternal 3-drug ART was assessed in multivariable analyses using Cox proportional hazards model allowing for heterogeneity between study/trials and adjusting for region as fixed effect and maternal antenatal CD4 cell count and birth weight (<2,500g) as categorical variables.

Finally, to investigate the relative contribution of risk factors to overall 24-month mortality in HEU children, we estimated the adjusted attributable fractions (AFs) of risks based on our final multivariable model (46, 47). The AF for a given factor was the number of deaths attributable to the factor divided by the total number of deaths in our population if the prevalence of other factors remained at the same level. To do this, we first obtained the total number of deaths at a given time by summing the individual predicted probabilities of survival for each child based on the predict

function in the R package “frailtypack”(48), then subtracted this number from the total population to derive the number of deaths. To estimate the number of deaths attributable to the exposure of interest, we computed the number of deaths in the population as if it was not exposed to the factor while exposures to other risk factors were unchanged. Non-exposure was simulated by setting all children to the reference category. For example, for deaths associated with low birth weight, all children were classified into the category of having birth weight over 2,500g. The number of deaths attributable to a specific factor was the difference between the total number of deaths calculated previously and the number of deaths in the unexposed population. We estimated the adjusted AFs of the identified risk factors at 6, 12 and 24 months of age and computed 95% confidence intervals (CIs) using bootstrapping(49). All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC). For the estimates of AF, we used the R packages “frailtypack”(48) and “boot”(49) using R version 3.3.2 (R Development Core Team, 2004).

RESULTS

Overall, 19,219 HEU children contributed to the analyses (Figure 1). Maternal/child baseline characteristics are shown in Table 2. Median child follow-up was 404 days (interquartile range [IQR]: 336-712). Over 75% of children were born in sub-Saharan Africa, mostly Southern Africa; nearly 70% were born prior to 2005. Most children were ever breastfed (69.8%) for a median 181 days (IQR: 126-365). Maternal antiretroviral exposure varied across studies (Supplementary file, Table 2), reflecting the timing of the study and prevailing ART and PMTCT recommendations(44). Overall, 23% of mothers received no antiretrovirals, 61% received mono/dual peripartum antiretrovirals for PMTCT, 12% received 3-drug ART for PMTCT and only 4% were on ART for life. Median antenatal CD4 count was 405 cells/mm^3 (IQR: 280-563); 58% of mothers had a CD4 count above 350 cells/mm^3 at first antenatal visit. Median antenatal CD4 count in women receiving ART for life was low at 214

cells/mm^3 (IQR: 147-361). Median duration of ART was 178 (IQR: 152-196) and 443 (IQR: 371-730) days for 3-drug ART for PMTCT and ART for life group respectively. Information on maternal viral load was missing for 16%, but among those with available information, median antenatal viral load was 4.0 log_{10} copies/ml (IQR: 3.3 to 4.6).

HEU child mortality

Cumulative incidence of death was 2.1% (394/18,012; 95%CI: 1.9-2.3), 3.1% (575/17,176; 95%CI: 2.9-3.4), 4.5% (797/12,153; 95%CI: 4.2 -4.8) and 5.5% (884/4,245; 95%CI: 5.1 -5.9) by age 3, 6, 12 and 24 months respectively. Median age at death was 111 days (IQR: 37-244). Mortality varied from 0% in PHPT-5 1st to 17.8% in Ditrame-ANRSb (Table 1). Stratified by geographical region (Figure 2) 24-month survival probability was significantly higher in Asia than Africa (P<.0001). Of the 300 children whose mothers died, 17% (n=51) did not survive after mother's death. Child mortality declined with increasing age at the time of mother's death: 52% if mother died within 1 month of delivery, 36% if she died between 1-3 months, 20% between 3-6 months, 6% in 6-12 months and 4% in 12-24 months. Mortality was highest among children with mothers not being on any antiretrovirals (6.1/100 child-years), with mortality in single/dual antiretrovirals for PMTCT 3.1/100, 3-drug ART for PMTCT 2.7/100, and ART for life 3.4/100 child-years. Of note, one- third of the single/dual antiretrovirals for PMTCT and the 3-drug ART for PMTCT groups respectively were comprised of mothers of children in PHPT trials where child deaths were rarely observed, which might explain lower mortality rates in these two groups.

Association with maternal/child characteristics

Univariably, LBW children were at 3-fold risk of dying as were never breastfed children (Table 3). Children whose mother had died were 16-times as likely also to die compared to children whose mothers survived; maternal antiretroviral exposure was associated with reduced child mortality but this did not reach statistical significance. Adjusting for region, maternal antenatal CD4 count, maternal antiretroviral exposure and maternal vital status, LBW and never breastfeeding remained significantly associated with increased mortality (Table 3); the association between maternal ART for life and reduced child mortality became statistically significant (adjusted Hazard Ratio [aHR]: 0.5; 95%CI: 0.3-0.9) after adjusting for maternal CD4 count (HR: 0.72 in univariate analysis, declining to 0.54 adjusting for maternal CD4 count only). Associations between mortality and the other antiretroviral categories did not reach statistical significance (single/dual antiretrovirals aHR 0.78, 95%CI: 0.50-1.22; 3-drug ART for PMTCT aHR 0.66, 95%CI: 0.39-1.13). Children whose mother had died remained at a substantially increased risk of death (aHR 11.1).

Additional analyses including ever-breastfed children only (n=13,418), treating breastfeeding cessation as a time-dependent variable, showed mortality risk to be significantly increased after breastfeeding cessation. Adjusting for region, birth weight, maternal CD4 count, and maternal antiretroviral exposure, breastfeeding cessation was associated with a 12.5-fold (95%CI: 10.3-15.3) risk of death. In this model, children with mother receiving 3-drug ART (both PMTCT and for life) were at significantly lower risk of death (aHR 0.51, 95%CI: 0.30-0.85 for 3-drug ART for PMTCT; aHR 0.45, 95%CI: 0.22-0.92 for ART for life, Table not shown) than children whose mother did not receive ARVs.

Sensitivity analyses

To investigate the sensitivity of our assumption on 44 women with no information on ARV exposure, we have run the analyses excluding these women: the aHR were virtually unchanged. Further, two additional analyses were carried out to verify the effects of the inclusion of 1,032 children with no

information on weaning date and our assumption on their breastfeeding cessation at 6 months. Excluding these children, in the model with breastfeeding treated as fixed-effect, all adjusted HRs were comparable to results shown in Table 3 (aHR: 3.0, 95%CI: 2.3-3.9 versus aHR: 2.5, 95%CI: 2.0-3.2). When breastfeeding was treated as a time-dependent variable, the risk related to breastfeeding cessation increased slightly but remained comparable to results presented in Table 3 (aHR: 16.9, 95%CI: 13.5-21.1 versus aHR: 13.1, 95%CI: 10.7-16.0).

Combined effects of maternal ART and breastfeeding

Mortality by 24 months of age differed significantly by breastfeeding and maternal 3-drug ART status at a given time (P<.0001) (Table 4). Compared to not currently breastfed children with mothers not receiving 3-drug ART (A), mortality risk in not currently breastfed children with mothers receiving 3-drug ART (B) was significantly reduced (HR: 0.6). In absence of maternal 3-drug ART, currently breastfed children (C) were significantly less likely to die (HR: 0.07). Currently breastfed children whose mothers were receiving 3-drug ART (D) had the lowest mortality risk (HR: 0.04).

Adjusted attributable fractions of risks

To investigate the impact of LBW, never breastfeeding, mother not on 3-drug ART for life and maternal death, we estimated the adjusted attributable fractions (AFs) of risks based on the parameter estimates obtained from our final model (Table 3). Mother not receiving 3-drug ART for life accounted for 45.6% (95%CI: 19.1-63.9) of child deaths by 24 months. LBW accounted for an estimated 16.2% of child deaths by 24 months, never breastfeeding for 10.8%, and maternal death for 4.3%. Combined, these four factors explained 63.6% (95%CI: 45.7-76.6) of deaths by 24 months of age. The adjusted attributable fractions of risks at 6 and 12 months related to these four factors did not significantly differ from those at 24 months (Table 5).

DISCUSSION

Using data from 21 studies/trials undertaken between 1995 and 2015 in Africa and Asia, our findings suggest that where mothers are alive, on ART for life and breastfeed their infants, 24-month mortality in HEU children is substantially reduced.

As reported previously (50-52), LBW, prevalent in 12% of these HEU children, was a major risk factor for mortality. However, the negative consequences of LBW, and non-breastfeeding, may be even greater in settings outside the context of well-resourced research studies. Almost half of HEU deaths occurred in the first three months of life, and two-thirds before six months, highlighting the importance for intervening programmatically in this early period.

The survival of mothers living with HIV had a major effect on the survival of HEU children; this association has also been reported among HUU children (53). In our analyses, the death of a mother, shortly after delivery was most hazardous for the survival of their HEU children.

Our results suggest that the risk of mortality in HEU children is reduced when mothers are either on ART until breastfeeding cessation or for life. Mother's initiation and continuation of ART likely improves her own health, which in turn increases the chances of child survival, through better breastfeeding practices, reduced exposure to co-morbidities, improved mother's care capacity and other unmeasured benefits at the household level.

The estimated attributable fractions (AFs) differed from the adjusted HRs, which indicates that the impact at population level, which reflects prevalence of risk factors, differs from that at individual level. The confidence interval around the AF estimate of mother not receiving 3-drug ART for life was particularly wide and caution is required in interpreting this result. Our estimated AFs show that 36% of HEU child mortality at 24 months could not be accounted for by the four risk factors identified, and highlight that HEU children are also at risk of death from other common causes of child mortality. The lack of contemporaneous mortality data from HUU children meant that we were

unable to categorically comment whether, if these four risk factors are fully addressed, HEU children are at any greater mortality risk.

Study Limitations

Although the analyses include a large number of HEU children from diverse settings, interpretation of findings is hindered by lack of detail on potentially important variables including gestational age, neonatal care practices (early initiation and type of breastfeeding), or household exposure to opportunistic infections (such as tuberculosis); these factors may account for much of the remaining 36% mortality.

Relatively few women were on ART for life and studies generally followed earlier WHO guidelines on HIV and infant feeding recommending breastfeeding for about six months only. Although we confirm the associations between reduced mortality risk and maternal ART for life and breastfeeding, our data does not allow us to fully capture the complex associations between different factors that influence child's survival outcome. The women on ART in our study are a highly select population and we cannot comment to what extent such reductions are facilitated by study-specific factors and whether such associations would be equally observed in women on ART in standard-of-care settings. Further, due to lack of data, we were unable to allow for cotrimoxazole prophylaxis and childhood immunization, which aim to prevent infectious morbidity in young children.

We were also unable to differentiate small-for-gestational age from premature infants in those with LBW; about 11% of all infants in Eastern and Southern Africa are born with LBW, and around 28% of infants in Southeast Asia(54). LBW has been associated with HIV infection in pregnant women in sub-Saharan Africa and with the protease inhibitor class of ART during pregnancy (55-57). While the

primary drivers for LBW may vary by region and HIV exposure, the relationship between LBW and mortality in both HEU and HUU is clear and strong, and has immediate programmatic implications.

Combination of 3-drug ART was introduced in about the middle of the timespan covered by the studies included; ART eligibility criteria varied over time as did inclusion for trials. Although we could not allow for these trends, these factors could have introduced selection bias. Each study had its own criteria for eligibility, including CD4 counts. Data included in our analysis were heterogeneous in terms of feeding, and duration of follow up, which limits our ability to generalize the results beyond these studies. Finally, exclusion of 457 children whose breastfeeding status was unknown might have led to underestimation of mortality rates as almost 29% (132/457) of these children died before 12 months of age; 105 died before 1 month, 17 between 1-3 months, and 10 died thereafter.

Future research priorities

We show substantial regional differences in 24-month mortality, which deserves further investigation, as do the issues surrounding breastfeeding. Explaining the missing fraction of HIV-related and other external mortality risk factors requires prospectively collected data from both HEU and HUU populations. It remains unclear whether HEU infants and children are immunologically impaired at a clinically significant level or whether increased exposure to opportunistic infections because of living in HIV-affected households would explain the missing fraction. Yet, perhaps the most germane question is whether increasing roll-out of lifelong ART among women living with HIV and fully supporting optimal infant feeding practices will mitigate the patterns of risks identified in these historical cohorts. With more and more women living with HIV being initiated on ART, understanding the interactions between fetal HIV and ART exposure, prematurity or small-for-gestational age on mortality and other long term outcomes including early child development, infectious morbidity or the risk of non-communicable diseases will be increasingly important.

CONCLUSION

Our findings show that not-breastfeeding and low birthweight were associated with considerable mortality risk and suggested that maternal ART, initiated before or during pregnancy, may substantially reduce child mortality in the first two years of life. With increasing numbers of HIV infected pregnant women now being initiated on ART, this would provide hope for reducing overall child mortality in settings of high HIV prevalence. The importance of delivering effective integrated care so that women living with HIV are not only initiated on ART but are also linked with other essential elements of maternal and child health care is clear. Eliminating paediatric HIV and improving the survival, health and development of HIV exposed uninfected children should not be separate from improving the wellbeing of mothers and children not affected by HIV, and our metric of success needs to evolve to 'HIV-free survival and development'. While integrated programmes and coordinated research and monitoring are unquestionably possible, continued global investment in these responses is perhaps the greatest challenge.

NOTES

Authors' contributions

RB, MLN and NR initiated and set the objectives of the collaboration. SA undertook the literature review, managed the data pooling, participated in the definition of the statistical analysis plan, performed statistical analysis and wrote the first draft of the paper. RB, MLN and NR defined the statistical analysis plans and substantially contributed to the writing of the manuscript. MR and PJ substantially contributed to the statistical analysis. GJ, JH, TF, GG, LK, RS, VL, SL, RCB, TD and SLC critically reviewed the manuscript and substantially contributed to the interpretation of the results. All other co-authors reviewed the manuscript.

Acknowledgements

BAN: Dr Charles van der Horst, Dr Denise Jamieson

Ditrame-ANRSa: Christiane Welffens-Ekra, Philippe Msellati

Ditrame-ANRSb: Nicolas Meda, Philippe Van de Perre

Ditrame Plus: Marguerite Timité-Konan, Clarisse Bosse

Good Start: Dr Mickey Chopra, Prof Debra Jackson, Ms Vundli Ramokolo, Prof Ameena Goga

HIVIGLOB: J Brooks Jackson, Laura A Guay, Philippa Musoke, Mary Glenn Fowler, Michael C Mubiru

PEP: Mike Urban (University of Stellenbosch)

PHPT: Marc Lallemant, Principal investigator of the PHPT clinical trials, all PHPT coinvestigators, the PHPT staff who help collect and manage the data, and Nicolas Salvadori for the preparation of the data-set of the PHPT studies.

PROMOTE2: Diane Havlir, Theodore Ruel.

SWEN: Amita Gupta, Jayagowri Sasty, Harjot K. Singh

ZEBS: The late Dr. Moses Sinkala (Lusaka District Health Management Team), Drs Chipepo Kankasa (University Teaching Hospital), Donald M. Thea (Boston University), Grace M. Aldrovandi (University of California Los Angeles)

Disclaimer:

The World Health Organization had no role in the study design, data collection, data analysis, or interpretation of data. The findings and conclusions in this paper are those of the authors and do not necessarily represent the official position of WHO or of the Centers for Disease Control and Prevention.

Funding

This work was funded by the World Health Organization.

Declaration of interests

All authors declare no competing interests.

REFERENCES

1. UNAIDS. Prevention Gap Report. Geneva: 2016.

2. UNAIDS. On the Fast-track to an AIDS-Free Generation. Geneva: 2016.

3. Evans C, Jones CE, Prendergast AJ. HIV-exposed, uninfected infants: new global challenges in the era of paediatric HIV elimination. Lancet Infect Dis. 2016;16(6):e92-e107. Epub 2016/04/07. doi: 10.1016/s1473-3099(16)00055-4. PubMed PMID: 27049574.

4. Marinda E, Humphrey JH, Iliff PJ, Mutasa K, Nathoo KJ, Piwoz EG, et al. Child mortality according to maternal and infant HIV status in Zimbabwe. Pediatric Infectious Disease Journal. 2007;26(6):519-26. doi: 10.1097/01.inf.0000264527.69954.4c.

5. Brahmbhatt H, Kigozi G, Wabwire-Mangen F, Serwadda D, Lutalo T, Nalugoda F, et al. Mortality in HIV-infected and uninfected children of HIV-infected and uninfected mothers in rural Uganda. J Acquir Immune Defic Syndr. 2006;41(4):504-8. Epub 2006/05/03. doi: 10.1097/01.qai.0000188122.15493.0a. PubMed PMID: 16652060.

6. Powis KM, Kitch D, Ogwu A, Hughes MD, Lockman S, Leidner J, et al. Increased risk of preterm delivery among HIV-infected women randomized to protease versus nucleoside reverse transcriptase inhibitor-based HAART during pregnancy. Journal of Infectious Diseases. 2011;204(4):506-14. doi: 10.1093/infdis/jir307.

7. Koyanagi A, Humphrey JH, Moulton LH, Ntozini R, Mutasa K, Iliff P, et al. Predictive value of weight loss on mortality of HIV-positive mothers in a prolonged breastfeeding setting. AIDS Res Hum Retroviruses. 2011;27(11):1141-8. Epub 2011/01/14. doi: 10.1089/aid.2010.0293. PubMed PMID: 21226627; PubMed Central PMCID: PMCPMC3243462.

8. Shapiro RL, Lockman S, Kim S, Smeaton L, Rahkola JT, Thior I, et al. Infant morbidity, mortality, and breast milk immunologic profiles among breast-feeding HIV-infected and HIV-uninfected women in Botswana. Journal of Infectious Diseases. 2007;196(4):562-9. doi: 10.1086/519847.

9. von Mollendorf C, von Gottberg A, Tempia S, Meiring S, de Gouveia L, Quan V, et al. Increased risk for and mortality from invasive pneumococcal disease in HIV-exposed but uninfected infants aged <1 year in South Africa, 2009-2013. Clin Infect Dis. 2015;60(9):1346-56. doi: 10.1093/cid/civ059. PubMed PMID: 25645212.

10. Henderson RA, Miotti PG, Saavedra JM, Dallabetta G, Chiphangwi J, Liomba G, et al. Longitudinal growth during the first 2 years of life in children born to HIV-infected mothers in Malawi, Africa. Pediatric AIDS and HIV infection. 1996;7(2):91-7. PubMed PMID: 11361486.

11. Moraleda C, de Deus N, Serna-Bolea C, Renom M, Quinto L, Macete E, et al. Impact of HIV exposure on health outcomes in HIV-negative infants born to HIV-positive mothers in Sub-Saharan Africa. J Acquir Immune Defic Syndr. 2014;65(2):182-9. doi: 10.1097/QAI.0000000000000019. PubMed PMID: 24442224.

12. Landes M, van Lettow M, Chan AK, Mayuni I, Schouten EJ, Bedell RA. Mortality and health outcomes of HIV-exposed and unexposed children in a PMTCT cohort in Malawi. PLoS One. 2012;7(10):e47337. Epub 2012/10/20. doi: 10.1371/journal.pone.0047337. PubMed PMID: 23082157; PubMed Central PMCID: PMCPMC3474798.

13. Patel D, Bland R, Coovadia H, Rollins N, Coutsoudis A, Newell ML. Breastfeeding, HIV status and weights in South African children: a comparison of HIV-exposed and unexposed children. Aids. 2010;24(3):437-45. Epub 2009/11/17. doi: 10.1097/QAD.0b013e3283345f91. PubMed PMID: 19915445.

14. Bailey RC, Kamenga MC, Nsuami MJ, Nieburg P, St Louis ME. Growth of children according to maternal and child HIV, immunological and disease characteristics: a prospective cohort study in Kinshasa, Democratic Republic of Congo. Int J Epidemiol. 1999;28(3):532-40. Epub 1999/07/16. PubMed PMID: 10405861.

15. Ndirangu J, Newell ML, Thorne C, Bland R. Treating HIV-infected mothers reduces under 5 years of age mortality rates to levels seen in children of HIV-uninfected mothers in rural South Africa. Antiviral Therapy. 2012;17(1):81-90. doi: 10.3851/IMP1991.

16. Thorne C IP, Chamla D, Romano S, Luo C, Newell ML. Morbidity and mortality in HIV-exposed uninfected children. Future Virology. 2015;10(9):1077-100.

17. Arikawa S, Rollins N, Newell ML, Becquet R. Mortality risk and associated factors in HIV-exposed, uninfected children. Trop Med Int Health. 2016;21(6):720-34. Epub 2016/04/20. doi: 10.1111/tmi.12695. PubMed PMID: 27091659; PubMed Central PMCID: PMCPmc5021152.

18. Taha TE, Hoover DR, Chen S, Kumwenda NI, Mipando L, Nkanaunena K, et al. Effects of cessation of breastfeeding in HIV-1-exposed, uninfected children in Malawi. Clinical Infectious Diseases. 2011;53(4):388-95. doi: 10.1093/cid/cir413.

19. Owor M, Mwatha A, Donnell D, Musoke P, Mmiro F, Allen M, et al. Long-term follow-up of children in the HIVNET 012 perinatal HIV prevention trial: five-year growth and survival. J Acquir Immune Defic Syndr. 2013;64(5):464-71. doi: 10.1097/QAI.0000000000000015. PubMed PMID: 24121753; PubMed Central PMCID: PMC4172334.

20. Kafulafula G, Hoover DR, Taha TE, Thigpen M, Li Q, Fowler MG, et al. Frequency of gastroenteritis and gastroenteritis-associated mortality with early weaning in HIV-1-uninfected children born to HIV-infected women in malawi. Journal of Acquired Immune Deficiency Syndromes. 2010;53(1):6-13. doi: 10.1097/QAI.0b013e3181bd5a47.

21. Chatterjee A, Bosch RJ, Hunter DJ, Fataki MR, Msamanga GI, Fawzi WW. Maternal disease stage and child undernutrition in relation to mortality among children born to HIV-infected women in Tanzania. J Acquir Immune Defic Syndr. 2007;46(5):599-606. Epub 2007/11/29. doi: 10.1097/QAI.0b013e31815a5703. PubMed PMID: 18043314.

22. Heidkamp RA, Stoltzfus RJ, Fitzgerald DW, Pape JW. Growth in late infancy among HIV-exposed children in urban Haiti is associated with participation in a clinic-based infant feeding support intervention. J Nutr. 2012;142(4):774-80. Epub 2012/03/02. doi: 10.3945/jn.111.155275. PubMed PMID: 22378328; PubMed Central PMCID: PMCPmc3301993.

23. Sutcliffe CG, Scott S, Mugala N, Ndhlovu Z, Monze M, Quinn TC, et al. Survival from 9 months of age among HIV-infected and uninfected Zambian children prior to the availability of antiretroviral

therapy. Clin Infect Dis. 2008;47(6):837-44. Epub 2008/08/06. doi: 10.1086/591203. PubMed PMID: 18680417; PubMed Central PMCID: PMCPMC2753245.

24. Marquez C, Okiring J, Chamie G, Ruel TD, Achan J, Kakuru A, et al. Increased morbidity in early childhood among HIV-exposed uninfected children in Uganda is associated with breastfeeding duration. J Trop Pediatr. 2014;60(6):434-41. doi: 10.1093/tropej/fmu045. PubMed PMID: 25145704; PubMed Central PMCID: PMC4303769.

25. Dabis F, Msellati P, Meda N, Welffens-Ekra C, You B, Manigart O, et al. 6-month efficacy, tolerance, and acceptability of a short regimen of oral zidovudine to reduce vertical transmission of HIV in breastfed children in Cote d'Ivoire and Burkina Faso: a double-blind placebo-controlled multicentre trial. DITRAME Study Group. DIminution de la Transmission Mere-Enfant. Lancet. 1999;353(9155):786-92. Epub 1999/08/25. PubMed PMID: 10459959.

26. Msellati P, Meda N, Leroy V, Likikouet R, Van de Perre P, Cartoux M, et al. Safety and acceptability of vaginal disinfection with benzalkonium chloride in HIV infected pregnant women in west Africa: ANRS 049b phase II randomized, double blinded placebo controlled trial. DITRAME Study Group. Sex Transm Infect. 1999;75(6):420-5. Epub 2001/02/07. PubMed PMID: 10754950; PubMed Central PMCID: PMCPmc1758266.

27. Kourtis AP, Wiener J, Kayira D, Chasela C, Ellington SR, Hyde L, et al. Health outcomes of HIV-exposed uninfected African infants. AIDS. 2013;27(5):749-59. Epub 2013/05/31. doi: 10.1097/QAD.0b013e32835ca29f. PubMed PMID: 23719347.

28. Becquet R, Bequet L, Ekouevi DK, Viho I, Sakarovitch C, Fassinou P, et al. Two-year morbidity-mortality and alternatives to prolonged breast-feeding among children born to HIV-infected mothers in Côte d'Ivoire. PLoS Medicine. 2007;4(1):0139-51. doi: 10.1371/journal.pmed.0040017.

29. Onyango-Makumbi C, Bagenda D, Mwatha A, Omer SB, Musoke P, Mmiro F, et al. Early weaning of hiv-exposed uninfected infants and risk of serious gastroenteritis: Findings from two perinatal hiv prevention trials in Kampala, Uganda. Journal of Acquired Immune Deficiency Syndromes. 2010;53(1):20-7. doi: 10.1097/QAI.0b013e3181bdf68e.

30. Chilongozi D, Wang L, Brown L, Taha T, Valentine M, Emel L, et al. Morbidity and mortality among a cohort of human immunodeficiency virus type 1-infected and uninfected pregnant women and their infants from Malawi, Zambia, and Tanzania. Pediatr Infect Dis J. 2008;27(9):808-14. Epub 2008/08/06. doi: 10.1097/INF.0b013e31817109a4. PubMed PMID: 18679152; PubMed Central PMCID: PMCPMC2739309.

31. Bork KA, Cournil A, Read JS, Newell ML, Cames C, Meda N, et al. Morbidity in relation to feeding mode in African HIV-exposed, uninfected infants during the first 6 mo of life: The Kesho Bora study. American Journal of Clinical Nutrition. 2014;100(6):1559-68. doi: 10.3945/ajcn.113.082149.

32. Shapiro RL, Kitch D, Ogwu A, Hughes MD, Lockman S, Powis K, et al. HIV transmission and 24-month survival in a randomized trial of HAART to prevent MTCT during pregnancy and breastfeeding in Botswana (The Mma Bana Study). AIDS (London, England). 2013;27(12):1911-20. PubMed PMID: PMC3987116.

33. Venkatesh KK, de Bruyn G, Marinda E, Otwombe K, van Niekerk R, Urban M, et al. Morbidity and mortality among infants born to HIV-infected women in South Africa: implications for child health in resource-limited settings. J Trop Pediatr. 2011;57(2):109-19. Epub 2010/07/06. doi: 10.1093/tropej/fmq061. PubMed PMID: 20601692; PubMed Central PMCID: PMCPMC3107462.

34. Natureeba P, Ades V, Luwedde F, Mwesigwa J, Plenty A, Okong P, et al. Lopinavir/ritonavir-based antiretroviral treatment (ART) versus efavirenz-based ART for the prevention of malaria among HIV-infected pregnant women. J Infect Dis. 2014;210(12):1938-45. Epub 2014/06/25. doi: 10.1093/infdis/jiu346. PubMed PMID: 24958908; PubMed Central PMCID: PMCPmc4296178.

35. Chopra M, Doherty T, Goga A, Jackson D, Persson LA. Survival of infants in the context of prevention of mother to child HIV transmission in South Africa. Acta Paediatrica, International Journal of Paediatrics. 2010;99(5):694-8. doi: 10.1111/j.1651-2227.2009.01675.x.

36. Kammerer B, Kacanek D, Mayondi GK, Lockman S. Pediatric neurodevelopmental functioning following in utero exposure to triple-NRTI-vs. PI-based ART in a randomized trial, Botswana. AIDS; Washington, D.C. 2012.

37. Rollins NC, Ndirangu J, Bland RM, Coutsoudis A, Coovadia HM, Newell ML. Exclusive breastfeeding, diarrhoeal morbidity and all-cause mortality in infants of HIV-infected and HIV uninfected mothers: An intervention cohort study in KwaZulu natal, South Africa. PLoS ONE. 2013;8(12). doi: 10.1371/journal.pone.0081307.

38. Kuhn L, Sinkala M, Semrau K, Kankasa C, Kasonde P, Mwiya M, et al. Elevations in mortality due to weaning persist into the second year of life among uninfected children born to HIV-infected mothers. Clinical Infectious Diseases. 2010;50(3):437-44. doi: 10.1086/649886.

39. Cressey TR, Punyawudho B, Urien S, Jourdain G, Le Coeur S, Ngo-Giang-Huong N, et al. Pharmacokinetics of daily nevirapine in neonates at high risk of HIV acquisition CROI; Boston, USA2016.

40. Lallemant M, Jourdain G, Le Coeur S, Mary JY, Ngo-Giang-Huong N, Koetsawang S, et al. Single-dose perinatal nevirapine plus standard zidovudine to prevent mother-to-child transmission of HIV-1 in Thailand. The New England journal of medicine. 2004;351(3):217-28. Epub 2004/07/13. doi: 10.1056/NEJMoa033500. PubMed PMID: 15247338.

41. Singh HK, Gupte N, Kinikar A, Bharadwaj R, Sastry J, Suryavanshi N, et al. High rates of all-cause and gastroenteritis-related hospitalization morbidity and mortality among HIV-exposed Indian infants. BMC Infectious Diseases. 2011;11. doi: 10.1186/1471-2334-11-193.

42. Lallemant M, Le Coeur S, Sirirungsi W, Cressey TR, Ngo-Giang-Huong N, Traisathit P, et al. Randomized non-inferiority trial of two maternal single-dose nevirapine sparing regimens to prevent perinatal HIV in Thailand (PHPT-5). AIDS (London, England). 2015;29(18):2497-507. doi: 10.1097/QAD.0000000000000865. PubMed PMID: PMC4871947.

43. WHO. Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants: Recommendations for a public health approach (2006 revision). Geneva, Switzerland: 2006.

44. WHO. Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants: Recommendations for a public health approach (2010 version). Geneva, Switzerland: 2010.

45. Inter-agency Task Team (IATT) on Prevention of HIV Infections in Pregnant Women MatI. HIV and Infant Feeding New evidence and programmatic experience: Report of a Technical Consultation. WHO, UNICEF, UNAIDS, UNFPA, 2006.

46. Ruckinger S, von Kries R, Toschke AM. An illustration of and programs estimating attributable fractions in large scale surveys considering multiple risk factors. BMC medical research methodology. 2009;9:7. Epub 2009/01/27. doi: 10.1186/1471-2288-9-7. PubMed PMID: 19166593; PubMed Central PMCID: PMCPmc2636839.

47. Benichou J. A review of adjusted estimators of attributable risk. Statistical methods in medical research. 2001;10(3):195-216. Epub 2001/07/12. doi: 10.1177/096228020101000303. PubMed PMID: 11446148.

48. Rondeau V, Marzroui Y, Gonzalez JR. frailtypack: An R Package for the Analysis of Correlated Survival Data with Frailty Models Using Penalized Likelihood Estimation or Parametrical Estimation. 2012. 2012;47(4):28. Epub 2012-04-17. doi: 10.18637/jss.v047.i04.

49. Canty A, Ripley BD. boot: Bootstrap R (S-Plus) Functions. 2017.

50. Wei R, Msamanga GI, Spiegelman D, Hertzmark E, Baylin A, Manji K, et al. Association between low birth weight and infant mortality in children born to human immunodeficiency virus 1-infected mothers in Tanzania. Pediatric Infectious Disease Journal. 2004;23(6):530-5. doi: 10.1097/01.inf.0000129691.42964.eb.

51. Kuhn L, Kasonde P, Sinkala M, Kankasa C, Semrau K, Scott N, et al. Does severity of HIV disease in HIV-infected mothers affect mortality and morbidity among their uninfected infants? Clinical Infectious Diseases. 2005;41(11):1654-61. doi: 10.1086/498029.

52. Slyker JA, Patterson J, Ambler G, Richardson BA, Maleche-Obimbo E, Bosire R, et al. Correlates and outcomes of preterm birth, low birth weight, and small for gestational age in HIV-exposed uninfected infants. BMC Pregnancy and Childbirth. 2014;14(1). doi: 10.1186/1471-2393-14-7.

53. Chikhungu LC, Newell ML, Rollins N. Under-five mortality according to maternal survival: a systematic review and meta-analysis. Bulletin of the World Health Organization 2017;95(4). Epub 312.

54. UNICEF. The state of the world's children 2016: A fair chance for every child. New York: United Nations Children's Fund, 2016.

55. Braddick MR, Kreiss JK, Embree JB, Datta P, Ndinya-Achola JO, Pamba H, et al. Impact of maternal HIV infection on obstetrical and early neonatal outcome. Aids. 1990;4(10):1001-5. Epub 1990/10/01. PubMed PMID: 2261113.

56. Bulterys M, Chao A, Munyemana S, Kurawige JB, Nawrocki P, Habimana P, et al. Maternal human immunodeficiency virus 1 infection and intrauterine growth: a prospective cohort study in Butare, Rwanda. Pediatr Infect Dis J. 1994;13(2):94-100. Epub 1994/02/01. PubMed PMID: 8190558.

57. Thorne C, Patel D, Newell ML. Increased risk of adverse pregnancy outcomes in HIV-infected women treated with highly active antiretroviral therapy in Europe. AIDS. 2004;18(17):2337-9. doi: 10.1097/00002030-200411190-00019.

Figures

Figure 1.

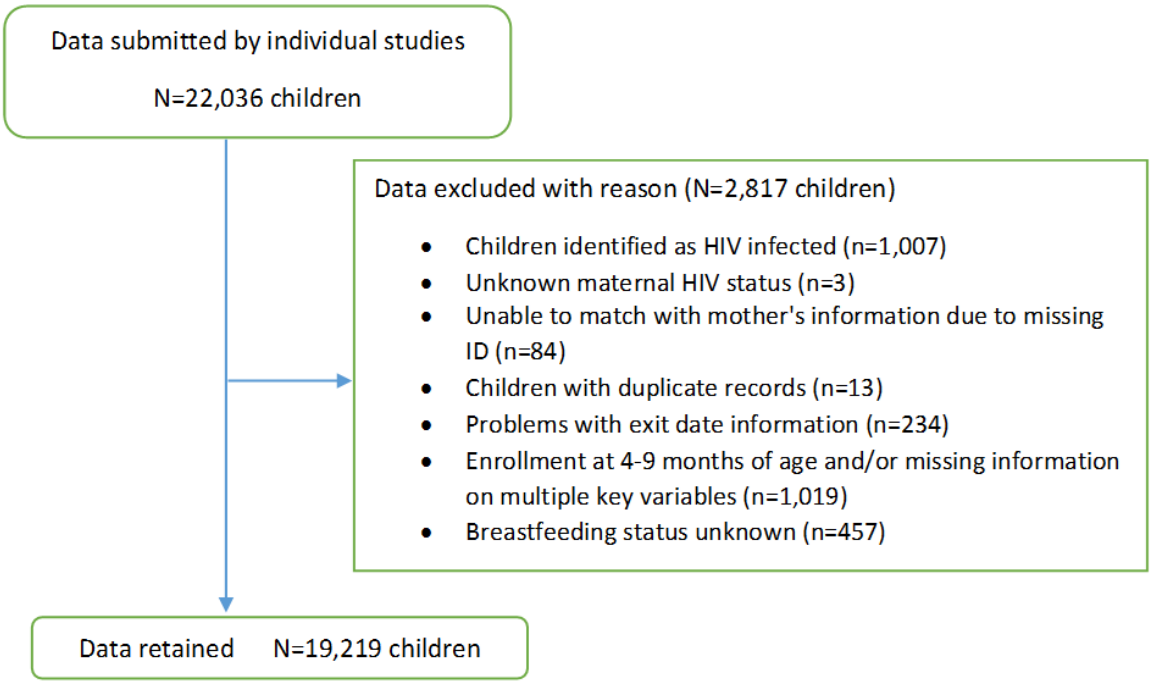
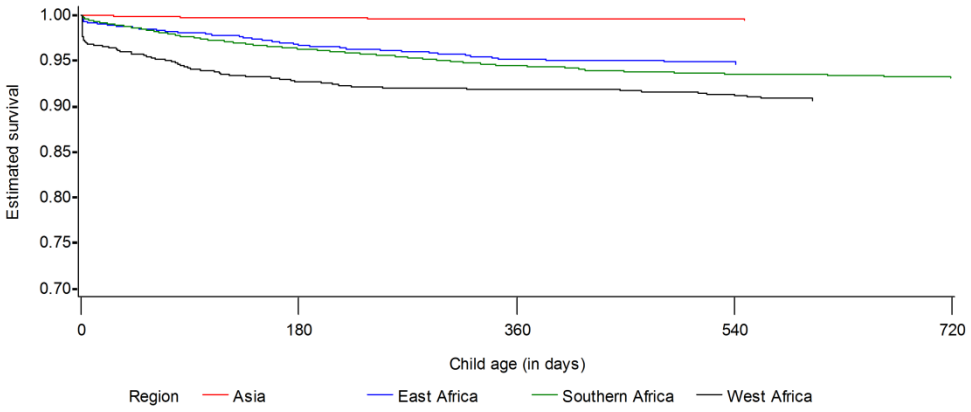


Figure 2.



Number at risk by region

	M0	M6	M12	M18	M24
Asia	4,433	4,283	3,195	1,456	250
East Africa	1,620	1,494	1,235	732	183
Southern Africa	11,769	10,197	6,608	4,785	3,309
West Africa	1,397	1,202	1,115	1,016	503