https://dspace.org/

Predictors of TB disease in HIV-exposed children from Southern Africa

Maritz, E. R.; Montepiedra, G.; Mitchell, C. D.; Madhi, S. A.; Bobat, R. ...

2023-08

International Union Against Tuberculosis and Lung Disease

https://hdl.handle.net/10539/49911

Maritz, E. R., Montepiedra, G., Mitchell, C. D., Madhi, S. A., Bobat, R., Violari, A., Hesseling, A. C., & Cotton, M. F. (2023). Predictors of TB disease in HIV-exposed children from Southern Africa. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease, 27(8), 619–625. https://doi.org/10.5588/ijtld.22.0439

Downloaded from a DSpace repository. https://dspace.org/

INT J TUBERC LUNG DIS 27(8):619–625
© 2023 The Union
http://dx.doi.org/10.5588/ijtld.22.0439

Predictors of TB disease in HIV-exposed children from Southern Africa

E. R. Maritz,[1] G. Montepiedra,[2] C. D. Mitchell,[3] S. A. Madhi,[4] R. Bobat,[5] A. Violari,[6] A. C. Hesseling,[7] M. F. Cotton[1]

[1]Family Center for Research with Ubuntu, Department of Paediatrics & Child Health, Stellenbosch University, Cape Town, South Africa; [2]Center for Biostatistics in AIDS Research, Harvard School of Public Health, Boston, MA, [3]Leonard M Miller School of Medicine Miami, University of Miami, FL, USA; [4]Vaccines and Infectious Diseases Analytics Research Unit, University of the Witwatersrand, Johannesburg, [5]Department of Paediatrics, University of KwaZulu-Natal, Durban, [6]Perinatal HIV Research Unit (PHRU), University of the Witwatersrand, Johannesburg, [7]Desmond Tutu TB Centre, Department of Paediatrics & Child Health, Stellenbosch University, Cape Town, South Africa

SUMMARY

BACKGROUND: P1041 was a randomised, placebo-controlled isoniazid prophylaxis trial in South Africa. We studied predictors for TB in HIV-exposed children participating in the P1041 trial.

METHODS: We included data from entry until Week 108. Predictors considered were type of housing, overcrowding, age, sex, ethnicity, tobacco exposure, weight-for-age percentile *Z*-score (WAZ), CD4%, viral load (VL), antiretroviral therapy (ART) and number of household smokers.

RESULTS: Of 543 HIV-positive (HIV+) and 808 HIV-exposed uninfected (HEU) infants at entry, median age was 96 days (interquartile range: 92–105). Of 1,351 caregivers, 125 (9%) had a smoking history, and 62/1,351 reported current smoking. In 594/1,351 (44%) households, there was at least one smoker. Smoking caregivers consumed 1–5 cigarettes daily. In the HIV+ cohort, significant baseline TB predictors after adjusting covariates were as follows: WAZ (adjusted hazard ratio [aHR] 0.76, $P = 0.002$) and $\log_{10}$ HIV RNA copies/ml (aHR 1.50, $P = 0.009$). Higher CD4% (aHR 0.88, $P = 0.002$) and ART (aHR 0.50, $P = 0.006$) were protective. In the HEU cohort, smoking exposure was associated with reduced TB-free survival on univariate analysis, but not after adjustment in the multivariate model.

CONCLUSION: Low WAZ and high VL were strong predictors of TB disease or death. Rising CD4 percentage and being on ART were protective in the HIV+ cohort.

KEY WORDS: tuberculosis; HIV-exposed; infants; predictors; tobacco; lung disease

HIV infection and TB infection often co-exist in children from high TB and HIV burden settings with significant morbidity and mortality.[1] Infants born to women living with HIV are highly exposed to *Mycobacterium tuberculosis* early in life.[2] While risk factors for TB in HIV-positive (HIV+) adults have been described, there are very few studies in HIV+ children.[3,4] To our knowledge, there are no such studies for HIV-exposed uninfected (HEU) children, even though increased infectious morbidity has been described.[5] From studies preceding the HIV pandemic, young children below 2 years of age had a high risk of developing TB after primary infection.[6] Risk factors identified in HIV+ children include CD4+ T-cell depletion, high viral load (VL) and not receiving antiretroviral therapy (ART).[3,7]

Smoking is a significant public health problem and nicotine is immunosuppressive.[8,9] Globally, 41% of children have at least one smoking parent. In Africa, approximately 13% of children are exposed to smokers. Children exposed to tobacco smoke are at an increased risk of sudden infant death syndrome, acute respiratory infections, hearing dysfunction and worsening of asthma. In 2016, 53,566 (6.1%) of deaths associated with secondhand smoking were in children under 5 years of age.[10]

Smoking increases the risk for *M. tuberculosis* infection and TB in adults and children.[8,11,12] However, the effect of passive smoking on TB disease in HIV-exposed infants and young children (<5 years) is less well studied. Therefore, we included passive smoking exposure with other risk factors for childhood TB-free survival in this population.

Correspondence to: Elke Regina Maritz, Family Center for Research with Ubuntu, Department of Paediatrics & Child Health, Stellenbosch University, Cape Town, South Africa. E-mail: elkemaritz@gmail.com; m_elke@hotmail.com
Article submitted 23 August 2022. Final version accepted 7 March 2023.

METHODS

Study design and participants

This secondary analysis used data from the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) P1041, a multicentre, Phase II/III randomised, double-blind, placebo-controlled trial determining the efficacy of isoniazid (INH) in preventing TB or death among HIV-exposed infants. P1041 was conducted at three South African sites (Chris Hani-Baragwanath Hospital, Johannesburg; Tygerberg Hospital, Cape Town; King Edward VIII Hospital, Durban) and one in Botswana (Princess Marina Hospital, Gaberone) from December 2004 to June 2008. The trial enrolled 548 HIV+ and 806 HEU infants between 91 and 120 days of age.[13] Documented receipt of bacille Calmette Guérin (BCG) vaccine was an inclusion criterion and exposure to a TB source case at baseline was an exclusion criterion. The study was stopped early for futility because of no INH benefit. Antiretroviral therapy (ART) was introduced to HIV+ participants during the trial.[13] Only data up to 108 weeks post-entry, when data collection was comprehensive, were analysed. The primary endpoint was TB-free survival, defined as either TB disease or death from any cause.

Measures

Data on demographic characteristics, primary caregiver, nutritional status and type of housing were collected at study entry. Demographics included age, sex, race and ethnicity. Nutritional status was assessed by the participant's birth weight and the following measures were collected at study entry: weight-for-age percentile *Z*-score (WAZ) and breastfeeding history. Environmental factors other than smoking exposure included details of primary guardian (biological mother, biological father, relative or other), housing type (formal or brick house vs. informal housing such as a shack) and housing density (number of persons in household, number of rooms for sleeping). Among the HIV+ participants, HIV disease markers, including VL, CD4 count and percentage, Centers for Diseases Control and Prevention (CDC) classification of disease severity and ART status were collected at study entry and at scheduled visits.

Information on participant exposure to smoking was based on the mother/guardian's self-reported smoking history at baseline and scheduled visits. Information was collected by trained counsellors using the caregivers' first language. Data included number of years of smoking and average number of cigarettes per day. Data on number of other household smokers were also collected. The endpoint of interest was the first occurrence of TB disease or all-cause mortality. Participants were screened for TB disease at each study visit. TB disease was classified as possible, probable or definite according to study-defined definitions.[13]

Institutional review boards of participating centres, the South African Health Products Regulatory Agency (Gauteng, South Africa) and the Division of AIDS at the National Institute of Allergy and Infectious Diseases (Bethesda, MD, USA) approved IMPAACT study P1041. Legal guardians of study participants gave written informed consent before randomisation.

Statistical analysis

Comparisons between the HIV+ and HEU cohorts used the Fisher's exact test or Pearson's χ^2 test for categorical variables and Wilcoxon's rank sum test for continuous variables. To evaluate the effect of smoking exposure, nutritional status, housing and overcrowding in the prediction of TB disease-free survival, univariate and multivariate Cox proportional hazard models were applied. Except for smoking exposure and ART, all were considered baseline predictors as were obtained at study enrolment. Because HIV+ and HEU children may have different risk factors for TB disease-free survival and loss to follow-up rates, modelling was performed separately on the two cohorts.

The baseline predictors were age (days), sex, race (Black vs. mixed ancestry), WAZ, ever breastfed, housing type (formal vs. informal) and whether 3 or more people shared a bedroom. For the HIV+ cohort, baseline CD4 percentage and HIV-1 RNA values, and whether ART was initiated at/before study entry were considered. A time-dependent dichotomous variable was constructed to represent whether a HIV+ participant was on ART at different follow-up periods.

Smoking exposure was considered in two ways in the prediction model. The first approach used a static measure: the number of smokers in the participant's household at study entry as follows: no smoker, 1 smoker or $\geq$2 smokers. The second approach incorporated more detailed information into the model, using one static measure and two dynamic measures. The static measure was the number of 'pack-years of smoking exposure' during pregnancy (in-utero exposure). The dynamic measures were 1) time-dependent number of household smokers (other than the primary caregiver), and 2) number of 'pack-years of smoking exposure' for the primary caregiver from delivery onwards. One pack-year of exposure to smoking is equivalent to secondhand tobacco exposure from 20 cigarettes daily for 1 year.[10] In calculating pack-years of in-utero exposure, we assumed that pregnancy duration was 40 weeks per participant.

All test results with probability (*P*) below 0.05 were considered significant and those with *P* between 0.05 and 0.10 were considered as having a notable signal or trend. SAS v9.2 (SAS Institute, Cary, NC, USA) was used for analysis.

RESULTS

Participant characteristics

All participants except one HIV+ and two HEU participants without follow-up, were included in this secondary analysis. As four participants in the HIV+ cohort were later identified as HEU using confirmatory testing, 543 participants were HIV+ and 808 were HEU. Baseline predictors by HIV status are shown in Table 1. At study entry, the median age was 96 days (interquartile range [IQR] 92–105); 97% were Black. There were slightly more males in the HIV+ cohort than the HEU cohort (51% vs. 43%, $P = 0.007$). The HIV+ cohort had significantly more infants with birth weight <2.5 kg (23% vs. 12%, $P < 0.001$), lower median WAZ (−0.58 vs. 0.35, $P < 0.001$), higher proportion ever breastfed (13% vs. 6%, $P < 0.001$), higher proportion receiving breast milk (5% vs. 1%, $P < 0.001$), lower proportion with mother as primary caregiver (92% vs. 99%, $P < 0.001$), and a lower proportion with over 3 people sleeping per bedroom (34% vs. 41%, $P = 0.011$). Only 1% of the HIV+ cohort were CDC Class C at study entry, 36% had a CD4 T-cell percentage below 25%, 4% had undetectable VL (plasma HIV RNA ≤400 copies/mL) and 31% initiated ART at or before study entry (Table 2).

The primary caregiver's smoking history and current smoking status and concurrent number of household smokers at study entry are given in the Supplementary Data. Of 1,351 primary caregivers, 125 (9%) reported a smoking history, with 62 (5%) reporting current smoking. One or more smokers were present in the households of 594 infants enrolled (44% of 1,351). During the study, the proportion of primary caregivers actively smoking and still on study ranged between 2% and 7%, with the proportion of households reporting one or more smokers, ranging from 33% to 45% and decreasing over time.

By Week 108 on study, 128 episodes of TB disease and 40 deaths without prior TB occurred (Table 3); 90% of deaths without prior TB were in the HIV+ cohort. Eight of those with TB in the HIV+ cohort died, with two having TB as cause of death. Two HEU children with prior TB died. The proportion of participants experiencing an endpoint (TB disease or death from any cause) was 12.4% (168/1,351)—19% (105/

Table 1 Participant characteristics of HIV-exposed children at study entry by HIV status

	HIV status			
	HIV+ ($n = 543$) *n* (%)	HEU ($n = 808$) *n* (%)	Total ($n = 1,351$) *n* (%)	*P*-value
Age, days, median [IQR]	96 [92 to 105]	96 [92 to 105]	96 [92 to 105]	0.508*
Male sex	236 (43)	412 (51)	648 (48)	0.007†
Race/ethnicity				
Black	532 (98)	779 (96)	1,311 (97)	0.096†
Mixed ancestry	11 (2)	29 (4)	40 (3)	
Birth weight <2.5 kg	124 (23)	98 (12)	222 (16)	<0.001†
Weight, kg, median [IQR]	5.30 [4.70 to 5.90]	6.10 [5.60 to 6.70]	5.80 [5.20 to 6.50]	<0.001*
WAZ, median [IQR]	−0.58 [−1.36 to 0.25]	0.35 [−0.29 to 1.02]	0.00 [−0.72 to 0.75]	<0.001*
Participant ever breastfed	73 (13)	48 (6)	121 (9)	<0.001†
Diet included breast milk	29 (5)	7 (1)	36 (3)	<0.001†
Primary caregiver				
Biological mother	500 (92)	796 (99)	1,296 (96)	<0.001‡
Biological father	16 (3)	11 (1)	27 (2)	
Relative	7 (1)	1 (<1)	8 (1)	
Other	20 (4)	0 (0)	20 (1)	
Housing type				
Formal (brick) house	343 (63)	470 (58)	813 (60)	0.066†
Informal (shack/wooden/dorm/hostel)	200 (37)	338 (42)	538 (40)	
Number of people in household, median [IQR]	4 [3 to 6]	5 [3 to 6]	4 [3 to 6]	0.243*
2	22 (4)	25 (3)	47 (3)	0.743†
3–4	259 (48)	378 (47)	637 (47)	
5–7	184 (34)	289 (36)	473 (35)	
≥8	78 (14)	116 (14)	194 (14)	
Number of rooms for sleeping, median [IQR]	2 [1 to 2]	2 [1 to 2]	2 [1 to 2]	0.731*
1	238 (44)	348 (43)	586 (43)	0.539†
2	176 (32)	288 (36)	464 (34)	
3	82 (15)	114 (14)	196 (15)	
4–8	47 (9)	58 (7)	105 (8)	
More than 3 sleep in a bedroom?				
Yes	186 (34)	332 (41)	518 (38)	0.011‡
No	356 (66)	476 (59)	832 (62)	
Not known	1 (<1)	0 (0)	1 (<1)	

* Wilcoxon test.
† χ^2 test.
‡ Fisher's Exact test.
HIV+ = HIV-positive; HEU = HIV-exposed uninfected; IQR = interquartile range; WAZ = weight-for-age *Z*-score.

Table 2 HIV-related characteristics at entry to an isoniazid prevention trial in the HIV+ cohort

	Total ($n = 543$) *n* (%)
CDC clinical classification	
N	354 (65)
A	142 (26)
B	37 (7)
C	5 (1)
Missing	5 (1)
CD4 %, median [IQR]	28.00 [21.00–35.15]
<20	111 (20)
20–<25	86 (16)
25–<35	187 (34)
>35	132 (24)
Missing	27 (5)
HIV-1 RNA, copies/mL, median [IQR]	625,000 [46,000–≥750,000]
≤400	20 (4)
401–19,999	87 (16)
20,000–749,999	177 (33)
≥750,000	245 (45)
Missing	14 (3)
ART initiated at/before study entry	
Yes	170 (31)
No	373 (69)

HIV+ = HIV-positive; CDC = Centers for Diseases Prevention and Control; IQR = interquartile range; ART = antiretroviral therapy.

543) for HIV+ and 8% (63/808) for HEU. The incidence rate of TB disease or death in the HIV+ cohort was 18.5 events per 100 person-years and 4.3 events per 100 person-years in the HEU cohort.

Predictors of TB disease-free survival in the HIV+ cohort

Lower WAZ, CD4 depletion, high VL and >3 people sharing a bedroom were significant risk factors before adjustment for covariates (Table 4). After adjustment, the risk of TB disease or death remained significantly associated with WAZ (adjusted hazard ratio [aHR] 0.76, 95% confidence interval [CI] 0.65–0.89, $P = 0.002$) and baseline VL (aHR 1.5, 95% CI 1.11–2.04). Being on ART (aHR 0.50, 95% CI 0.30–0.82) and higher CD4 percentage (aHR 0.88, 95% CI 0.78–0.98) were protective (Table 4). Each unit increase (one *Z*-score line) in WAZ at study entry was associated with 24% reduced risk of TB disease or death. ART initiation at or prior to study entry was associated with 50% reduction in risk. Every 5% increase in CD4% at study entry was associated with 12% reduction in risk and each unit increase in 1 $\log_{10}$ of VL was associated with 50% increase in risk. Smoking exposure had no influence on TB-free survival.

Table 3 Primary endpoints of HIV-exposed children participating in an isoniazid prevention trial

	HIV status		
Endpoint	HIV+ ($n = 543$) *n* (%)	HEU ($n = 808$) *n* (%)	Total ($n = 1,351$) *n* (%)
Definite TB	11 (2)	14 (2)	25 (2)
Probable TB	10 (2)	9 (1)	19 (1)
Possible TB	48 (9)	36 (4)	84 (6)
Death from any cause	36 (7)	4 (0*)	40 (3)
Endpoint free	438 (81)	745 (92)	1,183 (88)

* 0.0006%.
HIV+ = HIV-positive; HEU = HIV-exposed uninfected.

Predictors of TB disease-free survival in the HEU cohort

There were no significant predictors for TB or death in the multivariate model for the HEU cohort (Table 5). Prior to adjustment for other variables, the number of household smokers at study entry showed a notable trend, although not significant, predictor of TB disease-free survival in this cohort (overall $P = 0.06$). The unadjusted crude hazard ratio (cHR) corresponding to having ≥2 household smokers was significant (cHR 2.17, $P = 0.02$). However, this became insignificant in the multivariate model (overall $P = 0.23$). Similarly, using a more detailed modelling approach for smoking exposure (see Methods section), the number of pack-years of in-utero exposure (cHR 64.1, $P = 0.04$) and current exposure to more smokers in the household as a time-varying factor (cHR 1.24, $P = 0.08$) were also only associated with higher risk of TB disease or death in the unadjusted model.

DISCUSSION

In this secondary analysis of risk factors for TB disease or death in HIV-exposed infants from a randomised, double-blinded trial evaluating INH prevention, we identified that low WAZ and high VL were strong baseline risk factors in the HIV+ group. A rising CD4 percentage and being on ART were protective. In the HEU cohort, no predictors were identified, emphasising the extent to which HIV far outweighs other factors predisposing to TB. Our data for HIV are supported by similar studies, but in older children. A recent prospective study in Tanzania examining nutritional status and other predictors of mortality among older HIV+ children (median age: 5 years) initiating ART found that a history of TB at baseline was associated with increased mortality after ART initiation.[14] In a prospective cohort of 282 older HIV+ children from Côte d'Ivoire, the major risk factors were CD4 depletion and high VL. Very few had access to ART.[3]

ART is a well described mitigating factor for developing TB in young infants. In the Children with HIV Early-antiRetroviral (CHER) Trial, starting therapy at a median age of 7 weeks halved the incidence of TB compared to ART initiation at a median of 6 months of age.[15] This is supported by an earlier retrospective multicentre study from South Africa.[7] In another P1041 sub-study, Zeldow and colleagues also evaluated the role of ART. They separated TB disease and mortality, the combined endpoint in both the main trial and

Table 4 Predictors of TB disease or death in the HIV+ cohort participating in an isoniazid prevention trial using Cox proportional hazards model ($n = 543$)

	Univariate model		Multivariate model	
Covariate	cHR (95% CI)	*P*-value	aHR (95% CI)	*P*-value
Demographics				
Age, days	1.01 (0.99–1.03)	0.538	0.99 (0.97–1.01)	0.475
Male	0.93 (0.63–1.37)	0.705	0.78 (0.52–1.16)	0.215
Mixed ancestry (vs. Black race)	0.45 (0.06–3.20)	0.422	0.41 (0.05–3.28)	0.404
Nutritional status				
WAZ	0.76 (0.65–0.89)	<0.001*	0.76 (0.64–0.90)	0.002†
Study participant ever breastfed	0.71 (0.38–1.33)	0.288	0.63 (0.33–1.22)	0.169
HIV disease characteristics				
CD4% (every 5% increase)	0.89 (0.80–0.99)	0.029‡	0.88 (0.78–0.98)	0.022‡
HIV-1 RNA (log_{10} copies/mL)	1.40 (1.09–1.80)	0.008†	1.50 (1.10–2.04)	0.009†
ART initiated at/before study entry	0.92 (0.60–1.42)	0.718	1.78 (0.96–3.28)	0.067§
On ART (time-dependent)	0.72 (0.48–1.09)	0.119	0.50 (0.30–0.82)	0.006†
Housing and overcrowding				
Informal (vs. formal) housing	0.77 (0.51–1.16)	0.211	0.76 (0.50–1.17)	0.212
≥5 people living in the house	1.28 (0.87–1.88)	0.208	1.08 (0.71–1.64)	0.710
≥3 people sharing a bedroom	1.49 (1.01–2.19)	0.043‡	1.35 (0.89–2.05)	0.155
Smoking exposure				
Number of smokers in house		0.699		0.759
0 (reference)	1.00		1.00	
1	0.86 (0.56–1.30)	0.464	0.86 (0.57–1.32)	0.502
≥2	0.82 (0.41–1.64)	0.570	0.84 (0.41–1.74)	0.644

* $P < 0.001$.
† $P < 0.01$.
‡ $P < 0.05$.
§ $P < 0.10$.
HIV+ = HIV-positive; cHR = crude hazard ratio; CI = confidence interval; aHR = adjusted HR; WAZ = weight-for-age *Z*-score.

Table 5 Predictors of TB disease or death in the HIV-exposed uninfected cohort participating in an isoniazid prevention trial using Cox proportional hazards model ($n = 808$)

	Univariate model		Multivariate model	
Covariate	cHR (95% CI)	*P*-value	cHR (95% CI)	*P*-value
Demographics				
Age, days	0.99 (0.96–1.02)	0.581	0.99 (0.96–1.02)	0.648
Male	0.81 (0.49–1.32)	0.393	0.75 (0.45–1.24)	0.260
Coloured (vs. Black)	1.27 (0.40–4.05)	0.686	0.84 (0.25–2.82)	0.783
Nutritional status				
WAZ	0.80 (0.62–1.05)	0.105	0.80 (0.61–1.05)	0.114
Study participant ever breastfed	0.51 (0.12–2.09)	0.350	0.48 (0.12–2.01)	0.319
Housing and overcrowding				
Informal housing (vs. formal housing)	0.87 (0.52–1.45)	0.592	1.00 (0.59–1.70)	0.988
≥5 people living in the house	1.71 (1.02–2.86)	0.040*	1.45 (0.83–2.53)	0.197
≥3 people sharing a bedroom	1.36 (0.83–2.23)	0.220	1.16 (0.69–1.96)	0.570
Smoking exposure				
Total number of smokers in house		0.064†		0.232
0 (Reference)	1.00		1.00	
1	1.44 (0.82–2.51)	0.204	1.32 (0.75–2.33)	0.333
≥2	2.17 (1.12–4.18)	0.021*	1.82 (0.90–3.66)	0.095†

* $P < 0.05$.
† $P < 0.10$.
cHR = crude hazard ratio; CI = confidence interval; aHR = adjusted HR; WAZ = weight-for-age *Z*-score.

our sub-study, showing that ART's main effect was to reduce death rather than TB disease in this study.[16]

The most important risk factors for TB preceding the HIV era were exposure to TB source cases and young age.[17] Positive interferon-gamma results in HEU children were confirmed in P1041 sub-study from Cape Town, showing that 11.8% of children had *M. tuberculosis* infection.[18] In another P1041 sub-study, we showed that identifying TB in an infant or young child was not as easy, despite asking about contact with TB source cases at study visits, caregivers only remembered possible TB source cases when their children were actually considered to have TB.[19]

An important factor in P1041 was that exposure to a TB source case was an exclusion criterion to the study. Nevertheless, 128 cases of TB disease were identifed, emphasising the enormous TB burden at the study sites. The P1041 study was not primarily designed to collect

detailed information on predictors of TB disease such as passive smoking, WAZ scores and other risk factors. However, the study provided a unique opportunity to study a large cohort of HIV-exposed infants. Only a low percentage of mothers smoked, 9% overall. Of the 44% of households reporting smokers, by far the majority reported only a single smoker. Therefore, to assume a lack of association between TB-free survival and smoking is premature as a larger sample size is needed. Information on extent of smoking by household members other than the primary caregiver was not available. Nevertheless, passive smoking is a recognised predictor of TB infection in children, as confirmed in a community paediatric study in Cape Town where children were heavily exposed to tobacco smoke.[20] Although HIV infection was excluded, HEU status was not addressed.

Vitamin D has anti-inflammatory and anti-bacterial properties and tobacco smoke exposure can reduce vitamin D levels systemically and in the respiratory tract, thus increasing susceptibility to both inflammation and respiratory disease.[21] The same could apply for risk of TB. In a P1041 sub-study, Gupta et al. showed that children with low vitamin D levels had a 70% increased risk of developing TB disease or death.[22] Passive smoking was not considered but was unlikely to be a risk factor given the relatively low exposure in our study of the same population. We found that the number of household smokers and the number of pack-years of in-utero exposure had a marginally higher risk of TB-free survival in the unadjusted model for the HEU group, suggesting that smoking exposure could be a risk factor for TB disease but requires a larger sample size. Similarly, the trend for type of housing and overcrowding in predicting TB-free survival was marginally significant in HEU infants.

CONCLUSIONS

We confirmed that low WAZ, CD4 depletion and high VL increased the risk of TB disease or death in HIV+ children. Tobacco smoke exposure was not a risk factor for TB disease in either HIV+ or HEU children but larger studies are required.

Acknowledgements

The authors thank L Liu for assistance in analysis and data interpretation; Dr Owor, Botswana-Harvard School of Public Health AIDS Institute, Gaberone, Botswana for contribution to the clinical trial; the parents and legal guardians for allowing their children to participate in the clinical trial, the healthcare workers for providing care to the participants and other members of the P1041 team in conducting of the study.

Overall support for the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) was provided by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH; Bethesda, MD, USA), Award Numbers UM1AI068632 (IMPAACT LOC), UM1AI068616 (IMPAACT SDMC) and UM1AI106716 (IMPAACT LC), with co-funding from Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH). The content is solely responsibility of the authors and does not necessarily represent the official views of the NIH. This sub analysis was supported by the Statistical and Data Analysis Centre of IMPAACT and funding was received from the South African Tuberculosis AIDS Training (SATBAT), Fogarty International Center (FIC/NIH) (VAT-reg. Nr. 4310171493). All authors are part of the IMPAACT study group P1041.

Conflicts of interest: none declared.

References

1 Venturini E, et al. Tuberculosis and HIV co-infection in children. BMC Infect Dis 2014;14 (Suppl 1):S5.
2 Cotton MF, et al. Tuberculosis exposure in HIV-exposed infants in a high-prevalence setting. Int J Tuberc Lung Dis 2008;12:225–227.
3 Elenga N, et al. Diagnosed tuberculosis during the follow-up of a cohort of human immunodeficiency virus-infected children in Abidjan, Cote d'Ivoire: ANRS 1278 study. Pediatr Infect Dis J 2005;24:1077–1082.
4 Palme IB, et al. Impact of human immunodeficiency virus 1 infection on clinical presentation, treatment outcome and survival in a cohort of Ethiopian children with tuberculosis. Pediatr Infect Dis J 2002;21:1053–1061.
5 Slogrove A, et al. HIV-exposed uninfected infants are at increased risk for severe infections in the first year of life. J Trop Pediatr 2012;58:505–508.
6 Marais BJ, et al. The natural history of childhood intra-thoracic tuberculosis:a critical review of literature from the pre-chemotherapy era. Int J Tuberc Lung Dis 2004;8:392–402.
7 Martinson NA, et al. HAART and risk of tuberculosis in HIV-infected South African children:a multi-site retrospective cohort. Int J Tuberc Lung Dis 2009;13:862–867.
8 van Zyl Smit RN, et al. Global lung health:the colliding epidemics of tuberculosis, tobacco smoking, HIV and COPD. Eur Resp J 2010;35:27–33.
9 Sopori M. Effects of cigarette smoke on the immune system. Nat Rev Immunol 2002;2:372–377.
10 Yousuf H, et al. Estimated worldwide mortality attributed to secondhand tobacco smoke exposure, 1990–2016. JAMA Netw Open 2020;3:e201177.
11 Lam C, et al. Prevalence of tobacco smoking in adults with tuberculosis in South Africa [Short communication]. Int J Tuberc Lung Dis 2013;1:1354–1357.
12 Lindsay RP, et al. The Association between active and passive smoking and latent tuberculosis infection in adults and children in the United States:results from NHANES. PLoS One 2014;9: e93137.
13 Madhi SA, et al. Effect of primary isoniazid prophylaxis against tuberculosis in HIV-exposed children. N Eng J Med 2011;365:21–31.
14 Mwiru RS, et al. Nutritional status and other baseline predictors of mortality among HIV-infected children initiating antiretroviral therapy in Tanzania. J Int Assoc Provid AIDS Care 2015;14:172–179.
15 Violari A, et al. Early antiretroviral therapy and mortality among HIV-infected infants. N Engl J Med 2008;359:2233–2244.
16 Zeldow B, et al. Use of antiretrovirals in HIV-infected children in a tuberculosis prevention trial:IMPAACT P1041. Int J Tuberc Lung Dis 2017;21:38–45.
17 Marais BJ, et al. The clinical epidemiology of childhood pulmonary tuberculosis:a critical review of literature from the pre-chemotherapy era. Int J Tuberc Lung Dis 2004;8:278–285.
18 Cranmer LM, et al. high incidence of tuberculosis infection in HIV-exposed children exiting an isoniazid preventive therapy trial. Pediatr Infect Dis J 2018;37:e254–e256.

19 Maritz ER, et al. Source case identification in HIV-exposed infants and tuberculosis diagnosis in an isoniazid prevention study. Int J Tuberc Lung Dis 2016;20:1060–1064.
20 du Preez K, et al. Environmental tobacco smoke exposure increases *Mycobacterium tuberculosis* infection risk in children. Int J Tuberc Lung Dis 2011;15:1490–1497.
21 Mulligan JK, et al. Cigarette smoke exposure is associated with vitamin D3 deficiencies in patients with chronic rhinosinusitis. J Allergy Clin Immunol 2014;134:342–349.
22 Gupta A, et al. Low vitamin-D levels combined with PKP3-SIGIRR-TMEM16J host variants is associated with tuberculosis and death in HIV-infected and -exposed infants. PLoS One 2016;11:e0148649.

RÉSUMÉ

CONTEXTE: L'étude P1041 était un essai randomisé en double aveugle contrôlé par placebo sur la prophylaxie à l'isoniazide en Afrique du Sud. Nous avons étudié les facteurs prédictifs de la tuberculose chez les enfants exposés au VIH participant à l'essai P1041.

MÉTHODES: Nous avons inclus les données de l'entrée jusqu'à la semaine 108. Les facteurs prédictifs considérés étaient le type de logement, la surpopulation, l'âge, le sexe, l'origine ethnique, l'exposition au tabac, le score *Z* de poids pour l' âge (WAZ), le pourcentage de CD4, la charge virale (VL), la thérapie antirétrovirale (ART) et le nombre de fumeurs dans le foyer.

RÉSULTATS: Des 543 nourrissons VIH-positifs (VIH+) et les 808 nourrissons exposés au VIH non infectés (HEU) à l'entrée, l'âge médian était de 96 jours (intervalle interquartile: 92–105). Des 1 351 personnes s'occupant des enfants, 125 (9%) avaient des antécédents de tabagisme et 62/1 351 ont déclarer fumer actuellement. Dans 594/1 351 (44%) foyers, il y avait au moins un fumeur. Les personnes s'occupant des enfants fumeurs consommaient de 1 à 5 cigarettes par jour. Dans la cohorte VIH+, les facteurs prédictifs significatifs de la TB à l'entrée, après ajustement des covariables, étaient les suivants: WAZ (rapport de risque ajusté [aHR] 0,76; $P = 0{,}002$) et log10 copies/ml d'ARN du VIH (aHR 1,50; $P = 0{,}009$). Un pourcentage de CD4 plus élevé (aHR 0,88; $P = 0{,}002$) et l'ART (aHR 0,50; $P = 0{,}006$) étaient protecteurs. Dans la cohorte HEU, l'exposition au tabagisme était associée à une survie sans TB réduite dans l'analyse univariée, mais pas après ajustement dans le modèle multivarié.

CONCLUSION: Un faible WAZ et une VL élevée étaient des facteurs prédictifs forts de la TB ou du décès. Une augmentation du pourcentage de CD4 et la prise d'ART étaient protectrices dans la cohorte VIH+.