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INFECTIOUS DISEASES

# Anti-retroviral therapy reduces incident tuberculosis in HIV-infected children

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**Background** We aimed to estimate the effect of anti-retroviral therapy (ART) on incident tuberculosis (TB) in a cohort of HIV-infected children.

**Methods** We analysed data from ART-naïve, TB disease-free children enrolled between December 2004 and April 2008 into an HIV care program in Kinshasa, Democratic Republic of Congo. To estimate the effect of ART on TB incidence while accounting for time-dependent confounders affected by exposure, a Cox proportional hazards marginal structural model was used.

**Results** 364 children contributed 596.0 person-years of follow-up. At baseline, the median age was 6.9 years; 163 (44.8%) were in HIV clinical stage 3 or 4. During follow-up, 242 (66.5%) children initiated ART and 81 (22.3%) developed TB. At TB diagnosis, 41 (50.6%) were receiving ART. The TB incidence rate in those receiving ART was 10.2 per 100 person-years [95% confidence interval (CI) 7.4–13.9] compared with 20.4 per 100 person-years (95% CI 14.6–27.8) in those receiving only primary HIV care. TB incidence decreased with time on ART, from 18.9 per 100 person-years in the first 6 months to 5.3 per 100 person-years after 12 months of ART. The model-estimated TB hazard ratio for ART was 0.51 (95% CI 0.27–0.94).

**Conclusions** For HIV-infected children in TB-endemic areas, ART reduces the hazard of developing TB by 50%.

**Keywords** HIV, tuberculosis, anti-retroviral therapy, children, marginal structural model

## Background

Extensive epidemiologic synergy exists between HIV and tuberculosis (TB), particularly in sub-Saharan Africa where up to 60% of individuals with TB are HIV infected[1] and TB is the most common cause of morbidity and mortality among HIV-infected persons.[2] Since greater HIV-related immunodeficiency increases TB susceptibility,[3,4] immune reconstitution following effective anti-retroviral therapy (ART)[5] should decrease the incidence of TB. ART has been observed to reduce TB incidence in HIV-infected adults in settings including South Africa,[6] the USA[7] and Brazil.[8]

ART markedly improves clinical outcomes in children in both resource-rich[9] and resource-limited settings.[10] For HIV-infected children living in resource-limited, TB-endemic communities, ART may

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have substantial and important effects on reducing TB incidence and hence improving clinical outcomes.[11–13]

In this study, we report on an observational clinical cohort of children participating in an HIV treatment program in the Democratic Republic of Congo (DRC). ART outcomes in a non-randomized setting are likely to be biased by confounding by indication due to baseline and time-dependent factors. Therefore, to fulfill our primary aim of estimating the effect of ART on incident TB, we relied on a Cox proportional hazards marginal structural model (MSM).

# Methods

## Study design, population and measurements

This study was based at Kalembe Lembe Pediatric Hospital in Kinshasa, DRC, where HIV-infected children and first-line family members receive comprehensive HIV treatment and care, including ART if indicated. Children with at least 1 week of follow-up who were ART-naïve, TB disease-free and <18 years of age at HIV care initiation (between December 2004 and April 2008) were eligible for the study. HIV infection was verified by antibody testing. Children enrolled at age <18 months with a presumptive diagnosis of HIV were only included if the HIV diagnosis was serologically confirmed at age >18 months.

At the initial HIV care visit, data were collected on weight, age, history of previous TB treatment, World Health Organization (WHO) HIV clinical stage and CD4 cell count and percent. The decision to initiate ART was made 1 week later (per protocol) based on physician assessment and WHO[14,15] and DRC[16] anti-retroviral guidelines. As clinically indicated, ART could be initiated at any subsequent visit. The initial prescribed regimen was stavudine (d4T), lamivudine (3TC) and nevirapine (NVP), with zidovudine substituted for d4T in children weighing <15 kg. Patients receiving ART were scheduled to visit monthly, whereas patients not receiving ART were scheduled to visit quarterly. Individuals needing acute medical care also made unscheduled visits. Children did not receive prophylaxis against TB. CD4 cell count and percent were measured biannually at the DRC National AIDS Reference Laboratory.

Physicans diagnosed TB based on symptoms, chest X-ray (when available) and the Edwards scoring system,[17] a method in which points are assigned if clinical symptoms, signs or history information suggestive of childhood TB are present. In the absence of an exact TB diagnosis date ($n=23$), it was assumed that TB was diagnosed on the 15th of the month that TB treatment began. A lack of laboratory capacity prevented routine HIV viral load and TB culture.

A four-level severity of immunodeficiency score was calculated based on the 2006 WHO pediatric anti-retroviral guidelines,[15] using age and most recent CD4 cell count. Level of undernutrition was represented by the weight-for-age *Z*-score (WAZ).[18,19] WAZ was calculated using sex, weight and age, and Centers for Disease Control and Prevention growth chart standards.[20]

Parental informed consent for participation in the HIV care program was obtained from all participants; children ⩾12 years of age also provided their assent. The research was approved by the University of North Carolina at Chapel Hill Institutional Review Board and the Ethics Committee of the Kinshasa School of Public Health.

## Statistical analyses

Medians were compared by the Mann–Whitney test and proportions were compared by the mean score or chi-square test. We used an intention-to-treat approach assuming that patients beginning ART remained on therapy through to the end of follow-up. Patients who initiated ART contributed person-time to both the non-ART and ART groups; to the non-ART group from enrollment until ART initiation, and to the ART group from ART initiation until the end of follow-up. Follow-up was defined as time from HIV care enrollment to the first of TB diagnosis or one of four censoring events: death, transfer of care, loss to follow-up or the last clinic visit prior to analysis. Children were classified as lost to follow-up if they withdrew from the program or were not located by three tracking attempts following a missed visit. Unadjusted TB incidence rates and incidence rate ratios were calculated under a Poisson distribution; rates were expressed as number of events per 100 person-years.

We fit unadjusted pooled logistic models to estimate crude hazard ratios (HRs) and 95% confidence intervals (CIs) of the effect of time-dependent ART on incident TB. We then performed multivariable analyses by adding confounders measured at enrollment to this model to estimate the effect adjusting for baseline characteristics. Confounder selection was based on *a priori* knowledge and a causal diagram. Effect modification was assessed by comparing a main effects model to models with interaction terms of ART and other covariates via likelihood ratio testing ($P<0.10$).

The effect of time-dependent ART on TB incidence may be confounded by patient characteristics measured at enrollment (baseline), including history of previous TB treatment, severity of immunodeficiency, level of undernutrition, age and WHO HIV clinical stage. Additionally, estimation of the effect of time-dependent ART on incident TB must account for several time-dependent confounders that are themselves affected by prior ART. For example, severity of immunodeficiency is an independent predictor of developing TB and initiating ART, and is itself influenced by prior ART. In this study, we identified two such covariates: severity of immunodeficiency based on WHO pediatric guidelines, and level of undernutrition based on WAZ. A directed acyclic graph depicts the

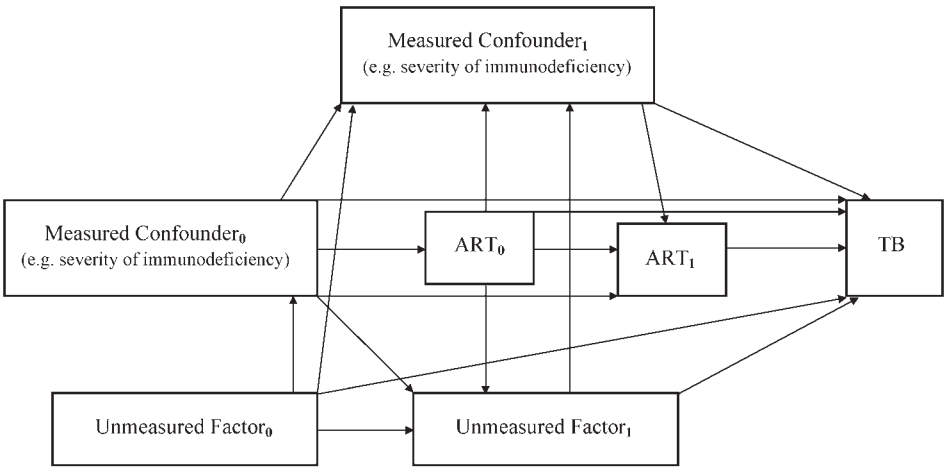



**Figure 1** Directed acyclic graph representing the causal effect of time-dependent ART on incident TB, including time-dependent measured confounders and unmeasured causal risk factors for incident TB. Numeric subscripts 0 and 1 denote the enrolment visit and subsequent visits, respectively

causal effect of time-dependent ART on incident TB in the presence of these two time-dependent factors that are both confounders and intermediates (Figure 1).[21]

Standard epidemiological methods for effect estimation are inadequate in the presence of time-dependent confounders that are themselves affected by previous exposure.[22] Therefore, we also fit Cox proportional hazards MSMs to estimate the effect of time-dependent ART on incident TB adjusting for both baseline and time-dependent confounding. After using each child's covariate history to predict subject and time-specific probabilities of treatment and censoring via separate logistic regression models, we constructed stabilized inverse-probability-of-treatment-and-censoring (IPTC) weights. We then estimated parameters of a Cox proportional hazards MSM using an IPTC-weighted pooled logistic model. Time was measured in person-days (a person-month data structure gave identical results), and we carried the last observation forward for missing covariate data. The change in baseline hazard with time was modeled with cubic splines (knots at the 5th, 27.5th, 50th, 72.5th and 95th percentiles of time), and we relied on robust 95% CIs to account for within-patient clustering.

Similar to other methodologies, our analyses assume the absence of unmeasured confounders, absence of unmeasured informative censoring, and no model misspecification. All analyses were completed in SAS (version 9.1.3; SAS Institute, Cary, NC, USA). Details of fitting Cox proportional hazards MSMs, including the SAS code, have been published.[23]

## Results

The 364 HIV-infected children were a median of 6.9 years of age (interquartile range [IQR] 4.0–10.4) at initiation of HIV care, and approximately one-half were female (52.7%) (Table 1). The majority of children were undernourished with a median WAZ of −2.4 (IQR −3.7 to −1.3), and 18.1% had previously received TB treatment. Almost one-half (44.8%) of patients had moderate to severe HIV disease progression with WHO HIV clinical stage 3 or 4, and 48.3% were classified as having severe immunodeficiency based on the WHO pediatric immunodeficiency scale.

ART was initiated by 242 children (66.5%), 189 (78.1%) of whom received d4T/3TC/NVP. During follow-up, 24 children switched to a second-line or alternative first-line regimen due to drug toxicity or treatment failure. Age at entry to HIV care was comparable by ART use ($P = 0.82$); however, fewer females than males initiated ART ($P = 0.02$). Children who received ART, compared with those who did not, started HIV care with more advanced HIV disease as indicated by WHO HIV clinical stage, CD4%, and level of immunodeficiency (all $P < 0.01$). Additionally, prior TB treatment was more common among children who received ART than those who did not (21.9 and 10.7%, respectively; $P < 0.01$), as was greater undernutrition (median WAZ −2.5 and −2.1, respectively; $P = 0.05$).

The majority of patients were followed until a first-incident TB event ($n = 81$, 22.3%) or the end of study follow-up ($n = 244$, 67.0%) (Figure 2). Twenty-three (6.3%) children were lost to follow-up or transferred their HIV care, with no difference as to whether the patient started, or did not start, ART (8.2 *vs* 5.4%, $P = 0.30$). Sixteen (4.4%) children died before an incident TB event or end of follow-up. Not accounting for person-time under observation, the proportion of children who died was smaller among those who initiated ART than those who did not (3.3 *vs* 6.6%, $P = 0.15$).

The 364 children contributed a total of 596.0 person-years of follow-up, with a median follow-up duration

**Table 1** Characteristics of 364 HIV-infected children initiating HIV care in Kinshasa, DRC, between December 2004 and April 2008

| | Total ($n=364$) | ART ($n=242$) | No ART ($n=122$) | $P$-value[a] |
|---|---|---|---|---|
| **Baseline** | | | | |
| Median age, years (IQR) | 6.9 (4.0–10.4) | 6.9 (4.0–10.5) | 6.9 (4.3–9.9) | 0.82 |
| **Age, years [*n* (%)]** | | | | |
| <1 | 11 (3.0) | 9 (3.7) | 2 (1.6) | |
| 1–2 | 52 (14.3) | 33 (13.6) | 19 (15.6) | |
| 3–4 | 59 (16.2) | 43 (17.8) | 16 (13.1) | |
| 5+ | 242 (66.5) | 157 (64.9) | 85 (69.7) | 0.46 |
| Female sex [*n* (%)] | 192 (52.7) | 117 (48.3) | 75 (61.5) | 0.02 |
| **HIV clinical stage (WHO) [*n* (%)]** | | | | |
| 1 | 68 (18.7) | 32 (13.2) | 36 (29.5) | |
| 2 | 133 (36.5) | 74 (30.6) | 59 (48.4) | |
| 3 | 147 (40.4) | 123 (50.8) | 24 (19.7) | |
| 4 | 16 (4.4) | 13 (5.4) | 3 (2.5) | <0.01 |
| Median CD4% (IQR) | 16 (10–23) | 13 (8–18) | 23 (18–27) | <0.01 |
| **Severity of immunodeficiency[b] (WHO) [*n* (%)]** | | | | |
| Not significant | 102 (28.7) | 41 (17.2) | 61 (52.1) | |
| Mild | 50 (14.0) | 23 (9.6) | 27 (23.1) | |
| Advanced | 32 (9.0) | 21 (8.8) | 11 (9.4) | |
| Severe | 172 (48.3) | 154 (64.4) | 18 (15.4) | <0.01 |
| History of TB treatment [*n* (%)] | 66 (18.1) | 53 (21.9) | 13 (10.7) | <0.01 |
| Median WAZ (IQR) | −2.4 (−3.7 to −1.3) | −2.5 (−4.0 to −1.4) | −2.1 (−3.4 to −1.1) | 0.05 |
| **Level of undernutrition [*n* (%)]** | | | | |
| WAZ $\geqslant -2$ | 153 (42.0) | 93 (38.4) | 60 (49.2) | |
| $-3 \leqslant$ WAZ $< -2$ | 74 (20.3) | 53 (21.9) | 21 (17.2) | |
| $-4 \leqslant$ WAZ $< -3$ | 58 (15.9) | 37 (15.3) | 21 (17.2) | |
| $-5 \leqslant$ WAZ $< -4$ | 34 (9.3) | 25 (10.3) | 9 (7.4) | |
| $-6 \leqslant$ WAZ $< -5$ | 12 (3.3) | 9 (3.7) | 3 (2.5) | |
| WAZ $< -6$ | 33 (9.1) | 25 (10.3) | 8 (6.6) | 0.06 |
| **Follow-up** | | | | |
| Died [*n* (%)] | 16 (4.4) | 8 (3.3) | 8 (6.6) | 0.15 |
| Follow-up loss or transfer [*n* (%)] | 23 (6.3) | 13 (5.4) | 10 (8.2) | 0.30 |
| Total person-years accrued | 596.0 | 469.4 | 126.6 | N/A |
| ART person-years accrued | 400.2 | 400.2 | 0.0 | N/A |
| Median months follow-up (IQR) | 23.2 (7.5–30.3) | 26.1 (11.1–34.9) | 8.2 (1.7–23.7) | <0.01 |
| Median months follow-up on ART (IQR) | 8.5 (0.0–26.1) | 23.9 (8.6–28.7) | N/A | N/A |
| Median number of program visits (IQR) | 21 (9–36) | 32 (15–39) | 8 (4–17) | <0.01 |
| Developed incident TB [*n* (%)] | 81 (22.3) | 41 (16.9) | 40 (32.8) | <0.01 |

[a]*P*-values are for the comparison of children who received ART with children who did not receive ART.
[b]Does not add to total due to missing data (percentages calculated from available data).

of 23.2 months (IQR 7.5–30.3). Children who initiated ART prior to an incident TB event or end of follow-up were followed for a median of 26.1 months (IQR 11.1–34.9), with a median of 23.9 of those months (IQR 8.6–28.7) occurring on ART since children typically initiated ART shortly after starting HIV care. Children who did not initiate ART were followed for a shorter time, a median of 8.2 months

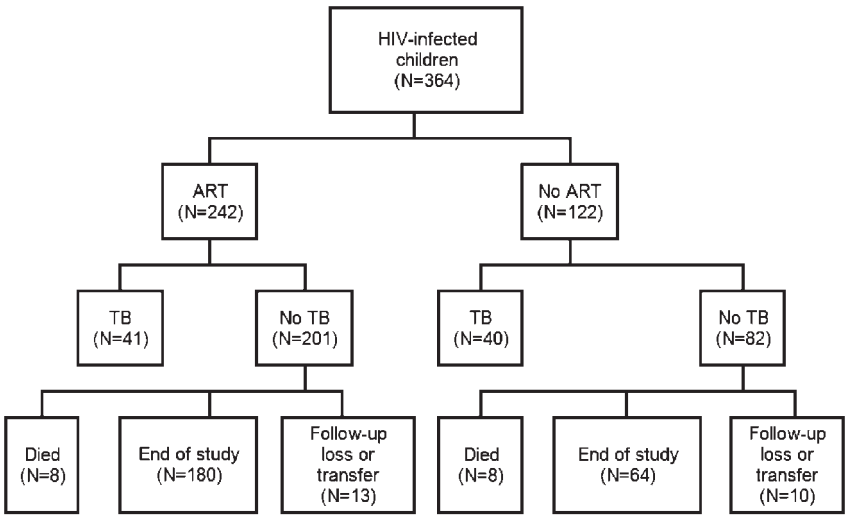



**Figure 2** Schematic overview of 364 HIV-infected children initiating HIV care in Kinshasa, DRC, between December 2004 and April 2008

(IQR 1.7–23.7) because they were more frequently lost to follow-up or died, and were newer to the program (ART is inevitably indicated as HIV progresses, so children with longer follow-up were more likely to initiate ART). While 469.4 person-years (78.8% of total person-time) were contributed by children who initiated ART, 400.2 person-years (67.1% of total person-time) were accrued on ART. Overall, the median number of visits was 21 (IQR 9–36). According to protocol, children who received ART were seen more often (median, 32 visits) than children who did not receive ART (median, 8 visits).

Over one-half of children who initiated ART during follow-up did so within 1 month of starting HIV care (Table 2). While 64.4% of children who received ART were severely immunodeficient at baseline, 76.5% of these children were severely immunodeficient at time of ART initiation. In a multivariable logistic regression model adjusted for time since HIV care initiation, advanced WHO HIV clinical stage at entry to HIV care was strongly related to an increased probability of receiving ART (Table 3). Time-updated severe immunodeficiency was also strongly associated with receiving ART. However, age, history of TB treatment and level of undernutrition were not associated with ART initiation.

Eighty-one (22.3%) children were diagnosed with incident TB during follow-up. TB was diagnosed a median of 6.2 months after HIV care initiation (IQR 1.6–11.6) at a median age of 7.7 years (Table 2). Forty-five (55.6%) children had advanced or severe immunodeficiency at time of TB diagnosis, and 41 (50.6%) were receiving ART.

Overall, the TB incidence rate was 13.6 per 100 person-years (95% CI 10.8–16.9), 10.2 per 100 person-years (95% CI 7.4–13.9) among children receiving ART and 20.4 per 100 person-years (95% CI 14.6–27.8) among children not receiving ART. Therefore, the crude TB incidence rate ratio contrasting children receiving ART with those remaining ART-naïve was 0.50 (95% CI 0.32–0.80).

Among the 40 children who developed TB while not receiving ART, the median time from enrollment into HIV care to TB was 3.4 months (IQR 0.6–7.8). Among the 41 children who developed TB while receiving ART, the median time from enrollment to TB was 7.5 months (IQR 3.6–14.1), and the median time from ART initiation to TB was 6.5 months (IQR 1.9–13.9). Children appeared to be at greatest risk of being diagnosed with TB shortly after starting ART, with TB incidence rates dropping with longer ART duration (Figure 3). Specifically, of the 41 TB cases that developed among children receiving ART, 12 (29.3%) occurred during the first 3 months of treatment, the period that 'unmasking' TB immune reconstitution inflammatory syndrome (IRIS) is believed to manifest most readily.[24]

In an unadjusted analysis, ART decreased the hazard of being diagnosed with TB, with a HR of 0.64 (95% CI 0.39–1.04). Adjusting for demographic and clinical characteristics, including severity of immunodeficiency and WHO HIV clinical stage at enrollment, the HR was 0.54 (95% CI 0.29–0.99). Finally, based on a Cox proportional hazards MSM that included all potential confounders measured at enrollment and time-dependent confounders, the HR was 0.51 (95% CI 0.27–0.94) (Table 4). In addition to indicating that ART lowered the risk of being diagnosed with TB during follow-up, this model also suggested that increased severity of WHO HIV clinical stage and greater degree of undernutrition contributed to a greater hazard of receiving a TB diagnosis. Age and history of TB treatment were not associated with TB.

**Table 2** Clinical and demographic characteristics at time of TB diagnosis and ART initiation of HIV-infected children initiating HIV care in Kinshasa, DRC, between December 2004 and April 2008

| | At time of incident TB ($n=81$) | At time of ART initiation ($n=242$) |
|---|---|---|
| Median months accrued (IQR) | 6.2 (1.6–11.6) | 1.1 (0.9–2.7) |
| Median ART months accrued[a] (IQR) | 6.5 (1.9–13.9) | N/A |
| Median age, years (IQR) | 7.7 (5.4–10.8) | 7.2 (4.1–11.0) |
| **Age, years [*n* (%)]** | | |
| <1 | 3 (3.7) | 4 (1.7) |
| 1–2 | 11 (13.6) | 34 (14.0) |
| 3–4 | 10 (12.3) | 42 (17.4) |
| 5+ | 57 (70.4) | 162 (66.9) |
| Median CD4%[b] (IQR) | 18 (10–24) | 12 (8–16) |
| **Severity of immunodeficiency[b,c] (WHO) [*n* (%)]** | | |
| Not significant | 27 (33.3) | 29 (12.2) |
| Mild | 9 (11.1) | 13 (5.5) |
| Advanced | 9 (11.1) | 14 (5.9) |
| Severe | 36 (44.4) | 182 (76.5) |
| Median WAZ (IQR) | −2.6 (−4.2 to −1.4) | −2.4 (−3.9 to −1.4) |
| **Level of undernutrition [*n* (%)]** | | |
| WAZ $\geqslant -2$ | 28 (34.6) | 98 (40.5) |
| $-3 \leqslant$ WAZ $< -2$ | 20 (24.7) | 55 (22.7) |
| $-4 \leqslant$ WAZ $< -3$ | 9 (11.1) | 35 (14.5) |
| $-5 \leqslant$ WAZ $< -4$ | 9 (11.1) | 25 (10.3) |
| $-6 \leqslant$ WAZ $< -5$ | 8 (9.9) | 7 (2.9) |
| WAZ $< -6$ | 7 (8.6) | 22 (9.1) |

[a]Among the 41 children who developed TB while receiving ART.
[b]As CD4 was not usually measured the same day as TB diagnosis or ART initiation, these values are representative of the most recent data at time of TB diagnosis or ART initiation.
[c]Does not add to total due to missing data (percentages calculated from available data).

## Discussion

This study is the first to estimate a causal effect of ART on incident TB in HIV-infected children. A Cox proportional hazards MSM, which controlled for time-dependent covariates affected by prior ART, revealed a strong protective effect of ART on incident TB (HR 0.51, 95% CI 0.27–0.94). Our results were similar to those from the only methodologically comparable study, one of HIV-infected South African adults (HR 0.61, 95% CI 0.46–0.81).[25] Whereas the small difference between the fully adjusted and unadjusted results suggests minimal overall baseline and time-dependent confounding in this clinical cohort, the utilized analytic approach accounted for this potential bias inherent to the observational, longitudinal design.

The ART-related reduction in TB incidence that we observed was similar to the 50–80% decrease seen in previous studies of HIV-infected adults[6–8] and children,[11,13] although studies using multivariable modeling did not appropriately account for time-dependent confounding. Our unadjusted TB incidence rate ratio for the effect of ART of 0.50 is close to the 0.58 observed among South African children.[12]

The substantial clinical benefits of ART on TB outcomes are likely due to a combination of reductions in HIV RNA replication and quantitative and functional immune reconstitution. Although the full benefits of ART on cellular immunity are to date poorly understood,[26] partial restoration of specific anti-mycobacterial immune responses in children have been documented.[27] The observed decrease in TB incidence with increasing time on ART also makes logical sense, as ART restores HIV-damaged immunity over time.[28] A study of South African adults suggests lower TB incidence rates after the first year of ART.[29]

While the inclusion of only children with known HIV infection precluded the comparison of TB incidence in children receiving ART with that in children without HIV, it is notable that the TB incidence observed among children receiving ART (10.2 per 100 person-years, or 10 200 per 100 000) exceeds

**Table 3** Baseline and longitudinal clinical and demographic patient characteristics associated with ART initiation among HIV-infected children initiating HIV care in Kinshasa, DRC, between December 2004 and April 2008[a]

| Characteristic | HR[b] | 95% CI |
|---|---|---|
| **Age at baseline (years)** | | |
| <1 | Ref. | |
| 1–2 | 0.98 | 0.42, 2.28 |
| 3–4 | 1.58 | 0.68, 3.67 |
| 5+ | 1.51 | 0.69, 3.31 |
| **Severity of immunodeficiency at baseline (WHO)** | | |
| Not significant | Ref. | |
| Mild | 1.16 | 0.58, 2.313 |
| Advanced | 2.35 | 1.03, 5.37 |
| Severe | 1.87 | 0.92, 3.79 |
| **Severity of immunodeficiency[c] (WHO)** | | |
| Not significant | Ref. | |
| Mild | 1.21 | 0.53, 2.75 |
| Advanced | 1.52 | 0.61, 3.80 |
| Severe | 7.53 | 3.92, 14.49 |
| **HIV clinical stage at baseline (WHO)** | | |
| 1 | Ref. | |
| 2 | 1.09 | 0.68, 1.74 |
| 3 | 2.09 | 1.29, 3.37 |
| 4 | 2.56 | 1.18, 5.53 |
| History of TB treatment | 1.17 | 0.80, 1.70 |
| **Level of undernutrition at baseline** | | |
| WAZ $\geqslant -2$ | Ref. | |
| $-3 \leqslant$ WAZ $< -2$ | 1.37 | 0.82, 2.31 |
| $-4 \leqslant$ WAZ $< -3$ | 1.23 | 0.67, 2.28 |
| $-5 \leqslant$ WAZ $< -4$ | 1.62 | 0.77, 3.40 |
| $-6 \leqslant$ WAZ $< -5$ | 1.69 | 0.68, 4.25 |
| WAZ $< -6$ | 1.63 | 0.58, 4.57 |
| **Level of undernutrition[c]** | | |
| WAZ $\geqslant -2$ | Ref. | |
| $-3 \leqslant$ WAZ $< -2$ | 0.63 | 0.38, 1.05 |
| $-4 \leqslant$ WAZ $< -3$ | 0.60 | 0.32, 1.13 |
| $-5 \leqslant$ WAZ $< -4$ | 0.43 | 0.20, 0.90 |
| $-6 \leqslant$ WAZ $< -5$ | 0.39 | 0.14, 1.10 |
| WAZ $< -6$ | 0.39 | 0.14, 1.13 |

[a]Among the 356 children with complete covariate data at baseline.
[b]Adjusted for all variables in the table as well as time since enrollment.
[c]Time-updated characteristic.
Ref = Reference.

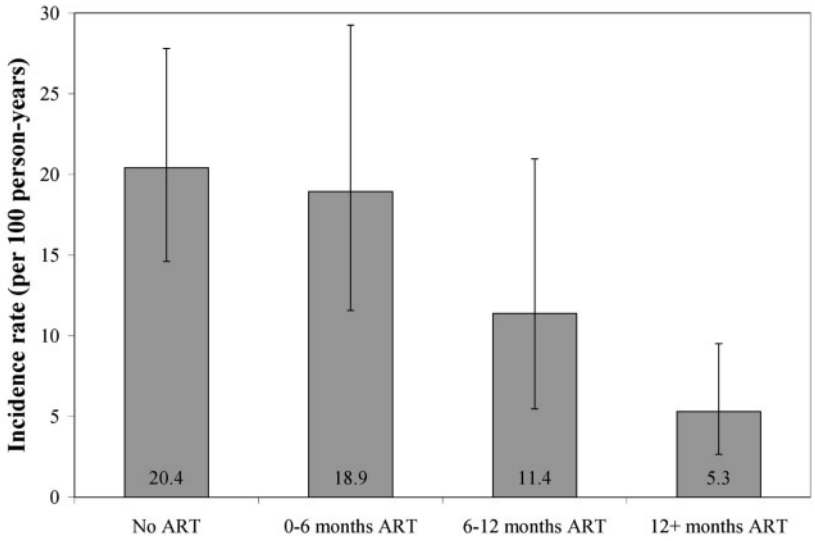
**Table 4** Estimates from Cox proportional hazards MSM to assess the causal effect of ART on incident TB among HIV-infected children initiating HIV care in Kinshasa, DRC, between December 2004 and April 2008[a]

| Characteristic | HR | Robust 95% CI |
|---|---|---|
| ART | 0.51 | 0.27–0.94 |
| **Age, years** | | |
| <1 | Ref. | |
| 1–2 | 0.91 | 0.17–4.76 |
| 3–4 | 0.71 | 0.13–3.80 |
| 5+ | 1.32 | 0.27–6.42 |
| **Severity of immunodeficiency (WHO)** | | |
| Not significant | Ref. | |
| Mild | 0.97 | 0.42–2.21 |
| Advanced | 1.28 | 0.54–3.00 |
| Severe | 0.97 | 0.51–1.83 |
| **HIV clinical stage (WHO)** | | |
| 1 | Ref. | |
| 2 | 1.30 | 0.60–2.81 |
| 3 | 1.78 | 0.77–4.11 |
| 4 | 2.49 | 0.82–7.58 |
| History of TB treatment | 0.90 | 0.50–1.63 |
| **Level of undernutrition** | | |
| WAZ $\geqslant -2$ | Ref. | |
| $-3 \leqslant$ WAZ $< -2$ | 1.13 | 0.61–2.11 |
| $-4 \leqslant$ WAZ $< -3$ | 1.20 | 0.57–2.52 |
| $-5 \leqslant$ WAZ $< -4$ | 2.16 | 1.04–4.45 |
| $-6 \leqslant$ WAZ $< -5$ | 1.47 | 0.43–5.06 |
| WAZ $< -6$ | 2.97 | 1.40–6.31 |

[a]Among the 356 children with complete covariate data at baseline. Parameters were approximated by stabilized IPTC-weighted pooled logistic regression. Model includes baseline covariates in the table along with a time-dependent intercept.
Ref = Reference.

surveillance-based TB incidence estimates in sub-Saharan African children.[30,31] It has been shown that the incidence of TB in individuals receiving ART, despite restored CD4 levels, may still be appreciably higher than the TB incidence in HIV-negative individuals.[6,26,27] This discrepancy may be due to deficiencies of reconstituted immune systems, a notion supported by the inability of ART to restore TB-specific, interferon-$\gamma$ secreting CD4 cells.[32] HIV-infected children may thus benefit from additional interventions including adjunctive treatments such as isoniazid prophylaxis,[33] although possible drug interactions with d4T currently used in first-line regimens in resource-limited settings would require careful consideration.[34]

The majority of children received a generic, fixed-dose combination ART (d4T/3TC/NVP), with




| | | | | |
|---|---|---|---|---|
| Number of TB events: | 40 | 20 | 10 | 11 |
| Person-years: | 195.9 | 105.6 | 87.7 | 206.9 |
| Incidence rate per 100 person years: | 20.4 | 18.9 | 11.4 | 5.3 |
| (95% CI): | (14.6–27.8) | (11.6–29.3) | (5.5–21.0) | (2.7–9.5) |

**Figure 3** TB incidence rates stratified by duration of ART among 364 HIV-infected children initiating HIV care in Kinshasa, DRC, between December 2004 and April 2008

split-drug dosages adjusted for body weight. Single-dose NVP is the most common anti-retroviral regimen used for the prevention of mother-to-child transmission (PTMCT) in resource-limited settings and resistance frequently develops and persists in infected infants.[35,36] While there were no data on whether the children had previously received NVP or whether they harboured HIV variants with NVP-associated mutations, it is anticipated that these scenarios were uncommon given the short history and limited coverage of PMTCT services in Kinshasa.[37] Additionally, since HIV RNA levels were unavailable, we were unable to assess virological response to ART. It is possible that a stronger protective effect of ART on incident TB would have been observed if we were able to identify the children who achieved and sustained virological suppression.

Increased TB incidence rates at more advanced immunodeficiency have been observed in children and adults,[1,13,29,38] and our results suggest an association between WHO HIV clinical stage and TB. Furthermore, we observed a trend between greater undernutrition and TB, also reported in a prior pediatric study.[13]

Diagnosis of TB in children, generally difficult and further complicated by HIV infection,[39,40] was hampered in this resource-limited setting by limited access to diagnostics. While it is not anticipated that outcome ascertainment differed by ART use, children receiving ART were seen more frequently than children not receiving ART. Fewer visits among ART-naïve children may have led not only to an underestimation of TB incidence in this group, but also to an underestimation of the effect of ART on incident TB. Additionally, the estimate may have been biased if children were more likely to be diagnosed with TB because of intensified case finding following program entry.

Lastly, this study could not address what proportion of the observed high incidence of TB soon after ART initiation was due to partial immune reconstitution or unmasking IRIS,[41] phenomena that may have impacted our estimate of the effect of ART on TB. The proportion of children initiating ART who developed unmasking TB IRIS has been observed to be relatively low (7.4% in South Africa and even lower in Thailand).[13,42]

In conclusion, ART had a strong, protective effect on incident TB in HIV-infected children in Kinshasa, DRC, through 2 years of therapy. Longer term follow-up of pediatric HIV-infected cohorts in resource-limited, TB-endemic areas is needed in order to assess whether this protective effect is sustained throughout the course of treatment.

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**KEY MESSAGES**

- Estimation of the causal effect of anti-retroviral therapy (ART) on incident tuberculosis (TB) in an observational study requires epidemiological methods that account for time-dependent confounders affected by prior exposure.
- ART was strongly protective against incident TB in a cohort of HIV-infected children in Kinshasa, Democratic Republic of Congo.
- The incidence rate of TB was observed to decrease with increasing time on ART.

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# Commentary: Reducing HIV-associated tuberculosis in children

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In both adults and children, the increased risk of tuberculosis as a result of advancing human immunodeficiency virus (HIV) infection is a major contributor to HIV-associated morbidity and mortality. This is especially so in African settings,

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