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Pediatric Antiretroviral Therapy Coverage and AIDS Deaths in the "Treat All" Era

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Abstract

OBJECTIVES: In 2015, CD4-based clinical staging criteria for antiretroviral therapy (ART) initiation were removed, expanding ART eligibility ("Treat All") for children, who shoulder an outsized burden of HIV-related deaths. To quantify the impact of "Treat All" on pediatric HIV outcomes, we examined shifts in pediatric ART coverage and AIDS mortality before and after "Treat All" implementation.

METHODS: We abstracted country-level ART coverage (proportion of children <15 years on ART) and AIDS mortality (deaths per 100 000 population) estimates over 11 years. For 91 countries, we also abstracted the year "Treat All" was incorporated into national guidelines. We used multivariable 2-way fixed effects negative binomial regression to estimate changes in pediatric ART coverage and AIDS mortality potentially attributable to "Treat All" expansion, reported as adjusted incidence rate ratios (adj.IRR) with 95% confidence intervals (95% CI).

RESULTS: From 2010 to 2020, pediatric ART coverage tripled (16% to 54%), and AIDS-related deaths were halved (240 000 to 99 000). Compared with the pre-implementation period, observed ART coverage continued increasing after "Treat All" adoption, but this rate of increase declined by 6% (adj.IRR 5 0.94, 95% CI: 0.91–0.98). AIDS mortality continued declining after "Treat All" adoption, but this rate of decline decreased by 8% (adj.IRR 5 1.08, 95% CI: 1.05–1.11) in the post-implementation period.

CONCLUSIONS: Although "Treat All" called for increased HIV treatment equity, ART coverage continues lagging in children and comprehensive approaches that address structural

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issues, including family-based services and intensified case-finding, are needed to close pediatric HIV treatment gaps.

Antiretroviral therapy (ART) has significantly reduced AIDS-related morbidity and mortality in people living with HIV. In 2015, the World Health Organization (WHO) revised global HIV guidelines and endorsed a “Treat All” approach (also referred to as “Universal Test and Treat” or “Test and Start”).[1] The “Treat All” policy was an update to previous guidelines for ART provision, which historically recommended ART initiation based on WHO HIV clinical stage or CD4 cell count.[1] Given emerging evidence of the clinical and epidemiologic benefits of earlier ART initiation,[2,3] “Treat All” facilitated ART initiation at the time of HIV diagnosis, greatly expanding treatment eligibility for adults and children. The adoption of “Treat All” is also aligned with the Joint United Nations Commission on HIV/AIDS (UNAIDS) global targets in achieving 95–95–95, which calls for 95% of people living with HIV to know their status, 95% of people who know their status to receive life-saving ART, and 95% of people on ART to have suppressed viral loads.[4]

Despite the promise of expanded ART access availed with the adoption of “Treat All,” gaps in ART coverage and AIDS-related deaths persist for certain populations. As of 2021, ART coverage in children (52%) lags substantially behind adults (76%).[5] children living with HIV (CLHIV) also shoulder an outsized burden of HIV-associated mortality, accounting for <5% of all people living with HIV but 15% of all AIDS-related deaths.[5] Even after diagnosis and ART initiation, CLHIV experience suboptimal treatment outcomes relative to adults, particularly lower rates of retention in care and viral load suppression.[6,7] Without timely diagnosis and treatment, half of perinatally infected CLHIV will die by age 2 years.[8] Multifactorial challenges to achieving the full impact of “Treat All” include but are not limited to missed opportunities for early infant diagnosis and pediatric case identification, continuity of treatment, stigma and fear from caregivers in seeking care for their children, gaps in pediatric-oriented training for HIV providers with subsequent lack of child-friendly services, and availability or supply of pediatric ART regimens.[9,10] Collectively, these challenges slow progress toward HIV epidemic control in the “Treat All” era.

Several studies have attempted to quantify the impact of “Treat All” implementation on population-level HIV clinical outcomes, but this research has primarily focused on adults living with HIV. Five seminal randomized trials in sub-Saharan Africa showed remarkable increases in population-level viral load suppression in communities where universal testing and treatment approaches were introduced and widely scaled-up.[11,12] Efficacy trials have been supplemented by observational studies of “Treat All” in Ethiopia,[13] South Africa,[14] Uganda,[15] and Zambia,[16] where noteworthy gains in ART coverage, viral load suppression, and AIDS-free survival were reported. Studies of pediatric HIV outcomes in the context of “Treat All” scale-up, however, remain scarce. One multicountry study of pooled clinical cohorts reported nonsignificant increases in CD4 and viral load monitoring among children and adolescents following “Treat All” adoption but did not measure changes in clinical outcomes before and after policy introduction.[17] Separately, a longitudinal study of children and adolescents in Zambia found that the implementation of “Treat All” was associated with increased ART coverage across age strata, but this study did not examine clinical outcomes

in the context of these policy changes.[18] Assessing the global impact of "Treat All" adoption on pediatric HIV outcomes can help discern progress toward HIV epidemic control, uncover geographic disparities in policy adoption, and identify contextually tailored strategies to close gaps in the pediatric HIV response. For these reasons, the current study examined temporal shifts from 2010 to 2020 in pediatric ART coverage and AIDS mortality before and after "Treat All" policy adoption globally.

METHODS

Data are derived from the Global AIDS Response Progress Reports (GARPR) and Spectrum model estimates of key HIV epidemic indicators, both courtesy of UNAIDS. Briefly, Spectrum estimates are generated annually and model national, regional, and global HIV burdens through integration of discrete data platforms, including national HIV clinic registries, antenatal care surveillance, household surveys, and epidemiologic studies.[19,20] Because HIV prevalence, incidence, and mortality cannot be precisely estimated from a single data source, Spectrum model estimates offer a robust approximation of the "true" underlying HIV pandemic, but estimates are still generated with some level of uncertainty. Indicators pertaining to policy implementation and expenditure are reported to UNAIDS through the GARPR, where they are compiled and disseminated annually. For this study, country-level Spectrum estimates and GARPR indicators were abstracted for all available reporting countries from 2010 to 2020, with observations indexed at the country-year level.

Key outcome measures included 2 national HIV epidemic indicators for CLHIV (<15 years), derived from Spectrum model estimates: ART coverage (proportion of CLHIV receiving ART) and number of AIDS-related deaths, which was transformed into a ratio measuring AIDS mortality by reporting the annual number of AIDS deaths in CLHIV as a fraction of the total national population (per 100 000 inhabitants). Countries with ART coverage and AIDS mortality estimates yielding extreme values (at either tail of the distribution) were imputed to the nearest integer (ART coverage: <1% ~1%, >98% ~98%; AIDS-related deaths: <1000 ~1000, <500 ~500, <200 ~200, <100 ~100).

Among countries with available data, the year of "Treat All" adoption into national HIV treatment guidelines was abstracted from GARPR data reported via a UNAIDSWHO joint laws and policies repository.[21] Countries that did not formally incorporate a "Treat All" policy into their national HIV treatment guidelines by 2020 were classified as nonadopters for the entirety of the observation period.

Other measured country-level attributes and characteristics, theorized to potentially affect the relationship between timing of "Treat All" adoption and HIV epidemic indicators, included: (1) total population size (obtained from the World Bank Open Data platform)[22]; (2) number of CLHIV (obtained from Spectrum estimates)[19,20]; (3) HIV epidemic type, defined as generalized/mixed (≥1% adult HIV prevalence) or concentrated (<1% adult HIV prevalence);[23,24] (4) income level, operationalized using the World Bank's Atlas method for standardizing gross national incomes across countries (reported as quartiles: low, low-middle, upper-middle, high);[25] and (5) UNAIDS regional classification (Asia-Pacific, Caribbean, East and Southern Africa, Latin America, Middle East and North Africa, West

and Central Africa).[5] Apart from UNAIDS regional classification, all independent variables were treated as time-varying and contained unique values for every year in the observation period.

Data were managed and analyzed in Stata/IC 15.1 (StataCorp LLC, College Station, TX). First, descriptive sample statistics were calculated to examine the frequencies and measures of dispersion for key outcomes and independent variables, cross-sectionally and longitudinally. Next, nonparametric trend tests were implemented to identify statistically significant ($P < .05$) differences in global and regional pediatric ART coverage and AIDS mortality over calendar time (from 2010 to 2020), irrespective of "Treat All" adoption status or the timing of "Treat All" incorporation into national HIV treatment guidelines.

Next, using a staggered pre- and post-design, 2-way fixed effects negative binomial regression models were fit to examine differences in pediatric ART coverage and AIDS mortality trends before and after "Treat All" implementation. The preand post-regression coefficients, reported as adjusted incidence rate ratio (adj.IRR) with 95% confidence intervals (95% CI), compare trends in ART coverage and AIDS mortality before (pre-implementation) and after (post-implementation) "Treat All" implementation. This approach allows quantification of changes in ART coverage and AIDS mortality observed in the post-implementation period that can be potentially attributed to "Treat All" introduction. Regression models were subsequently stratified by UNAIDS region to discern geographic heterogeneities in the potential impact of "Treat All" adoption on pediatric HIV outcomes. Across models, standard errors were clustered at the country level to account for repeated (nonindependent) observations among countries over time. Multivariable models adjusted for the following national indicators: UNAIDS region, epidemic type, number of CLHIV, and population size (the latter 2 of which were log-transformed to optimize precision and interpretability in regression modeling).

In sensitivity analyses, we excluded countries with imputed ART coverage estimates (<1%, n 5 7, or >98%, n 5 10) and implemented inverse probability of selection weights to correct for potential selection biases induced by excluding countries with missing ART coverage, AIDS mortality, or "Treat All" adoption data—neither of which substantially distorted results.

RESULTS

Of the 173 countries with available Spectrum estimates, 91 (53%) had complete pediatric ART coverage, AIDS mortality, and "Treat All" adoption year data for the 11-year observation period and were included in the analysis. The final analytic sample contributed 1001 country-years of observation to the study.

Fig 1 depicts changes in pediatric (<15 years) and adult ($15 years) ART coverage and pediatric AIDS mortality over calendar time. From 2010 to 2020, pediatric ART coverage tripled (16% to 54%, $P < .001$) but consistently lagged behind adult ART coverage (2010: 26%, 2020: 74%), whereas pediatric AIDS-related deaths were more than halved (240 000 to 99 000, P 5 .004) during the same period.

Table 1 presents annual pediatric ART coverage and AIDS mortality estimates over the observation period, overall and by region. Although there were increases in pediatric ART coverage in all regions, the most substantial were observed in the following regions: Asia-Pacific (23% to 81%, P 5 .005), East and Southern Africa (18% to 57%, P < .001), Middle East and North Africa (8% to 47%, P < .001), and West and Central Africa (7% to 35%, P < .001). From 2010 to 2020, reductions in pediatric AIDS-related deaths occurred in all regions but were most significant in East and Southern Africa (150 000 to 47 000, P < .001) and West and Central Africa (69 000 to 39 000, P < .001). By 2020, the global estimate for pediatric ART coverage (54%) exceeded regional estimates from West and Central Africa (35%), the Middle East and North Africa (47%), and the Caribbean (43%). Likewise, pediatric AIDS mortality in East and Southern Africa (47 000) and West and Central Africa (39 000) towered over other regional estimates in 2020.

By 2018, 89% of 91 countries adopted “Treat All” into national HIV treatment guidelines, and only 1 country had not yet formally adopted “Treat All” by 2020. Table 2 presents multivariable pre- and post-regression coefficients and 95% CIs comparing patterns in pediatric ART coverage and AIDS mortality, before and after “Treat All” adoption. Following the incorporation of “Treat All” into national HIV treatment guidelines, increases in pediatric ART coverage continue increasing from the pre- to post-implementation period, but the rate of increase declined by 6% (adj.IRR 0.94, 95% CI 0.91–0.98) after “Treat All” introduction. Likewise, pediatric AIDS mortality continued declining from the pre- to post-implementation period, but the rate of decline decreased by 8% (adj.IRR 1.08, 95% CI 1.05–1.11) following “Treat All” adoption.

Findings were comparable across regions, with the strongest attenuations in pediatric ART coverage expansion occurring in East and Southern Africa (adj.IRR 0.91, 95% CI 0.87–0.95) and West and Central Africa (adj.IRR 0.93, 95% CI 0.87–0.99) and the sharpest decelerations in pediatric AIDS mortality reductions observed in Asia-Pacific (adj.IRR 1.26, 95% CI 1.07–1.49), the Caribbean (adj.IRR 1.04, 95% CI 1.01–1.06), and East and Southern Africa (adj.IRR 1.10, 95% CI 1.08–1.14).

DISCUSSION

Globally and across regions, there were marked increases in pediatric ART coverage (16% to 54%) and substantial declines in AIDS mortality (240 000 to 99 000) from 2010 to 2020. Although this progress over a decade is a massive global achievement, study findings indicate that “Treat All” adoption did not accelerate the ART coverage gains nor AIDS mortality reductions observed in the pre-implementation period. Observed pediatric ART coverage increases in the post-implementation period were lower than expected, likely because many countries increased CD4 thresholds for ART initiation before “Treat All” adoption. Given that children with CD4 cell counts <500 per mm^3 were eligible for immediate ART initiation in a number of countries during the pre-implementation period,[1] “Treat All” may not have substantially increased the fraction of CLHIV eligible for treatment and, therefore, had limited impact on pediatric ART coverage. Furthermore, 2010 to 2015 was a period of intense focus on ensuring ART was available in the public sector and accessible to CLHIV, resulting in many countries improving their ART coverage

overall, so observed differences in pediatric ART coverage and AIDS mortality estimates in the pre- and post-implementation are potentially attributable to changes in the state of the HIV pandemic. Lastly, there are children that remain hard to reach with HIV testing and treatment services, despite “Treat All” implementation. A study from Burundi, for example, showed that index testing services were scaled-up extensively, but challenges were observed with respect to reaching children who did not live with their biological parents.[26] Optimized case-finding and enhanced linkage to care and treatment are, therefore, needed to close gaps in pediatric ART coverage and AIDS mortality in the “Treat All” era.

Even in the “Treat All” era, pediatric ART coverage falls well-below adult coverage. Across regions, West and Central Africa exhibited the lowest pediatric ART coverage (35%) and the second highest AIDS mortality rate (~39 per 100 000), indicating a majority of CLHIV in the region were not accessing life-saving HIV treatment in 2020. Because many West and Central African countries have mixed HIV epidemics,[27] predominant HIV service delivery models focus on key populations, and these models may require modifications to better reach families, especially pregnant and breastfeeding women, their HIV-exposed infants, and CLHIV. A study in Côte d’Ivoire from 2015 found that fewer than 60% of women received HIV testing before childbirth during their last pregnancy, and 30% had lost at least 1 child.[28] In a more recent study of women living with HIV in Cameroon, nearly 70% of participants reported that none of their children had received HIV testing before age 5.[29] There is an urgent need to ensure people who are pregnant or breastfeeding and living with HIV are reached with prevention of vertical transmission services. Their HIV-exposed infants must also be retained in care and followed up with early infant diagnosis services and monitored until a final outcome upon cessation of breastfeeding is completed. Although there has been a sharp decline in pediatric AIDS-related deaths, there is an urgent need to identify CLHIV with advanced HIV disease and provide them the appropriate package of care, while diagnosing and treating children earlier (before they develop advanced disease) to further reduce mortality.[30]

The siloed nature of HIV programs, which sometimes reach only certain subpopulations, can potentially lead to missed opportunities to diagnose and initiate CLHIV on life-saving treatment. Enhanced integration of HIV service delivery platforms (for adults and children) into strengthened primary care systems and through approaches like family-based models of care could optimize HIV testing and treatment of parents and facilitate more timely testing and ART initiation for their biological children. HIV testing should routinely be offered to all biological children of a parent living with HIV (or who may have died of HIV), which is often termed family-based index testing.[31] A study from Kenya found that a standardized family-based approach offering HIV testing to children accompanying caregivers is feasible to scale-up, resulting in 70% of caregivers completing testing for 1 or more children in either clinic-based or home-based settings.[32] A recently published randomized trial in Eswatini found significant increases in sustained viral suppression over a 12-month period among children enrolled in a family-centered HIV care model, where pediatric and adult HIV services were delivered simultaneously in a single clinical encounter with CLHIV and caregiver dyads.[33] The success of family-based HIV testing and treatment models in East and Southern Africa, especially through strengthened primary care and pediatric service

delivery platforms, offer a blueprint for increasing ART coverage, and AIDS-free survival among CLHIV in regions like West and Central Africa.

Study findings must be considered with various limitations in mind. First, the study's ecological design, with the highest level of granularity derived from estimates aggregated to the country level, limits inferences that can be made about the impact of "Treat All" on pediatric HIV outcomes at the individual level. However, given the limited availability of population-based studies enumerating pediatric HIV burdens and clinical outcomes,[34] ecological data are a suitable alternative to individual-level data. This ultimately underscores the importance of enumerating children in population-based HIV burden estimates derived from household surveys and network or venue-based bio-behavioral studies. Second, mathematically modeled Spectrum estimates were treated empirically (ie, as fixed values based on point estimates), rather than probabilistically. By not correcting for uncertainty bounds of pediatric ART coverage and AIDS mortality estimates derived from Spectrum models, observed associations between "Treat All" adoption and pediatric HIV outcomes are likely biased, though the magnitude of this bias is likely insufficient to distort results such that inferences would be different if measurement error were addressed were corrected in the current study. Third, analyses could not account for country-level heterogeneities in "Treat All" implementation, which likely modify the effect of "Treat All" on HIV clinical outcomes for children and adults alike. Fourth, data on the frequency and proportions of adults and children living with HIV eligible for ART based on CD4 criteria before "Treat All" adoption were unavailable. The impact of these eligibility criteria on changes in ART coverage and AIDS mortality estimates following "Treat All" adoption remains unclear. Lastly, although some country-level indicators from other data sources, including World Bank income level, were mined onto Spectrum estimates, this study did not include an exhaustive set of national indicators that could attenuate observed relationships between pediatric HIV outcomes and "Treat All" implementation. Future research should explore associations of national HIV epidemic metrics with legal and policy frameworks, development indices, and healthcare expenditure. This will require additional investments in pediatric HIV programs and data to monitor clinical outcomes.

CONCLUSIONS

Taken together, much progress has been made to increase ART coverage and reduce mortality among CLHIV, but alternative approaches to "Treat All" are needed to reach HIV epidemic control in children and adults alike, especially in regions with substantial HIV burdens and suboptimal pediatric HIV outcomes like West and Central Africa. Despite significant increases in pediatric treatment coverage and decreases in AIDS mortality over the last decade, our findings suggest that complementary approaches to "Treat All" must be scaled-up to accelerate momentum toward global HIV treatment equity for children. Early infant diagnosis, targeted case-finding strategies (ie, integration with adult index testing efforts), and prioritization of family-based service delivery models are key to closing the pediatric HIV treatment gaps in the "Treat All" era.[35–37]

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ABBREVIATIONS

ART	antiretroviral therapy
CLHIV	children living with HIV
GARPR	Global AIDS Response Progress Reports
UNAIDS	Joint United Nations Programme on HIV/AIDS
WHO	World Health Organization

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WHAT'S KNOWN ON THE SUBJECT:

Despite expansion of antiretroviral therapy eligibility to all children at time of diagnosis ("Treat All"), pediatric HIV treatment inequities persist. Studies have reaffirmed the positive impact of "Treat All" expansion on clinical outcomes, but this research has largely overlooked children.

WHAT THIS STUDY ADDS:

Although "Treat All" represented a major policy shift by universalizing ART eligibility, more effort is needed to ensure effective implementation of "Treat All" for children as well as address structural barriers to pediatric HIV treatment access and retention in care.

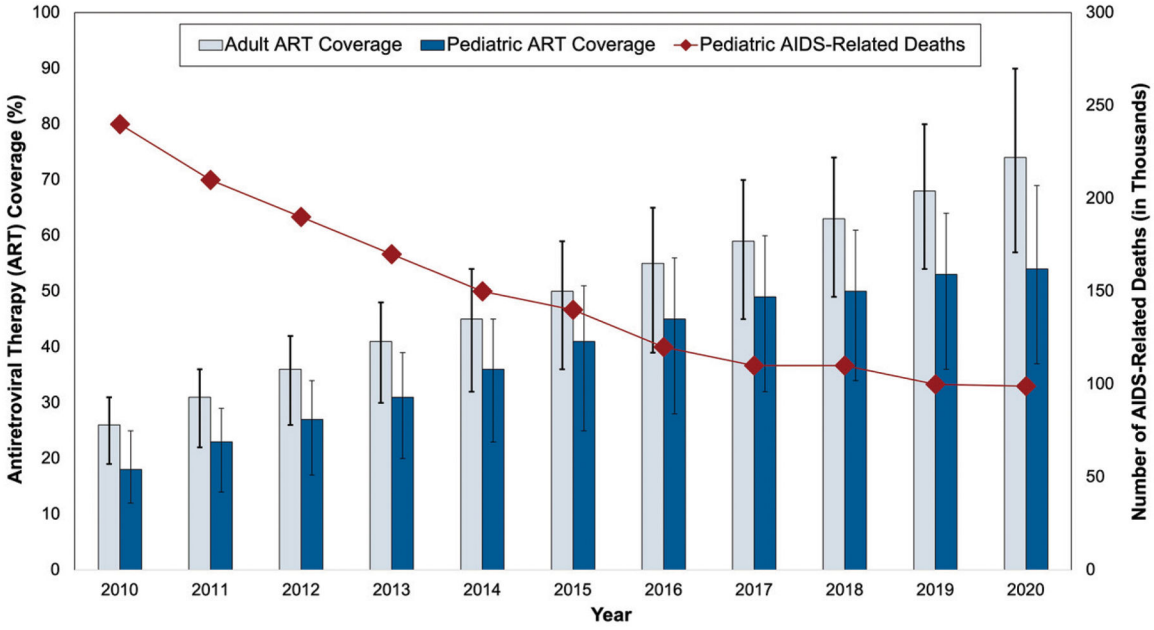

FIGURE 1.

Global estimates of adult (151 years) and pediatric (<15 years) antiretroviral therapy coverage estimates plotted against pediatric AIDS-related deaths, by year—2010 to 2020.

TABLE 1

Regional Estimates for Pediatric ART Coverage (%) and Number of Pediatric AIDS-Related Deaths, by Year, 2010–2020

	Year											Nonparametric Trend Test	
UNAIDS Region (No. of Countries)	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**	**2020**	**z-Score**	***P***
Pediatric ART coverage, %													
Asia-Pacific (*n* = 10)	23	28	34	42	48	55	64	60	70	76	81	2.81	.005
Caribbean (*n* = 4)	22	26	29	32	34	34	39	43	41	44	43	0.18	.857
East and Southern Africa (*n* = 19)	18	23	28	33	39	44	48	52	53	57	57	7.87	<.001
Latin America (*n* = 14)	42	42	43	43	45	47	47	48	49	51	54	1.23	.217
Middle East and North Africa (*n* = 11)	8	10	11	16	21	24	27	31	34	38	47	3.94	<.001
West and Central Africa (*n* = 23)	7	10	12	14	17	20	23	28	29	33	35	12.47	<.001
Global (*N* = 91)	16	21	25	29	35	39	44	47	49	53	54	10.66	<.001
Number of pediatric AIDS-related deaths in thousands													
Asia-Pacific (*n* = 10)	16	15	13	12	11	9.6	8.2	7.1	6.7	6.6	6.5	−1.77	.077
Caribbean (*n* = 4)	1.4	1.3	1	<1	<1	<1	<1	<1	<1	<1	<1	−0.82	.414
East and Southern Africa (*n* = 19)	150	130	110	92	81	74	65	65	56	52	47	−3.71	<.001
Latin America (*n* = 14)	3.5	3.2	3	2.8	2.6	2.4	2.1	2.1	1.8	1.6	1.6	−1.66	.096
Middle East and North Africa (*n* = 11)	1.1	1.1	1.1	1	1	<1	<1	<1	<1	<1	<1	−2.01	.044
West and Central Africa (*n* = 23)	69	65	61	55	50	46	42	41	39	38	39	−3.53	<.001
Global (*N* = 91)	240	210	190	170	150	140	120	110	110	100	99	−2.91	.004

No estimates for pediatric ART coverage or AIDS-related deaths are available for the following regions: (1) Eastern Europe and Central Asia and (2) Western and Central Europe and North America.

TABLE 2

Adjusted IRR and 95% CI of Country-Level Pediatric ART Coverage (%) and AIDS-related Deaths (Per 100 000 Population) Before and After National "Treat All" Adoption, 2010–2020

	Pediatric ART Coverage		Pediatric AIDS Mortality	
UNAIDS Regions	**adj.IRR (95% CI)**	***P***	**adj.IRR (95% CI)**	***P***
Global	0.94 (0.91–0.98)[a]	.001[a]	1.08 (1.05–1.11)[a]	<.001[a]
Asia-Pacific	0.94 (0.79–1.12)	.459	1.26 (1.07–1.49)[a]	.007[a]
Caribbean	0.94 (0.84–1.05)	.248	1.04 (1.01–1.06)[a]	.005[a]
East and Southern Africa	0.91 (0.87–0.95)[a]	<.001[a]	1.10 (1.05–1.14)[a]	<.001[a]
Latin America	0.99 (0.94–1.05)	.812	1.04 (0.97–1.10)	.324
Middle East and North Africa	1.03 (0.86–1.21)	.786	0.97 (0.79–1.19)	.782
West and Central Africa	0.93 (0.87—0.99)[a]	.029[a]	1.04 (1.00–1.08)	.052

Negative binomial regression models were estimated using 2-way fixed effects, with standard errors clustered at the country level to account for repeated observations. Multivariable models adjusted for UNAIDS region, epidemic type (generalized or mixed or concentrated), log-transformed annual number of children living with HIV, log-transformed population size, and World Bank income classification quartiles.

[a]Values represent statistically significant incidence rate ratios (at the $P < .05$ level or below).