Post-HAART Outcomes in Pediatric Populations: Comparison of Resource-Limited and Developed Countries

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KEY WORDS
HIV/AIDS, pediatric, HAART, mortality, resource-limited

ABBREVIATIONS
HAART—highly active antiretroviral therapy
ART—antiretroviral treatment
RLC—resource-limited country
DC—developed country
WAZ—weight-for-age *z* score
VL—viral load
DPCY—deaths per 100 child-years
WHO—World Health Organization

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abstract

CONTEXT: No formal comparison has been made between the pediatric post–highly active antiretroviral therapy (HAART) outcomes of resource-limited and developed countries.

OBJECTIVE: To systematically quantify and compare major baseline characteristics and clinical end points after HAART between resource-limited and developed settings.

METHODS: Published articles and abstracts (International AIDS Society 2009, Conference on Retroviruses and Opportunistic Infections 2010) were examined from inception (first available publication for each search engine) to March 2010. Publications that contained data on post-HAART mortality, weight-for-age *z* score (WAZ), CD4 count, or viral load (VL) changes in pediatric populations were reviewed. Selected studies met the following criteria: (1) patients were younger than 21 years; (2) HAART was given (≥3 antiretroviral medications); and (3) there were >20 patients. Data were extracted for baseline age, CD4 count, VL, WAZ, and mortality, CD4 and virologic suppression over time. Studies were categorized as having been performed in a resource-limited country (RLC) or developed country (DC) on the basis of the United Nations designation. Mean percentage of deaths per cohort and deaths per 100 child-years, baseline CD4 count, VL, WAZ, and age were calculated for RLCs and DCs and compared by using independent samples *t* tests.

RESULTS: Forty RLC and 28 DC publications were selected ($N = 17\,875$ RLCs; $N = 1835$ DC). Mean percentage of deaths per cohort and mean deaths per 100 child-years after HAART were significantly higher in RLCs than DCs (7.6 vs 1.6, $P < .001$, and 8.0 vs 0.9, $P < .001$, respectively). Mean baseline CD4% was 12% in RLCs and 23% in DCs ($P = .01$). Mean baseline VLs were 5.5 vs 4.7 $\log_{10}$ copies per mL in RLCs versus DCs ($P < .001$).

CONCLUSIONS: Baseline CD4% and VL differ markedly between DCs and RLCs, as does mortality after pediatric HAART. Earlier diagnosis and treatment of pediatric HIV in RLCs would be expected to result in better HAART outcomes. *Pediatrics* 2011;127:e423–e441

Highly active antiretroviral therapy (HAART) results in marked survival benefits for HIV-infected people.[1,2] In contrast to adults, who may defer HAART for several years, nearly half of HIV-1 infected children in Africa will die by the age of 2 if they are not treated.[3,4] By 2005 in Africa, where ~90% of the world's HIV-infected children reside, children represented 13% of the population in need of antiretroviral treatment (ART) and only ~5% of the population receiving ART.[5,6] The number of children receiving ART has since increased; however, children are still less likely than adults to receive therapy.[5]

Many factors impede the use of HAART in resource-limited settings, particularly in pediatric populations. Lack of infrastructure, health care professionals, and technology to diagnose HIV-1 and monitor treatment have initially delayed treatment of both adults and children.[7] The threat of poor adherence and viral resistance continues to be a concern in resource-limited settings.[8,9] Children face additional barriers to treatment including dosing, formulations, higher costs for pediatric antiretroviral drugs, and high infant mortality rates.[3,10–13]

Beginning in 2004, African countries began expanding access to antiretroviral medications as funding became available.[14,15] Better descriptions of clinical diagnosis, staging, and management of HIV-infected children facilitated scale-up of treatment.[16] A number of publications in which treatment outcomes for pediatric populations in resource-limited settings were described have recently emerged. These studies, including 2 recent reviews by Sutcliffe et al[14] and Ciaranello et al,[17] reference outcomes from developed-countries (DCs) publications for informal comparison; however, no study has systematically compared outcomes and characteristics of pediatric ART between resource-limited countries (RLCs) and DCs.

The purpose of this study was to review the literature to quantify and compare major clinical end points and baseline characteristics for children receiving HAART in DCs versus RLCs.

METHODS

Search Strategy

A systematic literature search was performed through March 2010 for all studies for which outcomes (mortality, weight-for-age *z* score [WAZ], CD4%, and viral load [VL]) were reported after initiation of HAART in pediatric patients. The following databases were searched: PubMed, EBSCO, Global Health Host, AIDSLine, and the Cochrane Library. Conference abstracts from the International AIDS Society 2009 and Conference on Retroviruses and Opportunistic Infections 2010 were searched, because these data likely have not had time to be published. Search terms included "pediatric," "children," "HIV," "HAART," "Africa," "resource-limited," "developing country," "outcomes," "mortality," "efficacy," and "adherence" (or equivalents of these terms [ie, HIV-1, ART, antiretrovirals, ARV, therapy, treatment]). This search strategy was supplemented by searching references in the bibliographies of articles.

Study Selection

Observational cohorts and clinical trial studies were selected for review on the basis of predefined criteria. Full-length articles published in a language other than English were included if they had an abstract in English. Studies were selected on the basis of the following criteria: (1) patients were younger than 21 years and not limited to a narrow age range such as <24 months or >13 years), (2) patients had received HAART (≥3 antiretroviral medications), (3) the sample size was >20 patients, and (4) patients had at least 6 months' follow-up on HAART. Outcome measures included mortality, weight change, CD4 counts and percentages, and VLs. Two authors reviewed the reports and came to agreement on inclusion or exclusion of the publications.

Data Extraction

In addition to the outcome measures, information was extracted on the focus of the study, regimen, previous ART exposure including prevention of mother-to-child transmission, time from presentation to initiation of HAART, disease severity, predictors of mortality, orphan status, hospitalization, follow-up time, percentage of patients lost to follow-up, and intent-to-treat versus as-treated analysis. Articles were separated into 2 categories, RLCs or DCs, according to rankings by the United Nations Statistics Division.[18] Articles were then subcategorized according to geographic location. Studies were also grouped on the basis of the cohorts' previous HAART exposure: HAART-naive (previous mono/dual therapy or antiretroviral naive) or HAART-exposed (3-drug regimen including a protease inhibitor or a nonnucleoside reverse transcriptase inhibitor).

Multiple reports were reviewed for the same study, and individual studies were compared for overlap. Overlap was evaluated by reviewing authors, location, date, duration, and specific interventions. When results overlapped, data from the largest cohort, most recent publication, or longest follow-up time were selected. Multiple reports for the same or overlapping cohort were included if they each provided unique outcome data (eg, 1 reported mortality, 1 reported CD4%, or each reported CD4 count at different time points). Unique outcome data were extracted and added so that no

overlapping data points were used in calculations. Reports were excluded if data were not used (see Appendix).

Calculations and Statistical Analysis

The mortality percentage was collected directly or calculated from reported results. Deaths per 100 child-years (DPCY) was calculated by using the number of deaths and time of the mortality measurement, unless reported directly in the article. The total number of child-years was estimated as the sum of years contributed by living patients at the time of mortality measurement and one-half of this follow-up time for deceased patients. These estimations are likely to be less accurate with longer follow-up times.

For articles in which mortality rates at multiple follow-up time points were provided, the mortality measurement nearest 12 months' follow-up was used, because it was the most commonly used follow-up time point.

Mean baseline characteristics and mortality rates were calculated for comparison between RLCs and DCs. All mean calculations were weighted on the basis of cohort size. Hereafter, weighted means will be referred to simply as means. The means, ranges, SDs, and confidence intervals of HAART-naive studies were calculated for both mortality percentage and DPCY for each geographic subregion, RLCs, and DCs. In addition, the RLC and DC means, ranges, SDs, and confidence intervals for baseline characteristics including CD4 T-cell percentage, VL ($\log_{10}$ copies per mL), age, and WAZ were calculated for HAART-naive studies and for all studies that included HAART-experienced cohorts. CD4% and the percentage of patients who achieved virologic suppression were graphed over time, and the mean levels 12 months after HAART were calculated. The RLC and DC baseline values and outcomes were compared by using independent-samples *t* tests.

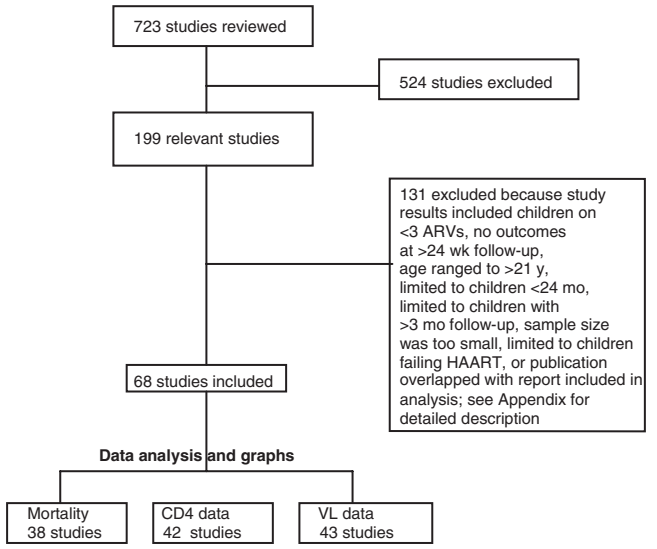

FIGURE 1
Study-selection flowchart. ARV indicates antiretroviral medication.

RESULTS

Study Selection and Characteristics

The initial literature search produced 723 publications: 313 published articles and 410 conference abstracts. Abstracts, methods, and/or results were reviewed, and 199 reports were found to contain some relevant selection criteria. Of these reports, 131 were excluded for reasons listed in Fig 1 and the Appendix, and the remaining 68 were used for analysis (RLCs = 40, total N = 18 882 and 17 875 approximately correcting for overlap; DCs = 28, total N = 3150 and 1835 approximately correcting for overlap). Characteristics of included studies are summarized in Table 1.

Baseline Mean/Median Age

The mean baseline age in RLC studies was 5.4 and 5.7 years in HAART-naive and all studies, respectively (Table 2). In DCs, the mean age of patients in HAART-naive and all studies was 6.5 and 6.7 years, respectively. There was no significant difference in the mean/median age at baseline between RLCs and DCs for HAART-naive cohorts (P = .1) or all studies (P = .2).

Baseline WAZ

The mean WAZ for children who were initiated on HAART in RLCs was −2.2 for both HAART-naive and all studies combined (Table 2). In DCs, the mean WAZ for both HAART-naive and all studies was −0.4. There was a large and statistically significant difference between baseline WAZ in RLCs and DCs ($P < .001$).

Post-HAART Mortality Outcomes

The mortality analysis included 38 cohorts: 30 cohorts from RLCs (N = 9663) and 8 cohorts from DCs (N = 1277). Only outcomes for patients on HAART (≥3 antiretroviral medications) were used in the analysis. Several calendar studies were excluded, because the authors reported mortality rates for birth cohorts without separating outcomes for patients on no ART, mono/dual therapy, or HAART; these studies revealed decreased mortality rates after the introduction of HAART.[2,80,83–85] In addition, 11 study reports provided mortality data but were

TABLE 1 Study Characteristics of Pediatric Cohorts in RLCs and DCs

Study Authors (Year)	Location	*N*	Age, Mean (b) or Median (a)	Study Details	Follow-up Time, Total (b) or Median (a), mo
RLCs					
Hien et al[19] (2009)	Burkina Faso	52	6.8 y[a]	IAS abstract	24[b]
Fassinou et al[20] (2004)	Cote d'Ivoire	78	7.2 y[a]	21% HAART-experienced	21[a]
Rouet et al[21] (2006)	Cote d'Ivoire	78	6.5 y[a]	PI vs NNRTI comparison	36[a]
Nyandiko et al[22] (2006)	Kenya	279	6.0 y[a]	Rural, orphan comparison	34[a]
Song et al[23] (2007)	Kenya	29	8.5 y[b]	Adult comparison	15[b]
Van Winghem et al[24] (2008)	Kenya	648	5.5 y[a]	Adherence: MSF	48[b]
Wamalwa et al[25] (2007)	Kenya	67	4.4 y[a]	Early response	9[a]
Reddi et al[26] (2007)	KwaZulu Natal	151	5.7 y[a]	16% HAART-experienced	8[a]
Leyenaar et al[27] (2009)	Lesotho	284	2.2 y[a]	BIPAI center of excellence	14[b]
Cohen et al[28] (2009)	Lesotho	283	NR	IAS abstract, rural: MSF	24[b]
Bong et al[29] (2007)	Malawi	439	6.0 y[a]	FDC	24[b]
—[16] (2006)	Malawi	A: 436	<15 y	FDC	6[b]
		B: 233		FDC	12[b]
Weigel et al[30] (2010)	Malawi	497	8.0 y[a]	CROI abstract, growth	24[b]
Marazzi et al[31] (2006)	Mozambique	297	4.4 y[b]	Integrated public health program	9[a]
Vaz et al[32] (2009)	Mozambique	1007	3.0 y[a]	IAS abstract, growth	48[b]
van Griensven et al[33] (2008)	Rwanda	315	7.2 y[a]	Nurse-based care: MSF	45[b]
Diack MBaye et al[34] (2005)	Senegal	98	5.0 y[a]	Non-specific focus	36[b]
Barth et al[35] (2008)	South Africa	66	8 mo to 11 y	Rural, ART-naive	12[b]
Eley[36] (2006)	South Africa	409	1.9 y[a]	Severe clinical disease	12[b]
Jaspan et al[37] (2008)	South Africa	391	2.2 y[a]	PI vs NNRTI comparison	48[b]
Jooste et al[38] (2005)	South Africa	100	1–14 y	Non-specific focus	6[b]
Smit et al[39] (2009)	South Africa	615	1.8 y[a]	IAS abstract: Cape Town	46[b]
Blè et al[40] (2007)	Tanzania	59	3 mo to 11 y	Orphan study	12[b]
Kamya et al[41] (2007)	Uganda	250	9.2 y[b]	Genotypic mutations	14[b]
Bolton-Moore et al[42] (2007)	Zambia	2938	6.8 y[a]	Providers (nonphysicians)	12[a]
Gupta et al[43] (2009)	Zambia	103	8.0 y[a]	IAS: Triomune FDC	36[b]
Walker et al[44] (2007)	Zambia	93	8.8 y[a]	Non-specific focus	24[b]
Janssens et al[45] (2007)	Cambodia	212	6.0 y[a]	Split FDC	36[b]
Myung et al[13] (2007)	Cambodia	117	5.5 y[a]	DOT	26[b]
Zhang et al[46] (2007)	China	A: 51	NR	HAART-naive	13[b]
		B: 32	NR	HAART-experienced	13[b]
Rajasekaran et al[47] (2009)	India	295	7.6 y[b]	Non-specific focus	10[a]
Kline et al[48] (2007)	Romania	414	13.0 y[b]	82% drug-experienced	51[a]
Aurpibul et al[49] (2009)	Thailand	225	7.4 y[a]	IAS: growth	55[b]
Lapphra et al[40] (2008)	Thailand	139	6.0 y[a]	Siriraj Hospital	36[a]
Puthanakit et al[51] (2007)	Thailand	192	7.6 y[b]	Chiang Mai Hospitals	29[a]
Romanelli et al[52] (2006)	Brazil	43	2.4 y[b]	Dual vs triple antiretroviral therapy	48[b]
Martins et al[53] (2009)	Brazil	196	NR	IAS: growth	6[b]
Martins et al[54] (2009)	Brazil	196	NR	IAS: immunosuppression	6[b]
George et al[12] (2007)	Haiti	236	6.3 y[a]	Treatment-naive	20[a]
Severe et al[55] (2005)	Haiti	94	<13 y	Adult and child study	12[b]
DCs					
Ghaffari et al[56] (2004)	US	40	7.1 y[a]	PI: University of Florida, Gainesville	22[b]
King et al[57] (2005)	US	41	6.4 y[a]	PACTG 403, PI nelfinavir	11[b]
Krogstad et al[58] (1999)	US	62	3 mo to 13 y	PI nelfinavir, age groups	10[a]
Krogstad et al[11] (2002)	US	192	6.2 y[a]	PACTG 377	11[b]
McKinney et al[59] (2007)	US	37	10.5 y[a]	PACTG 1021	22[b]
Melvin et al[60] (2002)	US	36	6.0 y[a]	5 patients overlap PACTG	29[a]
Patel et al[61] (2008)	US	1236	NR	PACTG 219 10-y follow-up	70[a]
Rosenblatt et al[62] (2005)	US	192	6.2 y[a]	PACTG 377	11[b]
Soh et al[63] (2003)	US	702	6.7 y[a]	PACTG 219 CD4 response	48[b]
Spector et al[64] (2000)	US	57	8.0 y[a]	PACTG 382	11[b]
Starr et al[65] (1999)	US	57	8.0 y[b]	PACTG 382	11[b]
Watson et al[66] (1999)	US	72	NR	Adherence and efficacy	9[a]
Wiznia et al[67] (2000)	US	192	6.2 y[a]	PACTG 377	11[b]
Yogev et al[68] (2002)	US	245	7.4 y[a]	PACTG 338 subset	11[b]
Bracher et al[69] (2007)	Denmark	49	6.7 y[a]	Long term follow-up	72[b]
Teglas et al[70] (2001)	France	33	12.5 y[a]	Efavirenz study	9[b]
Thuret et al[71] (1999)	France	22	6.5 y[a]	Non-specific focus	21[b]
Wintergerst et al[72] (2008)	Germany	33	8.2 y[a]	Efavirenz study	50[a]
Fraaij et al[73] (2005)	Netherlands	31	5.1 y[a]	Prospective PI study	48[b]
Scherpbier et al[74] (2007)	Netherlands	36	6.6 y[a]	Efavirenz study	11[a]

TABLE 1 Continued

Study Authors (Year)	Location	*N*	Age, Mean (b) or Median (a)	Study Details	Follow-up Time, Total (b) or Median (a), mo
van Rossum et al[75] (2002)	Netherlands	32	5.4 y[a]	Non-specific focus	22[b]
van Rossum et al[76] (2000)	Netherlands	28	6.0 y[a]	Non-specific focus	6[b]
Verweel et al[77] (2002)	Netherlands	24	5.2 y[a]	HAART effect on growth	22[b]
Nadal et al[78] (2000)	Switzerland	A: 37	6.3 y[a]	Ritonavir	28[a]
		B: 237	7.8 y[a]	Nelfinavir	28[a]
Rudin et al[79] (2008)	Switzerland	133	6.3 y[a]	PI comparison	66[b]
Judd et al[80] (2007)	UK, Ireland	156	NR	CHIPS 2003–2006 antiretroviral-naive	>9
Walker et al[81] (2004)	UK, Ireland	265	4.2 y[a]	CHIPS, antiretroviral-naive	24[b]
PENTA[82] (2002)	8 countries	103	5.3 y[a]	PENTA	11[b]

IAS indicates International AIDS Society; PI, protease inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; MSF, Medecins Sans Frontiere; BIPAI, Baylor International Pediatric AIDS Initiative; —, No author provided; FDC, fixed-dose combination treatment; CROI, Conference on Retroviruses and Opportunistic Infections; DOT, directly observed therapy; NR, not reported; PACTG, Pediatric AIDS Clinical Trial Group; CHIPS, Collaborative HIV Paediatric Study; PENTA, Paediatric European Network for Treatment of AIDS.

[a] Mean/total.

[b] Median.

TABLE 2 Pooled Summary Statistics: Comparison of RLCs and DCs

	RLCs	DCs	*P*
Mean mortality, %			
HAART-naive	7.6 (0 to 18.8)[a] ± <0.1[b] (8937)	1.6 (0 to 3.8)[a] ± <0.1[b] (1241)	<.001
Ref No.	12, 13, 16, 19, 22–25, 27, 28, 31, 33, 35, 42, 44, 45, 47, 51, and 52	59, 61, 69, 71, 73, 79, and 82	
All studies[c]	7.5 (0 to 18.8)[a] ± <0.1[b] (9663)	1.7 (0 to 3.8)[a] ± <0.1[b] (1277)	<.001
Ref No.	Additionally 21, 26, 46, and 48	Additionally 74	
Mean DPCY			
HAART-naive	8.0 (0 to 41.5)[a] ± 4.1[b] (8937)	0.9 (0 to 1.1)[a] ± 1.2[b] (1241)	<.001
Ref No.	12, 13, 16, 19, 22–25, 27, 28, 31, 33, 35–42, 44, 45, 47, 51, and 52	59, 61, 69, 71, 73, 79, and 82	
All studies[c]	7.7 (0 to 41.5)[a] ± 3.8[b] (9663)	1.0 (0 to 3.1)[a] ± 1.2[b] (1277)	<.001
Ref No.	Additionally 21, 26, 46, and 48	Additionally 74	
Mean baseline CD4%			
HAART-naive	12 (5 to 20)[a] ± 0.1[b] (8437)	23 (7 to 47)[a] ± 0.2[b] (647)	.01
Ref No.	12, 13, 19, 22, 25, 27, 29, 32, 33, 35–37, 39, 41, 42, 44, 45, 47, and 50–52	11, 56, 57, 59, 66, 69, 71, 73, 78, and 82	
All studies[c]	12 (5 to 20)[a] ± 0.1[b] (8666)	23 (7 to 47)[a] ± 0.1[b] (719)	.003
Ref No.	Additionally 21 and 26	Additionally 60 and 74	
Mean baseline VL, $\log_{10}$ copies per mL			
HAART-naive	5.5 (5.1 to 6.1)[a] ± 2.7[b] (1882)	4.7 (4.4 to 5.2)[a] ± 2.2[b] (647)	<.001
Ref No.	12, 19, 23, 25, 34–37, 41, 46A;, 51, and 52	56, 57, 59, 66, 67, 69, 71, 73, 78, and 82	
All studies[c]	5.5 (4.9 to 6.1)[a] ± 2.7[b] (1992)	4.7 (3.6 to 5.2)[a] ± 2.0[b] (752)	<.001
Ref No.	Additionally 21 and 46B	Additionally 60, 70, and 74	
Mean baseline age, y			
HAART-naive	5.4 (1.8 to 10.0)[a] ± 4.0[b] (9494)	6.5 (5.1 to 10.5)[a] ± 3.4[b] (575)	.1
Ref No.	12, 13, 19, 22-25, 27, 29, 31, 34, 36, 37, 39, 41, 42, 44, 45, 46, 47, and 50–52	56, 57, 59, 67, 69, 71, 73, 78, and 82	
All studies[c]	5.7 (1.8 to 13.0)[a] ± 3.8[b] (10169)	6.7 (5.1 to 12.5)[a] ± 2.9[b] (680)	.2
Ref No.	Additionally 21, 26, 46B, and 48	Additionally 60, 70, and 74	
Mean baseline WAZ			
HAART-naive	−2.2 (−3.8 to −1.6)[a] ± 2.1[b] (5748)	−0.4 (−0.8 to −0.3)[a] ± 0.1[b] (180)	<.001
Ref No.	13, 19, 23, 27, 30, 33, 36, 37, 40, 42, 44, 46, 49, 53, and 55	56, 59, 65, 71, and 77	
All studies[c]	−2.2 (−3.8 to −1.5)[a] ± 2.0[b] (6009)	−0.4 (−0.8 to −0.3)[a] ± 0.1[b] (180)	<.001
Ref No.	Additionally 20, 26, and 46B	—	

N is the total number of patients involved in the statistic. Ref 60 overlaps 2 patients with the Pediatric AIDS Clinical Trial Group 377.[87]

[a] Range.

[b] 95% confidence interval for weighted mean.

[c] Includes HAART-experienced patients.

not included in pooled analysis because of overlap with larger or more recent studies.*

Post-HAART mortality data for HAART-naive studies are shown in Fig 2 and Table 3. Geographic subregions used for RLCs were Africa (20 studies), Asia/Eastern Europe (4 studies), and South America/Caribbean (2 studies). The mean mortality rates in Africa, Asia/Eastern Europe, and South America/Caribbean were 7.4%, 8.8%, and 7.6% per cohort and 7.5, 11.9, and 8.4 DPCY, respectively. In US and European HAART-naive studies, the mean mortality rates were 1.6% per cohort and 0.9 DPCY.

Comparisons between RLCs and DCs are listed in Table 2. Post-HAART mortality rates for HAART-naive cohorts in RLCs were ~5 and 9 times greater than in DCs: 7.6% vs 1.6% and 8.0 vs 0.9 for mortality percentage and DPCY, respectively ($P = .002$ and $P < .001$, respectively). Mean mortality rates for all studies that included previously mono/dual protease inhibitor– and nonnucleoside reverse transcriptase inhibitor–treated children were 7.5% vs 1.7% mortality percentage and 7.7 vs 1.0 DPCY for RLCs and DCs, respectively.

*Refs 20, 29, 55, 56, 63, 65, 67, 78, and 86–88.

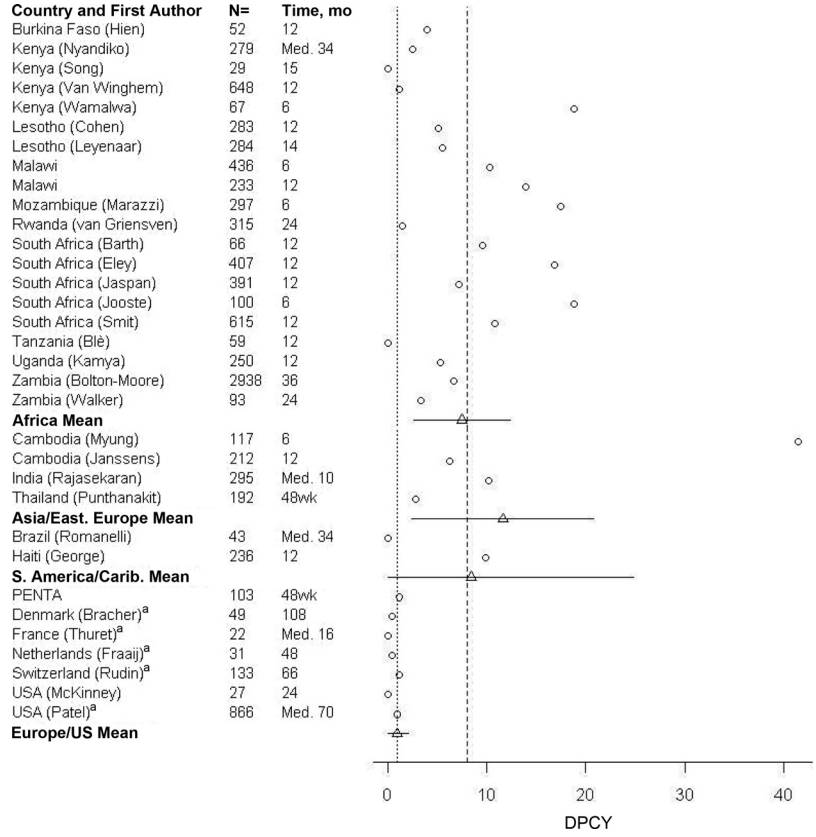

FIGURE 2

Pediatric DPCY after HAART: HAART-naive cohorts. [a] Includes mono/dual ART-experienced patients. Vertical line (. . .), DC mean DPCY for HAART-naive studies; vertical line (—), RLC mean DPCY for HAART-naive studies; horizontal lines, 95% confidence intervals for weighted mean.

Baseline and Post-HAART CD4 Levels

Forty-two study reports provided unique data for either baseline CD4% or CD4% over time: 25 from RLCs and 17 from DCs. Twenty-three RLC and 13 DC studies were pooled for baseline CD4%, restricting to 1 value from overlapping cohorts (Table 2). HAART-naive studies had mean baseline CD4% values of 12% (range: 5%–20%) and 23% (range: 7%–47%) for RLCs and DCs, respectively ($P = .01$). Twenty reports from RLCs and 9 reports from DCs described changes in CD4% after HAART initiation (Fig 3). In this graphical presentation, overlap exists between the Pediatric AIDS Clinical Trial Group publications (namely, refs 58, 60, 62, 63, and 65). Mean CD4% 12 months after HAART was significantly different between RLC and DC studies: 24% and 27%, respectively ($P = .03$).

Baseline VLs and Post-HAART Virologic Suppression

Forty-three study reports provided unique data for either baseline VL or percent virologic suppression: 21 from RLCs and 22 from DCs. Fourteen RLC and 14 DC studies reported baseline VL (Table 2). Baseline VLs in HAART-naive studies were 5.5 $\log_{10}$ copies per mL in RLCs and 4.7 $\log_{10}$ copies per mL in DCs ($P < .001$). Nineteen RLC and 20 DC reports described the percentage of patients who achieved virologic suppression (Fig 4). Viral suppression was defined as <400 copies per mL. Six study reports only defined viral suppression as <50 copies per mL.[26,39,43,51,60,72] Overlap exists between refs 11, 58, 64, 65, and 68; the Paediatric European Network for Treatment of AIDS overlaps with ref 81 but not with ref 80, because data from this reference were extracted for the 2003–2006 birth cohort. Twelve months after HAART, the mean percentage of children who achieved viral suppression was 65% in RLC and 49% in DC studies, and there was no significant difference between the 2 groups ($P = .4$). Eleven of the DC and 7 of the RLC studies reported using an intention-to-treat approach when evaluating the rate of virologic suppression.†

Predictors of Mortality

Weighted least-squares regression was used to determine if differences in mortality between RLCs and DCs diminished after controlling for baseline WAZ, CD4%, or VL. Adjusting for baseline CD4 level, the mortality difference between RLCs and DCs persisted (6.7% mortality difference; $P = .01$), and there was negligible evidence of confounding. There were fewer studies for which VL and WAZ were reported; however, the mortality difference between RLCs and DCs seemed to be confounded by baseline WAZ and VL.

Studies from both RLCs and DCs revealed associations between mortality rate, baseline CD4%, and VL.[11,12,13,36,42,61,63,68] Low WAZ was a risk factor for mortality.[12,26,27,40,44,77] Several RLC studies revealed that younger age was associated with mortality, whereas DC studies revealed conflicting findings regarding age and mortality.[12,22,36,51,73,80] Finally, 2 RLC studies revealed that orphans had a higher mortality rate, although programs with >50% orphans achieved relatively low mortality rates overall.[22,23,45]

†Refs 11, 21, 23, 35, 41, 45, 46, 51, 57, 59, 64, 65, 68, 72, 73, 75, 79, and 82.

TABLE 3 Pediatric Mortality Rates After HAART in RLCs and DCs

Country	*N*	Time	Lost to Follow-up, %	Mortality, %	DPCY
RLCs					
Burkina Faso (Hien et al[19])	52	12 mo	2	3.8	3.9
Kenya (Nyandiko et al[22])	279	34 mo (median)	11	6.8	2.5
Kenya (Song et al[23])	29	15 mo	3	0	0
Kenya (Van Winghem et al[24])	648	12 mo	NR	1.1	1.1
Kenya (Wamalwa et al[25])	67	6 mo	NR	9.0	18.8
Lesotho (Cohen et al[28])	283	12 mo	2	5.0	5.1
Lesotho (Leyenaar et al[27])	284	14 mo	1	6.3	5.5
Malawi A[16]	436	6 mo	11	5.0	10.3
Malawi B[16]	233	12 mo	15	13.0	13.9
Mozambique (Marazzi et al[31])	297	6 mo	NR	8.4	17.5
Rwanda (van Griensven et al[33])	315	24 mo	4	2.5	1.4[a]
South Africa (Barth et al[35])	66	12 mo	17	9.0	9.5
South Africa (Eley[36])	407	12 mo	NR	15.4	16.8
South Africa (Jaspan et al[37])	391	12 mo	2	6.9	7.2
South Africa (Jooste et al[38])	100	6 mo	3	9.0	18.8
South Africa (Smit et al[39])	615	12 mo	NR	10.2	10.8
Tanzania (Bl+è et al[40])	59	12 mo	0	0	0
Uganda (Kamya et al[41])	250	12 mo	1	5.2	5.3
Zambia (Bolton-Moore et al[42])	2938	36 mo	13	8.3	6.6[a]
Zambia (Walker et al[44])	93	24 mo	NR	6.5	3.3
Africa mean	n/a	n/a	NR	7.4 ± 0.6[b]	7.5 ± 4.9[b]
Cambodia (Myung et al[13])	117	6 mo	NR	18.8	41.5
Cambodia (Janssens et al[45])	212	12 mo	2	6.0	6.2
India (Rajasekaran et al[47])	295	10 mo (median)	2	8.1	10.2
Thailand (Puthanakit et al[51])	192	48 wk	NR	6.7	2.8[a]
Asia/Eastern Europe mean	n/a	n/a	NR	8.8 ± <0.1[b]	11.9 ± 9.2[b]
Brazil (Romanelli et al[52])	43	34 mo (median)	9.3	0	0
Haiti (George et al[12])	236	12 mo	10	9.0	9.9
South America/Caribbean mean	n/a	n/a	NR	7.6 ± 0.1[b]	8.4 ± 16.4[b]
DCs					
PENTA[82]	103	48 wk	NR	1.0	1.1
Denmark (Bracher et al[69])[c]	49	108 mo	NR	2.0	0.4[a]
France (Thuret et al[71])[c]	22	16 mo (median)	NR	0	0
Netherlands (Fraaij et al[73])[c]	31	48 mo	16	3.1	0.4
Switzerland (Rudin et al[79])[c]	133	66 mo	1	3.8	1.1[a]
US (McKinney et al[59])	27	24 mo	NR	0	0
US (Patel et al[61])[c]	866	70 mo (median)	NR	1.4	0.9[a]
Mean	n/a	n/a	NR	1.6 ± 0.2[b]	0.9 ± 1.2[b]

NR indicates not reported; n/a, not applicable.
[a] Directly reported number of child-years of follow-up.
[b] 95% confidence intervals for weighted mean.
[c] Included mono/dual ART-experienced patients.

Additional Study Characteristics

Information was also collected surrounding initiation of HAART. RLC studies referenced various World Health Organization (WHO) pediatric ART guidelines that recommend initiation of HAART at WHO stage 3 or 4 or at a CD4% of <15%, <20%, <15%, or <20%, depending on age, or <200 cells per μL. The authors of ref 45 (Cambodia) noted that 37% of evaluated children did not meet initiation criteria, and 10% of eligible children died before initiation. DC studies often did not report specific initiation criteria. Between 61% and 99% of children in RLC studies initiated HAART at WHO stage 3 or 4 disease.[27,36] Between 10% and 62% of children in DC studies had Centers for Disease Control and Prevention class C disease.[78,82] Only 1 RLC study[42] (Zambia) reported median age at diagnosis: 5.5 years. The authors of ref 69 (Denmark) reported median age of diagnosis at 1.5 years; median age of initiation was 6.7 years. Another study[80] found that between 2004 and 2006 foreign-born children presented later than UK-born children: 7.6 versus 0.8 years, respectively. Four RLC studies reported time between diagnosis and HAART initiation ranging from a median of 53 days to 26 months.[20,33,40,44] RLC studies reported that <10% of subjects received antiretroviral medications in attempt to prevent vertical transmission (<1%–12%); however, it is possible that perinatal nevirapine exposure was not systematically ascertained or was underreported.[16,20,25,26,27,33,38,41] Prevention of mother-to-child transmission was reported as being widely available in DCs, but rates of utilization were not specified.[11,61,67,80]

DISCUSSION

In this study, we determined and compared baseline status and outcomes of children who initiated HAART in RLCs and DCs. As anticipated, mortality rates were dramatically lower with HAART than in studies before HAART and <10% in both settings. Mortality rates were higher in RLCs than in DCs, but the mortality difference observed was less than would have been expected on the basis of general childhood mortality estimates from those regions, which suggests that the added contact with care providers enhances survival beyond baseline, likely by prevention of common infectious diseases. RLC cohorts involved children with significantly lower baseline CD4 counts and WAZ and higher VLs, all of which would be expected to also contribute to increased mortality rates. Efforts to initiate HAART earlier would be expected to identify children before substantial immunosuppression, which should translate into improved survival rates.

Comparisons between observational studies have inherent limitations; nonetheless, these comparisons are

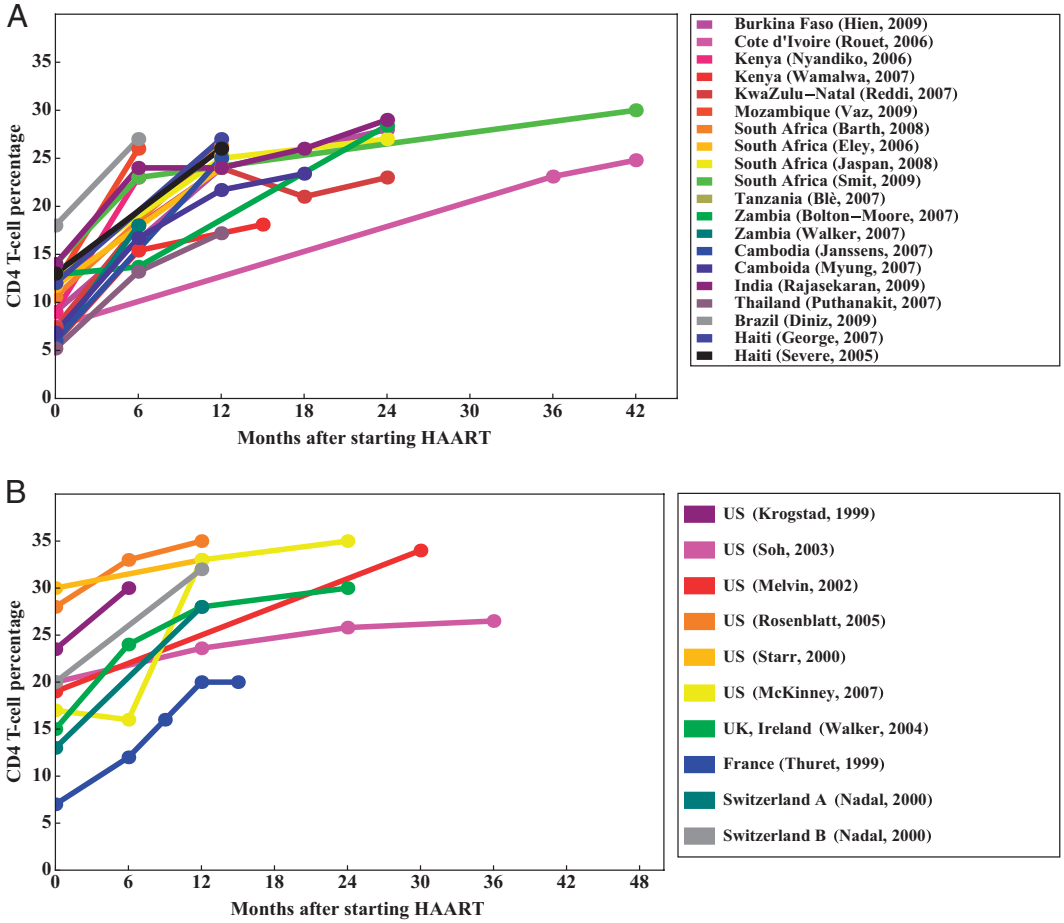

FIGURE 3
CD4 T-cell percentage change over time. A, RLCs; B, DCs.

important for the evaluation of programs and to guide future treatment. Although authors of recent reviews have described post-HAART outcomes in Africa, none has systematically compared outcomes between regions.[14] RLC outcomes have been compared informally to DC outcomes without careful consideration of the cohort selection criteria or treatment regimens. Informal comparisons have been made to DC study reports that provided outcomes according to calendar years, including patients not on ART and those on HAART for years, infant studies, overlapping studies, and cohorts of < 20 patients.[2,14,17,80–85,89–91] Publications included in this study were systematically screened on the basis of age, cohort size, and regimens. Outcome data were extracted to avoid analysis of data from overlapping cohorts, and standardized outcomes were compared.

The post-HAART mortality rates for HAART-naive children were fivefold to ninefold greater in RLCs than in DCs. Although not directly comparable, this difference was less than the difference between overall mortality rates for children between the ages of 1 and 5 years in RLCs and DCs (exceptions included Brazil and Thailand).[92] Six studies from Zambia, Kenya, Rwanda, and Tanzania found that post-HAART mortality rates fell below 3.5 DPCY despite higher regional child mortality rates (range: 37–56 deaths per 1000 live births between the ages of 1 and 5 years, as estimated by subtracting infant mortality rates from mortality rates of children <5 years old).[22–24,33,40,44,92] Although HIV contributes to overall child mortality rates in high HIV-prevalence areas, HAART seems to provide some survival benefits to patients, perhaps by simply bringing children in contact with medical services.[93,94]

The CD4 and VL data provide important contextual information for interpretation of the mortality results by demonstrating that HAART programs in RLCs have reported efficient and comparable increases in CD4% and declines in VLs as DC programs. Significantly lower CD4 levels observed in RLCs 12 months after HAART are likely a result of

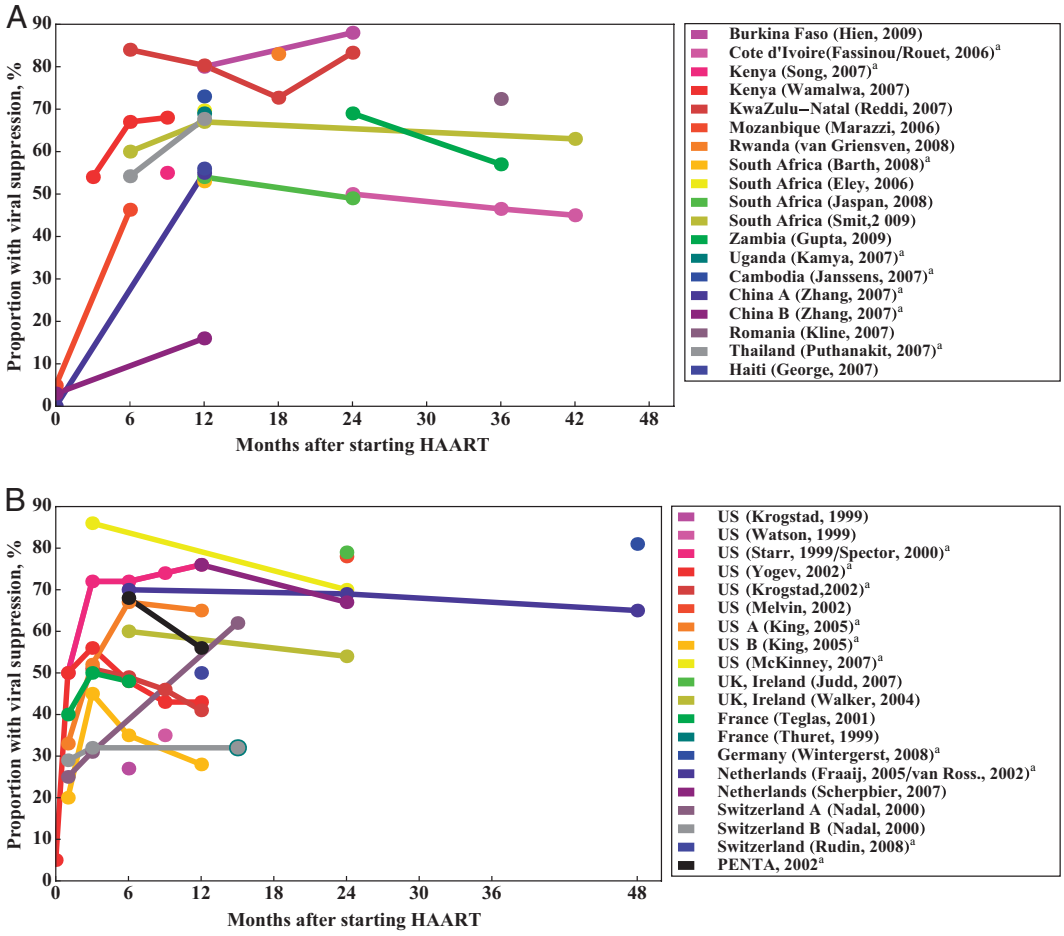

FIGURE 4
Percentage of patients who achieved viral suppression over time. A, RLCs; B, DCs. [a] Intention-to-treat analysis.

markedly lower baseline CD4 levels. In contrast, post-HAART VL-suppression rates were not significantly different between DCs and RLCs after HAART despite significantly higher baseline VL in RLCs.

Strengths of this analysis include the large number of studies evaluated, the study-selection process, and the standardized comparisons of mortality rates, baseline CD4 percentage, and baseline VLs. This comprehensive comparison spanned 11 years of publications, during which drug regimens, guidelines, and patient populations evolved, particularly in DCs. Although later publications from DCs would be expected to use more potent medications, earlier study reports described larger HAART-naive cohorts, which provides better comparison of baseline characteristics and perhaps slightly underestimates the difference between DCs and RLCs.[74] A limitation of the study is that outcomes were likely biased toward better outcomes, because children lost to follow-up could include unreported deaths or immunologic and virologic nonresponders. We excluded cohorts that had only included children with a minimum amount of follow-up for the same reason. The studies we included had survivor bias (mean baseline age: >5 years); in RLCs, untreated HIV-infected children have only 50% survival rates below 2 years. As-treated analysis also results in overestimation of virologic suppression, because the proportion of children who achieved virologic suppression has been reported within the denominator of patients with VL data rather than the total number of patients who initiated treatment.

Low baseline CD4, WAZ, and high VL levels were identified by individual studies as strong predictors of mortality in both RLCs and DCs. In multivariate analysis, mortality-rate differences between RLCs and DCs persisted even after adjusting for baseline CD4 count. However, we found that at least a portion of the mortality-rate difference was attributable to differences in WAZ or VL in these different settings. In RLCs, children were older at the time of diagnosis and had more advanced disease, and the majority of deaths oc-

curred in the first 6 months of treatment.‡ Earlier identification of children could improve post-HAART outcomes by identifying children with less advanced disease.[95,96] Revised 2010 WHO treatment guidelines recommend treatment for all children younger than 24 months and a new CD4 threshold of 25% or 750 cells per μL for children aged 2 to 5 years. Additional studies are needed to evaluate the effect of these new guidelines on post-HAART outcomes.[97]

‡Refs 12, 13, 20, 29, 33, 40, 42, 69, and 80.

CONCLUSIONS

Pediatric HAART programs in RLCs are successfully achieving a reduction in HIV- related mortality; however, post-HAART mortality rates remain higher than the rates in DCs. Currently, children in RLCs begin HAART at higher baseline VLs and lower baseline CD4 levels. Continuing to improve child health with interventions including nutritional support and prevention and treatment of coinfections may additionally improve survival rates. With increased availability of treatment and earlier treatment, regions with high HIV prevalence should realize marked declines in HIV-related child mortality.

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REFERENCES

1. Hammer S, Squires K, Hughes M, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. AIDS Clinical Trials Group 320 Study Team. *N Engl J Med*. 1997; 337(11):725–733
2. Gortmaker SL, Hughes M, Cervia J, et al; Pediatric AIDS Clinical Trials Group Protocol 219 Team. Effect of combination therapy including protease inhibitors on mortality among children and adolescents infected with HIV-1. *N Engl J Med*. 2001; 345(21):1522–1528
3. Newell M, Coovadia H, Cortina-Borja M, Rollins N, Gaillard P, Dabis F. Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. *Lancet*. 2004;364(9441): 1236–1243
4. Spira R, Lepage P, Msellati P, et al. Natural history of human immunodeficiency virus type 1 infection in children: a five-year prospective study in Rwanda. Mother-to-Child HIV-1 Transmission Study Group. *Pediatrics*. 1999;104(5). Available at: www.pediatrics.org/cgi/content/full/104/5/e56
5. Joint United Nations Programme on HIV/AIDS. 2008 report on the global AIDS epidemic. Available at: www.unaids.org/en/KnowledgeCentre/HIVData/GlobalReport/2008/2008_Global_report.asp. Accessed December 23, 2009
6. Boerma J, Stanecki K, Newell M, et al. Monitoring the scale-up of antiretroviral therapy programmes: methods to estimate coverage. *Bull World Health Organ*. 2006; 84(2):145–150
7. American Academy of Pediatrics, Committee on Pediatric AIDS, Section on International Child Health; Havens PL, Gibb DM. Increasing antiretroviral drug access for children with HIV infection. *Pediatrics*. 2007;119(4):838–845
8. Gill C, Hamer D, Simon J, Thea D, Sabin L. No room for complacency about adherence to antiretroviral therapy in sub-Saharan Africa. *AIDS*. 2005;19(12): 1243–1249
9. Church JA, Hughes M, Chen J, et al; Pediatric AIDS Clinical Trials Group P1005 Study Team. Long term tolerability and safety of enfuvirtide for human immunodeficiency virus 1-infected children. *Pediatr Infect Dis J*. 2004;23(8):713–718
10. O'Brien D, Sauvageot D, Zachariah R, Humblet P. In resource-limited settings good early outcomes can be achieved in children using adult fixed-dose combination antiretroviral therapy. *AIDS*. 2006;20(15): 1955–1960
11. Krogstad P, Lee S, Johnson G, et al; Pediatric AIDS Clinical Trials Group 377 Study Team. Nucleoside-analogue reverse-transcriptase inhibitors plus nevirapine, nelfinavir, or ritonavir for pretreated children infected with human immunodeficiency virus type 1. *Clin Infect Dis*. 2002; 34(7):991–1001
12. George E, Noël F, Bois G, et al. Antiretroviral therapy for HIV-1-infected children in Haiti. *J Infect Dis*. 2007;195(10):1411–1418
13. Myung P, Pugatch D, Brady M, et al. Directly observed highly active antiretroviral therapy for HIV-infected children in Cambodia. *Am J Public Health*. 2007;97(6):974–977
14. Sutcliffe C, van Dijk J, Bolton C, Persaud D, Moss W. Effectiveness of antiretroviral therapy among HIV-infected children in sub-Saharan Africa. *Lancet Infect Dis*. 2008;8(8):477–489
15. WHO and UNAIDS release update that focuses on HIV prevention. *IAVI Rep*. 2005; 9(5):20
16. Antiretroviral therapy for children in the routine setting in Malawi. *Trans R Soc Trop Med Hyg*. 2007;101(5):511–516
17. Ciaranello A, Chang Y, Margulis A, et al. Effectiveness of pediatric antiretroviral therapy in resource-limited settings: a systematic review and meta-analysis. *Clin Infect Dis*. 2009;49(12):1915–1927
18. United Nations Statistics Division. Composition of macro geographical (continental) regions, geographical sub-regions, and selected economic and other groupings. Available at: http://unstats.un.org/unsd/methods/m49/m49regin.htm. Accessed April 30, 2010
19. Hien H, Nacro B, Zouré E, et al. Once-a-day paediatric HAART with DDI+3TC+EFV in West Africa: 24 month virological and immunological outcomes [abstract MOPEB031]. ANRS12103/12167 trial. Presented at: 5th International AIDS Society conference on HIV Pathogenesis and Treatment; July 19–22, 2009; Cape Town, South Africa. Available at: www.ias2009.org/abstract.aspx?elementId=200722693. Accessed December 15, 2010
20. Fassinou P, Elenga N, Rouet F, et al. Highly active antiretroviral therapies among HIV-1 infected children in Abidjan, Cote d'Ivoire. *AIDS*. 2004;18(14):1905–1913
21. Rouet F, Fassinou P, Inwoley A, et al; ANRS 1244/1278 Programme Enfants Yopougon. Long-term survival and immunovirological response of African HIV-1-infected children to highly active antiretroviral therapy regimens. *AIDS*. 2006; 20(18):2315–2319
22. Nyandiko W, Ayaya S, Nabakwe E, et al. Outcomes of HIV-infected orphaned and non-orphaned children on antiretroviral therapy in western Kenya. *J Acquir Immune Defic Syndr*. 2006;43(4):418–425
23. Song R, Jelagat J, Dzombo D, et al. Efficacy of highly active antiretroviral therapy in

HIV-1 infected children in Kenya. *Pediatrics*. 2007;120(4). Available at: www.pediatrics.org/cgi/content/full/120/4/e856

24. Van Winghem J, Telfer B, Reid T, et al. Implementation of a comprehensive program including psycho-social and treatment literacy activities to improve adherence to HIV care and treatment for a pediatric population in Kenya. *BMC Pediatr*. 2008;8:52
25. Wamalwa D, Farquhar C, Obimbo E, et al. Early response to highly active antiretroviral therapy in HIV-1-infected Kenyan children. *J Acquir Immune Defic Syndr*. 2007; 45(3):311–317
26. Reddi A, Leeper S, Grobler A, et al. Preliminary outcomes of a paediatric highly active antiretroviral therapy cohort from KwaZulu-Natal, South Africa. *BMC Pediatr*. 2007;7:13
27. Leyenaar J, Novosad P, Ferrer K, et al. Early clinical outcomes in children enrolled in human immunodeficiency virus infection care and treatment in Lesotho. *Pediatr Infect Dis J*. 2010;29(4):340–345
28. Cohen R, Lynch S, Bygrave H, et al. Nurse-driven, community-supported HIV/AIDS care and treatment: 2 year antiretroviral treatment outcomes from a primary care level programme in rural Lesotho [abstract MOAD102]. Presented at: 5th International AIDS Society conference on HIV Pathogenesis and Treatment; July 19–22, 2009; Cape Town, South Africa. Available at: www.ias2009.org/abstract.aspx?elementId=200722512. Accessed December 15, 2010
29. Bong C, Yu J, Chiang H, et al. Risk factors for early mortality in children on adult fixed-dose combination antiretroviral treatment in a central hospital in Malawi. *AIDS*. 2007;21(13):1805–1810
30. Weigel R, Keiser O, Gumulira J, et al. Growth response to ART in HIV-infected children from Lilongwe, Malawi [paper 848]. Presented at: 17th Conference on Retroviruses and Opportunistic Infections; February 16–19, 2010; San Francisco, CA. Available at: www.retroconference.org/2010/Abstracts/37992.htm. Accessed December 15, 2010
31. Marazzi M, Germano P, Liotta G, Buonomo E, Guidotti G, Palombi L. Pediatric highly active antiretroviral therapy in Mozambique: an integrated model of care [in Italian]. *Minerva Pediatr*. 2006;58(5): 483–490
32. Vaz P, Santos P, Augusto O, Macassa E, Blanche S, Andersson S. The impact of antiretroviral treatment on growth of HIV-1 infected children in Maputo, Mozambique [abstract WEPEB197]. Presented at: 5th International AIDS Society conference on HIV Pathogenesis and Treatment; July 19–22, 2009; Cape Town, South Africa. Available at: www.ias2009.org/abstract.aspx?elementId=200722321. Accessed December 15, 2010
33. van Griensven J, De Naeyer L, Uwera J, Asiimwe A, Gazille C, Reid T. Success with antiretroviral treatment for children in Kigali, Rwanda: experience with health center/nurse-based care. *BMC Pediatr*. 2008;8:39
34. Diack MBaye A, Signaté Sy H, Diagne Guèye NR, et al. Epidemiological and clinical aspects of paediatric HIV infections in Albert-Royer Paediatric Hospital (Dakar, Senegal) [in French]. *Arch Pediatr*. 2005;12(4): 404–409
35. Barth R, van der Meer J, Hoepelman A, et al. Effectiveness of highly active antiretroviral therapy administered by general practitioners in rural South Africa. *Eur J Clin Microbiol Infect Dis*. 2008;27(10): 977–984
36. Eley B. Addressing the paediatric HIV epidemic: a perspective from the Western Cape region of South Africa. *Trans R Soc Trop Med Hyg*. 2006;100(1):19–23
37. Jaspan H, Berrisford A, Boulle A. Two-year outcomes of children on non-nucleoside reverse transcriptase inhibitor and protease inhibitor regimens in a South African pediatric antiretroviral program. *Pediatr Infect Dis J*. 2008;27(11):993–998
38. Jooste J, Van Zyl A, Baker A, Crawford W, Jassen A. Antiretroviral treatment in the Northern Cape. *S Afr Med J*. 2005;95(11): 812
39. Smit EJ, Rabie H, Prozesky H, Cotton M. Pediatric outcome 42 months after highly active antiretroviral therapy availability in the public sector: the Tygerberg Children's Hospital experience [abstract MOPEB079]. Presented at: 5th International AIDS Society conference on HIV Pathogenesis and Treatment; July 19–22, 2009; Cape Town, South Africa. Available at: www.ias2009.org/abstract.aspx?elementId=200721774. Accessed December 15, 2010
40. Blè C, Floridia M, Muhale C, et al. Efficacy of highly active antiretroviral therapy in HIV-infected, institutionalized orphaned children in Tanzania. *Acta Paediatr*. 2007; 96(7):1090–1094
41. Kamya MR, Mayanja-Kizza H, Kambugu A, et al; Academic Alliance for AIDS Care and Prevention in Africa. Predictors of long-term viral failure among Ugandan children and adults treated with antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2007;46(2):187–193
42. Bolton-Moore C, Mubiana-Mbewe M, Cantrell R, et al. Clinical outcomes and CD4 cell response in children receiving antiretroviral therapy at primary health care facilities in Zambia. *JAMA*. 2007;298(16): 1888–1899
43. Gupta RK, Ford D, Kabamba D, et al. Two year virological outcomes in HIV-1 infected Zambian children using adult Triomune (fixed dose combination d4T, 3TC and NVP) [abstract MOPEB056]. Presented at: 5th International AIDS Society conference on HIV Pathogenesis and Treatment; July 19–22, 2009; Cape Town, South Africa. Available at: www.ias2009.org/abstract.aspx?elementId=200722143. Accessed December 15, 2010
44. Walker AS, Mulenga V, Ford D, et al; CHAP Team. The impact of daily cotrimoxazole prophylaxis and antiretroviral therapy on mortality and hospital admissions in HIV-infected Zambian children. *Clin Infect Dis*. 2007;44(10):1361–1367
45. Janssens B, Raleigh B, Soeung S, et al. Effectiveness of highly active antiretroviral therapy in HIV-positive children: evaluation at 12 months in a routine program in Cambodia. *Pediatrics*. 2007;120(5). Available at: www.pediatrics.org/cgi/content/full/120/5/e1134
46. Zhang F, Haberer J, Zhao Y, et al. Chinese pediatric highly active antiretroviral therapy observational cohort: a 1-year analysis of clinical, immunologic, and virologic outcomes. *J Acquir Immune Defic Syndr*. 2007;46(5):594–598
47. Rajasekaran S, Jeyaseelan L, Ravichandran N, Gomathi C, Thara F, Chandrasekar C. Efficacy of antiretroviral therapy program in children in India: prognostic factors and survival analysis. *J Trop Pediatr*. 2009; 55(4):225–232
48. Kline M, Rugina S, Ilie M, et al. Long-term follow-up of 414 HIV-infected Romanian children and adolescents receiving lopinavir/ritonavir-containing highly active antiretroviral therapy. *Pediatrics*. 2007;119(5). Available at: www.pediatrics.org/cgi/content/full/119/5/e1116
49. Aurpibul L, Puthanakit T, Taecharoenkul S, Sirisanthana V. Impact of non-nucleoside reverse transcriptase inhibitor (NNRTI)-based antiretroviral therapy (ART) on weight and height of antiretroviral-naive HIV-infected children [abstract CDB103]. Presented at: 5th International AIDS Society conference on HIV Pathogenesis and Treatment; July 19–22, 2009; Cape Town, South Africa. Available at: www.ias2009.org/abstract.aspx?elementId=200721497. Accessed December 15, 2010
50. Lapphra K, Vanprapar N, Chearskul S, et al. Efficacy and tolerability of nevirapine- ver-

sus efavirenz-containing regimens in HIV-infected Thai children. *Int J Infect Dis*. 2008;12(6):e33–e38

51. Puthanakit T, Aurpibul L, Oberdorfer P, et al. Hospitalization and mortality among HIV-infected children after receiving highly active antiretroviral therapy. *Clin Infect Dis*. 2007;44(4):599–604
52. Romanelli R, Pinto J, Melo L, Vasconcelos M, Pereira RM. Effectiveness of dual and triple antiretroviral therapy in the treatment of HIV-infected children [in Portuguese]. *J Pediatr (Rio J)*. 2006;82(4):260–265
53. Martins Oliveira Diniz L, Marie Martins Maia M, Silveira Camargos L, Custódio Amaral L, Goulart E, Andrade Pinto J. Long-term effects of HAART on weight and height among Brazilian children infected with HIV [abstract CDB105]. Presented at: 5th International AIDS Society conference on HIV Pathogenesis and Treatment; July 19–22, 2009; Cape Town, South Africa. Available at: www.ias2009.org/abstract.aspx?elementId=200722217. Accessed December 15, 2010
54. Martins Oliveira Diniz L, Marie Martins Maia M, Silveira Camargos L, Custódio Amaral L, Goulart E, Andrade Pinto J. Long-term effects of HAART on $CD4^+$ cell percentage among Brazilian children infected with HIV [abstract MOPEB087]. Presented at: 5th International AIDS Society conference on HIV Pathogenesis and Treatment; July 19–22, 2009; Cape Town, South Africa. Available at: www.ias2009.org/abstract.aspx?elementId=200722230. Accessed December 15, 2010
55. Severe P, Leger P, Charles M, et al. Antiretroviral therapy in a thousand patients with AIDS in Haiti. *N Engl J Med*. 2005;353(22):2325–2334
56. Ghaffari G, Passalacqua D, Caicedo J, Goodenow M, Sleasman J. Two-year clinical and immune outcomes in human immunodeficiency virus-infected children who reconstitute CD4 T cells without control of viral replication after combination antiretroviral therapy. *Pediatrics*. 2004;114(5). Available at: www.pediatrics.org/cgi/content/full/114/5/e604
57. King J, Nachman S, Yogev R, et al. Efficacy, tolerability and pharmacokinetics of two nelfinavir-based regimens in human immunodeficiency virus-infected children and adolescents: pediatric AIDS clinical trials group protocol 403. *Pediatr Infect Dis J*. 2005;24(10):880–885
58. Krogstad P, Wiznia A, Luzuriaga K, et al. Treatment of human immunodeficiency virus 1-infected infants and children with the protease inhibitor nelfinavir mesylate. *Clin Infect Dis*. 1999;28(5):1109–1118
59. McKinney RJ, Rodman J, Hu C, et al; Pediatric AIDS Clinical Trials Group Protocol P1021 Study Team. Long-term safety and efficacy of a once-daily regimen of emtricitabine, didanosine, and efavirenz in HIV-infected, therapy-naive children and adolescents: Pediatric AIDS Clinical Trials Group Protocol P1021. *Pediatrics*. 2007;120(2). Available at: www.pediatrics.org/cgi/content/full/120/2/e416
60. Melvin A, Lewis P, Mohan K, Naugler W, Frenkel L. Efficacy and toxicity of antiretroviral therapy using 4 or more agents: application of a strategy for antiretroviral management in human immunodeficiency virus-infected children. *Arch Pediatr Adolesc Med*. 2002;156(6):568–573
61. Patel K, Hernan M, Williams P, et al; Pediatric AIDS Clinical Trials Group 219/219C Study Team. Long-term effectiveness of highly active antiretroviral therapy on the survival of children and adolescents with HIV infection: a 10-year follow-up study. *Clin Infect Dis*. 2008;46(4):507–515
62. Rosenblatt H, Stanley K, Song L, et al. Immunological response to highly active antiretroviral therapy in children with clinically stable HIV-1 infection. *J Infect Dis*. 2005;192(3):445–455
63. Soh C, Oleske J, Brady M, et al; Pediatric AIDS Clinical Trials Group. Long-term effects of protease-inhibitor-based combination therapy on CD4 T-cell recovery in HIV-1-infected children and adolescents. *Lancet*. 2003;362(9401):2045–2051
64. Spector S, Hsia K, Yong F, et al. Patterns of plasma human immunodeficiency virus type 1 RNA response to highly active antiretroviral therapy in infected children. *J Infect Dis*. 2000;182(6):1769–1773
65. Starr S, Fletcher C, Spector S, et al. Combination therapy with efavirenz, nelfinavir, and nucleoside reverse-transcriptase inhibitors in children infected with human immunodeficiency virus type 1. Pediatric AIDS Clinical Trials Group 382 Team. *N Engl J Med*. 1999;341(25):1874–1881
66. Watson D, Farley J. Efficacy of and adherence to highly active antiretroviral therapy in children infected with human immunodeficiency virus type 1. *Pediatr Infect Dis J*. 1999;18(8):682–689
67. Wiznia A, Stanley K, Krogstad P, et al. Combination nucleoside analog reverse transcriptase inhibitor(s) plus nevirapine, nelfinavir, or ritonavir in stable antiretroviral therapy-experienced HIV-infected children: week 24 results of a randomized controlled trial—PACTG 377. Pediatric AIDS Clinical Trials Group 377 Study Team. *AIDS Res Hum Retroviruses*. 2000;16(12):1113–1121
68. Yogev R, Lee S, Wiznia A, et al; Pediatrics AIDS Clinical Trials Group 338 Study Team. Stavudine, nevirapine and ritonavir in stable antiretroviral therapy-experienced children with human immunodeficiency virus infection. *Pediatr Infect Dis J*. 2002;21(2):119–125
69. Bracher L, Valerius N, Rosenfeldt V, et al. Long-term effectiveness of highly active antiretroviral therapy (HAART) in perinatally HIV-infected children in Denmark. *Scand J Infect Dis*. 2007;39(9):799–804
70. Teglas J, Quartier P, Treluyer J, Burgard M, Gregoire V, Blanche S. Tolerance of efavirenz in children. *AIDS*. 2001;15(2):241–243
71. Thuret I, Michel G, Chambost H, et al. Combination antiretroviral therapy including ritonavir in children infected with human immunodeficiency. *AIDS*. 1999;13(1):81–87
72. Wintergerst U, Hoffmann F, Jansson A, et al. Antiviral efficacy, tolerability and pharmacokinetics of efavirenz in an unselected cohort of HIV-infected children. *J Antimicrob Chemother*. 2008;61(6):1336–1339
73. Fraaij P, Verweel G, van Rossum A, et al. Sustained viral suppression and immune recovery in HIV type 1-infected children after 4 years of highly active antiretroviral therapy. *Clin Infect Dis*. 2005;40(4):604–608
74. Scherpbier H, Bekker V, Pajkrt D, Jurriaans S, Lange J, Kuijpers T. Once-daily highly active antiretroviral therapy for HIV-infected children: safety and efficacy of an efavirenz-containing regimen. *Pediatrics*. 2007;119(3). Available at: www.pediatrics.org/cgi/content/full/119/3/e705
75. van Rossum A, Geelen S, Hartwig N, et al. Results of 2 years of treatment with protease-inhibitor–containing antiretroviral therapy in Dutch children infected with human immunodeficiency virus type 1. *Clin Infect Dis*. 2002;34(7):1008–1016
76. van Rossum A, Niesters H, Geelen S, et al. Clinical and virologic response to combination treatment with indinavir, zidovudine, and lamivudine in children with human immunodeficiency virus-1 infection: a multicenter study in the Netherlands. On behalf of the Dutch Study Group for Children With HIV-1 infections. *J Pediatr*. 2000;136(6):780–788
77. Verweel G, van Rossum A, Hartwig N, Wolfs T, Scherpbier H, de Groot R. Treatment with highly active antiretroviral therapy in human immunodeficiency virus type 1-infected children is associated with a

sustained effect on growth. *Pediatrics*. 2002;109(2). Available at: www.pediatrics.org/cgi/content/full/109/2/e25

78. Nadal D, Steiner F, Cheseaux J, et al. Long-term responses to treatment including ritonavir or nelfinavir in HIV-1-infected children [published correction appears in *Infection*. 2000;28(6):402]. Pediatric AIDS Group of Switzerland. *Infection*. 2000; 28(5):287–296
79. Rudin C, Burri M, Shen Y, Rode R, Nadal D. Long-term safety and effectiveness of ritonavir, nelfinavir, and lopinavir/ritonavir in antiretroviral-experienced HIV-infected children. *Pediatr Infect Dis J*. 2008;27(5):431–437
80. Judd A, Doerholt K, Tookey P, et al; Collaborative HIV Paediatric Study (CHIPS); National Study of HIV in Pregnancy and Childhood (NSHPC). Morbidity, mortality, and response to treatment by children in the United Kingdom and Ireland with perinatally acquired HIV infection during 1996–2006: planning for teenage and adult care. *Clin Infect Dis*. 2007;45(7): 918–924
81. Walker A, Doerholt K, Sharland M, Gibb D. Response to highly active antiretroviral therapy varies with age: the UK and Ireland Collaborative HIV Paediatric Study. *AIDS*. 2004;18(14):1915–1924
82. Paediatric European Network for Treatment of AIDS. Comparison of dual nucleoside-analogue reverse-transcriptase inhibitor regimens with and without nelfinavir in children with HIV-1 who have not previously been treated: the PENTA 5 randomised trial. *Lancet*. 2002;359(9308):733–740
83. Caudill S, Goldman T, Marconi K. Evaluation of pediatric HIV care provided in Ryan White CARE Act Title IV Women, Infants, Children, and Youth Clinics. *AIDS Patient Care STDS*. 2003;17(2):65–73
84. Lindsey J, Hughes M, McKinney R, et al. Treatment-mediated changes in human immunodeficiency virus (HIV) type 1 RNA and CD4 cell counts as predictors of weight growth failure, cognitive decline, and survival in HIV-infected children. *J Infect Dis*. 2000;182(5):1385–1393
85. Resino S, Resino R, Maria Bellón J, et al; Spanish Group of Pediatric HIV Infection. Clinical outcomes improve with highly active antiretroviral therapy in vertically HIV type-1-infected children. *Clin Infect Dis*. 2006;43(2):243–252
86. Pelton S, Johnson D, Chadwick E, Baldwin Z, Yogev R. A one year experience: T cell responses and viral replication in children with advanced human immunodeficiency virus type 1 disease treated with combination therapy including ritonavir. *Pediatr Infect Dis J*. 1999;18(7):650–652
87. de Martino M, Tovo P, Balducci M, et al. Reduction in mortality with availability of antiretroviral therapy for children with perinatal HIV-1 infection. Italian Register for HIV Infection in Children and the Italian National AIDS Registry. *JAMA*. 2000;284(2): 190–197
88. Kline M, Matusa R, Copaciu L, Calles N, Kline N, Schwarzwald H. Comprehensive pediatric human immunodeficiency virus care and treatment in Constanta, Romania: implementation of a program of highly active antiretroviral therapy in a resource-poor setting. *Pediatr Infect Dis J*. 2004;23(8):695–700
89. Doerholt K, Duong T, Tookey P, et al; Collaborative HIV Paediatric Study. Outcomes for human immunodeficiency virus-1-infected infants in the United kingdom and Republic of Ireland in the era of effective antiretroviral therapy. *Pediatr Infect Dis J*. 2006; 25(5):420–426
90. Funk M, Linde R, Wintergerst U, et al. Preliminary experiences with triple therapy including nelfinavir and two reverse transcriptase inhibitors in previously untreated HIV-infected children. *AIDS*. 1999; 13(13):1653–1658
91. Gibb D, Goodall R, Giacomet V, McGee L, Compagnucci A, Lyall H. Adherence to prescribed antiretroviral therapy in human immunodeficiency virus-infected children in the PENTA 5 trial. *Pediatr Infect Dis J*. 2003;22(1):56–62
92. United Nations Children's Fund. Information by country and programme. Available at: www.unicef.org/infobycountry/index.html. Accessed April 17, 2010).
93. Adetunji J. Trends in under-5 mortality rates and the HIV/AIDS epidemic. *Bull World Health Organ*. 2000;78(10): 1200–1206
94. Newell M, Brahmbhatt H, Ghys P. Child mortality and HIV infection in Africa: a review. *AIDS*. 2004;18(suppl 2):S27–S34
95. Violari A, Cotton M, Gibb D, et al; CHER Study Team. Early antiretroviral therapy and mortality among HIV-infected infants. *N Engl J Med*. 2008;359(21):2233–2244
96. Eley B. Antiretroviral therapy during infancy: essential intervention for resource-limited settings. *Expert Rev Anti Infect Ther*. 2008;6(5):585–589
97. World Health Organization. *Antiretroviral Therapy for HIV in Infants and Children: Towards Universal Access—Recommendations for a Public Health Approach*. 2010 revision. Geneva, Switzerland: World Health Organization; 2010. Available at: www.who.int/hiv/pub/paediatric/infants/en/index.html. Accessed July 26, 2010
98. Adjé-Touré C, Hanson D, Talla-Nzussouo N, Borget M, Kouadio L, Tossou O, et al. Virologic and immunologic response to antiretroviral therapy and predictors of HIV type 1 drug resistance in children receiving treatment in Abidjan, Côte d'Ivoire. *AIDS Res Hum Retroviruses*. 2008;24(7): 911–917
99. Biadgilign S, Deribew A, Amberbir A, Deribe K. Adherence to highly active antiretroviral therapy and its correlates among HIV infected pediatric patients in Ethiopia. *BMC Pediatr*. 2008;8:53
100. Onankpa B, Airede L, Paul I, Dorcas I. Pattern of pediatric HIV/AIDS: a five-year experience in a tertiary hospital. *J Natl Med Assoc*. 2008;100(7):821–825
101. Cowburn C, Hatherill M, Eley B, Nuttall J, Hussey G, Reynolds L, et al. Short-term mortality and implementation of antiretroviral treatment for critically ill HIV-infected children in a developing country. *Arch Dis Child*. 2007;92(3):234–241
102. Eley B, Nuttall J, Davies M, Smith L, Cowburn C, Buys H, et al. Initial experience of a public sector antiretroviral treatment programme for HIV-infected children and their infected parents. *S Afr Med J*. 2004; 94(8):643–646
103. Prendergast A, Mphatswe W, Tudor-Williams G, Rakgotho M, Pillay V, Thobakgale C, et al. Early virological suppression with three-class antiretroviral therapy in HIV-infected African infants. *AIDS*. 2008; 22(11):1333–1343
104. van Kooten Niekerk NK, Knies MM, Howard J, Rabie H, Zeier M, van Rensburg A, et al. The first 5 years of the family clinic for HIV at Tygerberg Hospital: family demographics, survival of children and early impact of antiretroviral therapy. *J Trop Pediatr*. 2006;52(1):3–11
105. Atakouma D, Tsolenyanu E, Gbadoe A, Gbetoglo V, Lawson-Evi K, Agbere A, et al. [Primary results of antiretroviral treatment among HIV/AIDS infected children in Lomé (Togo)]. *Arch Pediatr*. 2007;14(10): 1178–1182
106. Polisset J, Ametonou F, Arrive E, Aho A, Perez F. Correlates of Adherence to Antiretroviral Therapy in HIV-Infected Children in Lomé, Togo, West Africa. *AIDS Behav*. 2009;13(1):23–32
107. Fallo A, DobrzanskiNisiewicz W, Sordelli N, Cattaneo M, Scott G, López E. Clinical and epidemiologic aspects of human immunodeficiency virus-1-infected children in Bue-

nos Aires, Argentina. *Int J Infect Dis*. 2002; 6(1):9–16

108. Matida L, Marcopito L, Succi R, Marques H, Della Negra M, Grangeiro A, et al. Improving survival among Brazilian children with perinatally-acquired AIDS. *Braz J Infect Dis*. 2004;8(6):41–423
109. Candiani T, Pinto J, Cardoso C, Carvalho I, Dias A, Carneiro M, et al. Impact of highly active antiretroviral therapy (HAART) on the incidence of opportunistic infections, hospitalizations and mortality among children and adolescents living with HIV/AIDS in Belo Horizonte, Minas Gerais State, Brazil. *Cad Saude Publica*. 2007;23 Suppl 3:S414–423
110. Samayoa B, Anderson M, Grazioso C, Rivera B, Harrison M, O'Brien W, et al. Experience of a pediatric HIV clinic in Guatemala City. *Rev Panam Salud Publica*. 2009;25(1): 51–55
111. Evans-Gilbert T, Pierre R, Steel-Duncan J, Rodriguez B, Whorms S, Hambleton I, et al. Antiretroviral drug therapy in HIV-infected Jamaican children. *West Indian Med J*. 2004;53(5):322–326
112. Madec Y, Laureillard D, Pinoges L, Fernandez M, Prak N, Ngeth C, et al. Response to highly active antiretroviral therapy among severely immuno-compromised HIV-infected patients in Cambodia. *AIDS*. 2007; 21(3):351–359
113. Kumarasamy N, Venkatesh K, Devaleenol B, Poongulali S, Mothi S, Solomon S. Safety, tolerability and effectiveness of generic HAART in HIV-infected children in South India. *J Trop Pediatr*. 2009;55(3):155–159
114. Lodha R, Upadhyay A, Kabra SK. Antiretroviral therapy in HIV-1 infected children. *Indian Pediatr*. 2005;42(8):789–796
115. Natu S, Daga S. Antiretroviral therapy in children: Indian experience. *Indian Pediatr*. 2007;44(5):339–343
116. Pensi T. Fixed Dose Combination of Lamivudine, Stavudine and Nevirapine in the Treatment of Pediatric HIV infection: A Preliminary Report. *Indian Pediatr*. 2007; 44(7):519–521
117. Ferris M, Burau K, Schweitzer A, Mihale S, Murray N, Preda A, et al. The influence of disclosure of HIV diagnosis on time to disease progression in a cohort of Romanian children and teens. *AIDS Care*. 2007;19(9): 1088–1094
118. Chearskul P, Chokephaibulkit K, Chearskul S, Phongsamart W, Plipat N, Lapphra K, et al. Effect of antiretroviral therapy in human immunodeficiency virus-infected children. *J Med Assoc Thai*. 2005;88 Suppl 8:S221–S231
119. Koekkoek S, Eggermont L, De Sonneville L, Jupimai T, Wicharuk S, Apateerapong W, et al. Effects of highly active antiretroviral therapy (HAART) on psychomotor performance in children with HIV disease. *J Neurol*. 2006;253(12):1615–1624
120. Plipat N, Cressey T, Vanprapar N, Chokephaibulkit K. Efficacy and plasma concentrations of indinavir when boosted with ritonavir in human immunodeficiency virus-infected Thai children. *Pediatr Infect Dis J*. 2007;26(1):86–88
121. Arrivé E, Kyabayinze DJ, Marquis B, Tumwesigye N, Kieffer MP, Azondekon A, et al. Cohort profile: the paediatric antiretroviral treatment programmes in lower-income countries (KIDS-ART-LINC) collaboration. *Int J Epidemiol*. 2008;37(3): 474–480
122. The KIDS-ART-LINC Collaboration. Low Risk of Death, but Substantial Program Attrition, in Pediatric HIV Treatment Cohorts in Sub-Saharan Africa. *J Acquir Immune Defic Syndr*. 2008;49(5):523–531
123. Saez-Llorens X, Violari A, Ndiweni D, Yogev R, Cashat M, Wiznia A, et al. Long-term safety and efficacy results of once-daily emtricitabine-based highly active antiretroviral therapy regimens in human immunodeficiency virus-infected pediatric subjects. *Pediatrics*. 2008;121(4):e827–e835
124. Weidle P, Abrams E, Gvetadze R, Rivadeneira E, Kline M. A simplified weight-based method for pediatric drug dosing for zidovudine and didanosine in resource-limited settings. *Pediatr Infect Dis J*. 2006; 25(1):59–64
125. Hazra R, Stoszek SK, Freimanis Hance L, Pinto J, Marques H, Peixoto M, et al. Cohort Profile: NICHD International Site Development Initiative (NISDI): a prospective, observational study of HIV-exposed and HIV-infected children at clinical sites in Latin American and Caribbean countries. *Int J Epidemiol*. 2009;38(5):1207–1214
126. Hainaut M, Peltier C, Gérard M, Marissens D, Zissis G, Levy J. Effectiveness of antiretroviral therapy initiated before the age of 2 months in infants vertically infected with human immunodeficiency virus type 1. *Eur J Pediatr*. 2000;159(10):778–782
127. Aboulker J, Babiker A, Chaix M, Compagnucci A, Darbyshire J, Debré M, et al. Highly active antiretroviral therapy started in infants under 3 months of age: 72-week follow-up for CD4 cell count, viral load and drug resistance outcome. *AIDS*. 2004; 18(2):237–245
128. Faye A, Bertone C, Teglas J, Chaix M, Douard D, Firtion G, et al. Early multitherapy including a protease inhibitor for human immunodeficiency virus type 1-infected infants. *Pediatr Infect Dis J*. 2002;21(6):518–525
129. Wintergerst U, Hoffmann F, Sölder B, Notheis G, Petropoulou T, Eberle J, et al. Comparison of two antiretroviral triple combinations including the protease inhibitor indinavir in children infected with human immunodeficiency virus. *Pediatr Infect Dis J*. 1998;17(6):495–499
130. Canani R, Spagnuolo M, Cirillo P, Guarino A. Decreased needs for hospital care and antibiotics in children with advanced HIV-1 disease after protease inhibitor-containing combination therapy. *AIDS*. 1999;13(8):1005–1006
131. Chiappini E, Galli L, Tovo P, Gabiano C, Lisi C, Gattinara G, et al. Changing patterns of clinical events in perinatally HIV-1-infected children during the era of HAART. *AIDS*. 2007;21(12):1607–1615
132. Viganò A, Schneider L, Giacomet V, Bianchi R, Cicero M, Soster F, et al. Efficacy and tolerability of multiple drug therapy in HIV-infected children. *J Infect*. 2005;50(5): 404–411
133. Cohen Stuart JW, Slieker WA, Rijkers GT, Noest A, Boucher CA, Suur MH, et al. Early recovery of CD4+ T lymphocytes in children on highly active antiretroviral therapy. Dutch study group for children with HIV infections. *AIDS*. 1998;12(16): 2155–2159
134. Larrú B, Resino S, Bellón J, de José M, Fortuny C, Navarro M, et al. Long-term response to highly active antiretroviral therapy with lopinavir/ritonavir in pre-treated vertically HIV-infected children. *J Antimicrob Chemother*. 2007
135. Resino S, Bellón JM, Ramos JT, Resino R, Gurbindo MD, Mellado MJ, et al. Impact of highly active antiretroviral therapy on CD4+ T cells and viral load of children with AIDS: a population-based study. *AIDS Res Hum Retroviruses*. 2004;20(9):927–931
136. Sánchez J, Ramos Amador J, Fernández de Miguel S, González Tomée M, Rojo Conejo P, Fernado Vivas P, et al. Impact of highly active antiretroviral therapy on the morbidity and mortality in Spanish human immunodeficiency virus-infected children. *Pediatr Infect Dis J*. 2003;22(10):863–867
137. Guillén Martín S, Ramos Amador J, Resino García R, Bellón Cano J. [Epidemiological trends in new diagnoses of HIV-1 infection in children]. *An Pediatr (Barc)*. 2005;63(3): 199–202
138. Steiner F, Kind C, Aebi C, Wyler-Lazarevitch C, Cheseaux J, Rudin C, et al. Growth in human immunodeficiency virus type 1-infected children treated with protease

inhibitors. *Eur J Pediatr*. 2001;160(10):611–616

139. Newell M, Patel D, Goetghebuer T, Thorne C. CD4 cell response to antiretroviral therapy in children with vertically acquired HIV infection: is it associated with age at initiation? *J Infect Dis*. 2006;193(7):954–962
140. Goetghebuer T, Haelterman E, Le Chenadec J, Dollfus C, Gibb D, Judd A, et al. Effect of early antiretroviral therapy on the risk of AIDS/death in HIV-infected infants. *AIDS*. 2009;23(5):597–604
141. Abrams E, Weedon J, Bertolli J, Bornschlegel K, Cervia J, Mendez H, et al. Aging cohort of perinatally human immunodeficiency virus-infected children in New York City. New York City Pediatric Surveillance of Disease Consortium. *Pediatr Infect Dis J*. 2001;20(5):511–517
142. Benjamin DJ, Miller W, Benjamin D, Ryder R, Weber D, Walter E, et al. A comparison of height and weight velocity as a part of the composite endpoint in pediatric HIV. *AIDS*. 2003;17(16):2331–2336
143. Berrien V, Salazar J, Reynolds E, McKay K. Adherence to antiretroviral therapy in HIV-infected pediatric patients improves with home-based intensive nursing intervention. *AIDS Patient Care STDS*. 2004;18(6):355–363
144. Blazevic V, Jankelevich S, Steinberg S, Jacobsen F, Yarchoan R, Shearer G. Highly active antiretroviral therapy in human immunodeficiency virus type 1-infected children: analysis of cellular immune responses. *Clin Diagn Lab Immunol*. 2001;8(5):943–948
145. Borkowsky W, Stanley K, Douglas S, Lee S, Wiznia A, Pelton S, et al. Immunologic response to combination nucleoside analogue plus protease inhibitor therapy in stable antiretroviral therapy-experienced human immunodeficiency virus-infected children. *J Infect Dis*. 2000;182(1):96–103
146. Brady M, Oleske J, Williams P, Elgie C, Mofenson L, Dankner W, et al. Declines in mortality rates and changes in causes of death in HIV-1-infected children during the HAART era. *J Acquir Immune Defic Syndr*. 2010;53(1):86–94
147. Brogly S, Williams P, Seage Gr, Oleske J, Van Dyke R, McIntosh K. Antiretroviral treatment in pediatric HIV infection in the United States: from clinical trials to clinical practice. *JAMA*. 2005;293(18):2213–2220
148. Brundage R, Yong F, Fenton T, Spector S, Starr S, Fletcher C. Intrapatient variability of efavirenz concentrations as a predictor of virologic response to antiretroviral therapy. *Antimicrob Agents Chemother*. 2004;48(3):979–984
149. Buchacz K, Cervia J, Lindsey J, Hughes M, Seage Gr, Dankner W, et al. Impact of protease inhibitor-containing combination antiretroviral therapies on height and weight growth in HIV-infected children. *Pediatrics*. 2001;108(4):E72
150. Chadwick E, Rodman J, Britto P, Powell C, Palumbo P, Luzuriaga K, et al. Ritonavir-based highly active antiretroviral therapy in human immunodeficiency virus type 1-infected infants younger than 24 months of age. *Pediatr Infect Dis J*. 2005;24(9):793–800
151. Chadwick E, Capparelli E, Yogev R, Pinto J, Robbins B, Rodman J, et al. Pharmacokinetics, safety and efficacy of lopinavir/ritonavir in infants less than 6 months of age: 24 week results. *AIDS*. 2008;22(2):249–255
152. Chougnet C, Jankelevich S, Fowke K, Liewehr D, Steinberg S, Mueller B, et al. Long-term protease inhibitor-containing therapy results in limited improvement in T cell function but not restoration of interleukin-12 production in pediatric patients with AIDS. *J Infect Dis*. 2001;184(2):201–205
153. Church JA, Cunningham C, Hughes M, Palumbo P, Mofenson LM, Delora P, et al. Safety and antiretroviral activity of chronic subcutaneous administration of T-20 in human immunodeficiency virus 1-infected children. *Pediatr Infect Dis J*. 2002;21(7):653–659
154. Essajee S, Kim M, Gonzalez C, Rigaud M, Kaul A, Chandwani S, et al. Immunologic and virologic responses to HAART in severely immunocompromised HIV-1-infected children. *AIDS*. 1999;13(18):2523–2532
155. Flynn P, Rudy B, Douglas S, Lathey J, Spector S, Martinez J, et al. Virologic and immunologic outcomes after 24 weeks in HIV type 1-infected adolescents receiving highly active antiretroviral therapy. *J Infect Dis*. 2004;190(2):271–279
156. Flynn P, Rudy B, Lindsey J, Douglas S, Lathey J, Spector S, et al. Long-term observation of adolescents initiating HAART therapy: three-year follow-up. *AIDS Res Hum Retroviruses*. 2007;23(10):1208–1214
157. Glikman D, Walsh L, Valkenburg J, Mangat P, Marcinak J. Hospital-based directly observed therapy for HIV-infected children and adolescents to assess adherence to antiretroviral medications. *Pediatrics*. 2007;119(5):e1142–e1148
158. Gona P, Van Dyke R, Williams P, Dankner W, Chernoff M, Nachman S, et al. Incidence of opportunistic and other infections in HIV-infected children in the HAART era. *JAMA*. 2006;296(3):292–300
159. Jankelevich S, Mueller B, Mackall C, Smith S, Zwerski S, Wood L, et al. Long-term virologic and immunologic responses in human immunodeficiency virus type 1-infected children treated with indinavir, zidovudine, and lamivudine. *J Infect Dis*. 2001;183(7):1116–1120
160. Johnston A, Valentine M, Ottinger J, Baydo R, Gryszowka V, Vavro C, et al. Immune reconstitution in human immunodeficiency virus-infected children receiving highly active antiretroviral therapy: a cohort study. *Pediatr Infect Dis J*. 2001;20(10):941–946
161. King J, Acosta E, Yogev R, Wiznia A, Kraimer J, Graham B, et al. Steady-state pharmacokinetics of lopinavir/ritonavir in combination with efavirenz in human immunodeficiency virus-infected pediatric patients. *Pediatr Infect Dis J*. 2009;28(2):159–161
162. Kline M, Fletcher C, Harris A, Evans K, Brundage R, Remmel R, et al. A pilot study of combination therapy with indinavir, stavudine (d4T), and didanosine (ddI) in children infected with the human immunodeficiency virus. *J Pediatr*. 1998;132(3 Pt 1):543–546
163. Lee G, Gortmaker S, McIntosh K, Hughes M, Oleske J. Quality of life for children and adolescents: impact of HIV infection and antiretroviral treatment. *Pediatrics*. 2006;117(2):273–283
164. Luzuriaga K, Bryson Y, Krogstad P, Robinson J, Stechenberg B, Lamson M, et al. Combination treatment with zidovudine, didanosine, and nevirapine in infants with human immunodeficiency virus type 1 infection. *N Engl J Med*. 1997;336(19):1343–1349
165. Luzuriaga K, McManus M, Mofenson L, Britto P, Graham B, Sullivan J. A trial of three antiretroviral regimens in HIV-1-infected children. *N Engl J Med*. 2004;350(24):2471–2480
166. McConnell MS, Byers RH, Frederick T, Peters VB, Dominguez KL, Sukalac T, et al. Trends in antiretroviral therapy use and survival rates for a large cohort of HIV-infected children and adolescents in the United States, 1989–2001. *J Acquir Immune Defic Syndr*. 2005;38(4):488–494
167. Melvin A, Mohan K, Arcuino L, Edelstein R, Frenkel L. Clinical, virologic and immunologic responses of children with advanced human immunodeficiency virus type 1 disease treated with protease inhibitors. *Pediatr Infect Dis J*. 1997;16(10):968–974
168. Mueller B, Nelson RJ, Sleasman J, Zuckerman J, Heath-Chiozzi M, Steinberg S, et al. A

phase I/II study of the protease inhibitor ritonavir in children with human immunodeficiency virus infection. *Pediatrics*. 1998; 101(3 Pt 1):335–343

169. Mueller B, Sleasman J, Nelson RJ, Smith S, Deutsch P, Ju W, et al. A phase I/II study of the protease inhibitor indinavir in children with HIV infection. *Pediatrics*. 1998;102(1 Pt 1):101–109
170. Nachman S, Stanley K, Yogev R, Pelton S, Wiznia A, Lee S, et al. Nucleoside analogs plus ritonavir in stable antiretroviral therapy-experienced HIV-infected children: a randomized controlled trial. Pediatric AIDS Clinical Trials Group 338 Study Team. *JAMA*. 2000;283(4):492–498
171. Palumbo P, Raskino C, Fiscus S, Pahwa S, Schutzbank T, Spector S, et al. Virologic and immunologic response to nucleoside reverse-transcriptase inhibitor therapy among human immunodeficiency virus-infected infants and children. *J Infect Dis*. 1999;179(3):576–583
172. Patel K, Hernán M, Williams P, Seeger J, McIntosh K, Dyke R, et al. Long-term effects of highly active antiretroviral therapy on CD4+ cell evolution among children and adolescents infected with HIV: 5 years and counting. *Clin Infect Dis*. 2008;46(11): 1751–1760
173. Pelton S, Stanley K, Yogev R, Fletcher C, McIntosh K, Wiznia A, et al. Switch from ritonavir to indinavir in combination therapy for HIV-1-infected children. *Clin Infect Dis*. 2005;40(8):1181–1187
174. Polis M, Sidorov I, Yoder C, Jankelevich S, Metcalf J, Mueller B, et al. Correlation between reduction in plasma HIV-1 RNA concentration 1 week after start of antiretroviral treatment and longer-term efficacy. *Lancet*. 2001;358(9295):1760–1765
175. Reddington C, Cohen J, Baldillo A, Toye M, Smith D, Kneut C, et al. Adherence to medication regimens among children with human immunodeficiency virus infection. *Pediatr Infect Dis J*. 2000;19(12):1148–1153
176. Robbins B, Capparelli E, Chadwick E, Yogev R, Serchuck L, Worrell C, et al. Pharmacokinetics of High-Dose Lopinavir/Ritonavir with and without Saquinavir or Non-Nucleoside Reverse Transcriptase Inhibitors in HIV Infected Pediatric and Adolescent Patients Previously Treated with Protease Inhibitors - Study PACTG P1038. *Antimicrob Agents Chemother*. 2008
177. Rutstein R, Feingold A, Meislich D, Word B, Rudy B. Protease inhibitor therapy in children with perinatally acquired HIV infection. *AIDS*. 1997;11(12):F107–F111
178. Storm D, Boland M, Gortmaker S, He Y, Skurnick J, Howland L, et al. Protease inhibitor combination therapy, severity of illness, and quality of life among children with perinatally acquired HIV-1 infection. *Pediatrics*. 2005;115(2):e173–e182
179. Van Dyke R, Lee S, Johnson G, Wiznia A, Mohan K, Stanley K, et al. Reported adherence as a determinant of response to highly active antiretroviral therapy in children who have human immunodeficiency virus infection. *Pediatrics*. 2002;109(4):e61
180. Viani R, Araneta M, Deville J, Spector S. Decrease in hospitalization and mortality rates among children with perinatally acquired HIV type 1 infection receiving highly active antiretroviral therapy. *Clin Infect Dis*. 2004;39(5):725–731
181. Wiznia A, Church J, Emmanuel P, Eppes S, Rowell L, Evans C, et al. Safety and efficacy of enfuvirtide for 48 weeks as part of an optimized antiretroviral regimen in pediatric human immunodeficiency virus 1-infected patients. *Pediatr Infect Dis J*. 2007;26(9):799–805
182. Ayaya S, Nyandiko W, Vreeman R, Wafula S, Rotch J. Progression of HIV Infection in children attending the academic model providing access to healthcare (AMPATH) clinics in Western Kenya [abstract CDB006]. Presented at: 5th International AIDS Society conference on HIV Pathogenesis and Treatment; July 19–22, 2009; Cape Town, South Africa
183. McGrath C, Chung M, Richardson B, et al. Growth in HIV-1-infected children in Kenya following the initiation of HAART [abstract WEPEB191]. Presented at: 5th International AIDS Society conference on HIV Pathogenesis and Treatment; July 19–22, 2009; Cape Town, South Africa
184. Owiso G, Odawo P, Njoroge A, Meresey J, Muriithi C. Partnering with community health workers to improve pediatrics HIV testing and ART adherence [abstract WEPEB279]. Presented at: 5th International AIDS Society conference on HIV Pathogenesis and Treatment; July 19–22, 2009; Cape Town, South Africa
185. Wamalwa D, Obimbo E, Farquhar C, et al. Predictors of mortality in HIV-1 infected children on antiretroviral therapy in Kenya [abstract MOPEB086]. Presented at: 5th International AIDS Society conference on HIV Pathogenesis and Treatment; July 19–22, 2009; Cape Town, South Africa
186. Ndirangu J, Bland R, Newell ML. Weight and weight gain in HIV-infected children receiving antiretroviral therapy in rural KwaZulu-Natal [abstract WEPEB188]. Presented at: 5th International AIDS Society conference on HIV Pathogenesis and Treatment; July 19–22, 2009; Cape Town, South Africa
187. Braun M, Kabue M, Chirwa M, et al. Challenges in pediatric HIV referral: evidence for PMTCT, infant diagnosis, and pediatric HIV clinic integration in Lilongwe, Malawi [abstract WEPED218]. Presented at: 5th International AIDS Society conference on HIV Pathogenesis and Treatment; July 19–22, 2009; Cape Town, South Africa
188. Dow A, Dube Q, Chirambo CM, Moore M, Heyderman R, Van Rie A. Community based early infant testing and treatment: experience from Blantyre, Malawi [abstract CDB098]. Presented at: 5th International AIDS Society conference on HIV Pathogenesis and Treatment; July 19–22, 2009; Cape Town, South Africa
189. Kabue MM, Buck WC, Kazembe PN, Kline MW. Discontinuation of standard first-line antiretroviral therapy in a cohort of 1434 Malawian children [abstract WEPED175]. Presented at: 5th International AIDS Society conference on HIV Pathogenesis and Treatment; July 19–22, 2009; Cape Town, South Africa
190. Kabue MM, Braun M, Aetker L, et al. ART initiation and increased survival of infants traced from PMTCT to pediatric HIV care: highlighting the need for program coordination in Lilongwe, Malawi [abstract WEPDD103]. Presented at: 5th International AIDS Society conference on HIV Pathogenesis and Treatment; July 19–22, 2009; Cape Town, South Africa
191. Chouraya C, Mahdi MA, Kieffer MP, Lukhele B. Implementing early antiretroviral treatment for infants in Swaziland [abstract CDB078]. Presented at: 5th International AIDS Society conference on HIV Pathogenesis and Treatment; July 19–22, 2009; Cape Town, South Africa
192. Colvin CJ, Knight L, Van Cutsem G, et al. Paediatric outcomes after five years on ART in Khayelitsha Township, South Africa [abstract CDB109]. Presented at: 5th International AIDS Society conference on HIV Pathogenesis and Treatment; July 19–22, 2009; Cape Town, South Africa
193. Coovadia A, Abrams E, Strehlau R, et al. Randomized clinical trial of switching to nevirapine-based therapy for infected children exposed to nevirapine prophylaxis [abstract MOAB103]. Presented at: 5th International AIDS Society conference on HIV Pathogenesis and Treatment; July 19–22, 2009; Cape Town, South Africa
194. Fatti G, Bock P, Grimwood A, Wampold S, Eley B. Antiretroviral therapy outcomes in rural and urban children attending public health facilities in South Africa [abstract

MOPEB077]. Presented at: 5th International AIDS Society conference on HIV Pathogenesis and Treatment; July 19–22, 2009; Cape Town, South Africa

195. Fenner L, Keiser O, Brinkhof M, et al. Mortality, loss to follow-up and transfer-out in paediatric ART programmes in Southern Africa [abstract WEPEB276]. Presented at: 5th International AIDS Society conference on HIV Pathogenesis and Treatment; July 19–22, 2009; Cape Town, South Africa
196. Kaplan R, Bekker LG, Zwane E, Campbell E, Orrell C, Wood R. Long term programmatic outcomes for adults and children at a primary health care antiretroviral clinic in South Africa [abstract MOAD105]. Presented at: 5th International AIDS Society conference on HIV Pathogenesis and Treatment; July 19–22, 2009; Cape Town, South Africa
197. Kekitiinwa A, Maganda A, Tumbu P, Asiimwe Rwego A, Kiboneka E. Mortality rate among malnourished HIV-infected children in Kampala, Uganda: implications for time to initiate HAART [abstract MOPEB046]. Presented at: 5th International AIDS Society conference on HIV Pathogenesis and Treatment; July 19–22, 2009; Cape Town, South Africa
198. Augustinova D, Ban B, Kong C, et al. Health care of children diagnosed HIV positive before 18 months in Chea Chumneas Hospital, Takhmao, Cambodia [abstract CDC026]. Presented at: 5th International AIDS Society conference on HIV Pathogenesis and Treatment; July 19–22, 2009; Cape Town, South Africa
199. Isaakidis P, Raguenaud ME, Te V, et al. High survival and treatment success sustained after up to three years of ART for children in Cambodia [abstract MOAB102]. Presented at: 5th International AIDS Society conference on HIV Pathogenesis and Treatment; July 19–22, 2009; Cape Town, South Africa
200. Sophan S, Vibol U, Chanatheany H, et al. Lopinavir/ritonavir-based second line antiretroviral treatment in children at National Pediatric Hospital, Phnom Penh, Cambodia [abstract CDD020]. Presented at: 5th International AIDS Society conference on HIV Pathogenesis and Treatment; July 19–22, 2009; Cape Town, South Africa
201. Gnana Durai Pandian AG, Kandaswamy R, Nadol P, Chandrasekar S. Clinical and immunological response to highly active antiretroviral therapy (HAART) in paediatric patients - a retrospective cohort study at Government Hospital of Thoracic Medicine, India [abstract CDB102]. Presented at: 5th International AIDS Society conference on HIV Pathogenesis and Treatment; July 19–22, 2009; Cape Town, South Africa
202. McConnell M, Yuktanont P, Siangphoe U, et al. Survival rates following expansion of the national pediatric antiretroviral treatment program, Thailand, 2000–2005 [abstract MOAB101]. Presented at: 5th International AIDS Society conference on HIV Pathogenesis and Treatment; July 19–22, 2009; Cape Town, South Africa
203. Rezende R, Maia M, Diniz L, Camargos L, Amaral L, Pinto J. Impact of HAART in growth parameters of HIV-infected children in Minas Gerais, Brazil [abstract CDB104]. Presented at: 5th International AIDS Society conference on HIV Pathogenesis and Treatment; July 19–22, 2009; Cape Town, South Africa
204. Carter RJ, Katyal M, Toro P, Abrams EJ. Immunologic response and survival of infants initiating antiretroviral treatment (ART) at less than one year of age compared to older children enrolled at MTCT-Plus Initiative sites in 8 African countries and Thailand [abstract MOPEB048]. Presented at: 5th International AIDS Society conference on HIV Pathogenesis and Treatment; July 19–22, 2009; Cape Town, South Africa
205. Hansudewechakul R, Naiwatanakul T, Faikratok W, et al. Clinical outcomes in a community-based pediatric HIV care network in Chiang Rai, Thailand, 2002–2008 [MOPEB084]. Presented at: 5th International AIDS Society conference on HIV Pathogenesis and Treatment; July 19–22, 2009; Cape Town, South Africa
206. Davies MA, Wood R, Van Cutsem G, et al. Virologic failure and second-line antiretroviral therapy (ART) in children in South Africa: the international epidemiologic databases to evaluate AIDS (IeDEA) Southern Africa collaboration [abstract MOAB104]. Presented at: 5th International AIDS Society conference on HIV Pathogenesis and Treatment; July 19–22, 2009; Cape Town, South Africa
207. Palumbo P, Violari A, Lindsey J, et al. Nevirapine (NVP) vs lopinavir-ritonavir (LPV/r)-based antiretroviral therapy (ART) in single dose nevirapine (sdNVP)-exposed HIV-infected infants: preliminary results from the IMPAACT P1060 trial [abstract LBPEB12]. Presented at: 5th International AIDS Society conference on HIV Pathogenesis and Treatment; July 19–22, 2009; Cape Town, South Africa
208. Bognon T, Azondekon A, Homawoo E, et al. Networking between medical centers and ART pediatric site: what are the benefits for children? [abstract WEPDD105]. Presented at: 5th International AIDS Society conference on HIV Pathogenesis and Treatment; July 19–22, 2009; Cape Town, South Africa
209. Venkatesh K, De Bruyn G, Marinda E, et al. Morbidity and Mortality among Infants Born to HIV-infected Women in South Africa: Implications for Child Health in Resource-limited Settings [paper 841]. Presented at: 17th Conference on Retroviruses and Opportunistic Infections; February 16–19 2010; San Francisco, CA
210. Achan J, Ruel T, Li P, et al. Incidence of Early Virological Failure and the Evolution of Antiretroviral Drug Resistance Mutations in Ugandan Children [paper 849]. Presented at: 17th Conference on Retroviruses and Opportunistic Infections; February 16–19 2010; San Francisco, CA
211. Becquet R, et al. Survival of Children HIV-infected Perinatally or through Breastfeeding: A Pooled Analysis of Individual Data from Sub-Saharan Africa [paper 840]. Presented at: 17th Conference on Retroviruses and Opportunistic Infections; February 16–19 2010; San Francisco, CA
212. Pandian PG, Chandran P, Kandasamy C. Persistence of Stunting after HAART in HIV-infected Children in South India [paper 847]. Presented at: 17th Conference on Retroviruses and Opportunistic Infections; February 16–19 2010; San Francisco, CA
213. Sudjaritruk T, Aurpibul L, Puthanakit T, Sirisanthana T, Sirisanthan V. Causes of Hospitalization for HIV^{+} Children: Comparison of the Pre-PCP Prophylaxis, Pre-ART, and ART Era [paper 856]. Presented at: 17th Conference on Retroviruses and Opportunistic Infections; February 16–19 2010; San Francisco, CA
214. Palladino C, Briz V, Negre-Policarpo S, et al. Long-term (>180 Weeks) Efficacy and Safety of Fosamprenavir in HIV-infected Pediatric Patients in Clinical Practice [paper 876]. Presented at: 17th Conference on Retroviruses and Opportunistic Infections; February 16–19 2010; San Francisco, CA
215. Nachman S, Samson P, Acosta E, et al. Pharmacokinetic, Safety, and Efficacy Data on Cohort IIA; Youth Aged 6 to 11 Years from IMPAACT P1066: A Phase I/II Study to Evaluate Raltegravir in HIV-1-infected Youth [paper 873]. Presented at: 17th Conference on Retroviruses and Opportunistic Infections; February 16–19 2010; San Francisco, CA

APPENDIX Excluded Studies

Country	Author	Reason for Exclusion
1. Cote d'Ivoire	Adje-Toure et al[98]	Overlap with Fassinou et al[20], subset analysis excluded patients who died
2. Ethiopia	Biadgilign et al[99]	Adherence study, cross-sectional
3. Nigeria	Onankpa et al[100]	Epidemiology study, no post-HAART outcomes reported
4. South Africa	Cowburn et al[101]	Mortality not reported, hospitalization study
5. South Africa 2004	Eley[102]	Overlap with Eley,[36] data not used in analysis
6. South Africa	Prendergast et al[103]	Limited to infants followed from birth
7. South Africa	van Kooten et al[104]	Cohort too small (17 patients)
8. South Africa	Violari et al[95]	Age limited to 6–12 wk, early vs delayed antiretroviral medication
9. Togo	Atakouma et al[105]	Cross-sectional study
10. Togo	Polisset et al[106]	Adherence study, no post-HAART outcomes reported
11. Argentina	Fallo et al[107]	Calendar-year comparisons
12. Brazil	Matida et al[108]	Calendar surveillance
13. Brazil	Candiani et al[109]	No. on HAART not specified
14. Guatemala	Samayoa et al[110]	Results combine HAART and non-HAART
15. Jamaica	Evans-Gilbert et al[111]	Mortality not reported, hospitalization
16. Cambodia	Madec et al[112]	Age limited to >13 y
17. India	Kumarasamy et al[113]	Excluded patients with follow-up at <18 mo
18. India	Lodha et al[114]	Excluded patients with follow-up at <3 mo
19. India	Natu et al[115]	Mortality not reported
20. India	Pensi et al[116]	Cohort too small (13 patients)
21. Romania	Ferris et al[117]	Overlap with Kline et al,[48] focus on disclosure
22. Romania 2004	Kline et al[88]	Overlap with Kline et al,[48] data not used in analysis
23. Thailand	Chearskul et al[118]	Overlap with Lapphra et al[40], data not used in analysis
24. Thailand	Koekkoek et al[119]	Cohorts too small (16 patients)
25. Thailand	Plipat et al[120]	Cohort too small (19 patients)
26. Multiple	O'Brien et al[10]	Overlap with multiple studies
27. Multiple	Arrive et al[121]	Overlap with multiple studies
28. Multiple	KIDS ART-LINC[122]	Overlap with multiple studies
29. Multiple	Saez-Llorens et al[123]	Did not isolate data from RLCs and DCs
30. Africa/Romania	Weidle et al[124]	Mortality not reported, dosing study
31. Lat. America	Hazra et al[125]	Results combined HAART- and non–HAART-treated patients
Europe		
32. Belgium	Hainaut et al[126]	Cohort too small (4 patients), age limited to <2 mo
33. France	Aboulker et al[127]	Age limited to <3 mo
34. France	Faye et al[128]	Age limited to <1 y
35. Germany	Funk et al[90]	Cohort too small (16 patients)
36. Germany 1998	Wintergerst et al[129]	Cohort too small (15 patients)
37. Italy	Canani et al[130]	Cohort too small (10 patients)
38. Italy	Chiappini et al[131]	Overlap with de Martino et al[87], calendar study
39. Italy	de Martino et al[87]	Overlap with PENTA,[82] data not used in analysis
40. Italy	Vigano et al[132]	Cohort too small (11 patients), heavily pretreated
41. Netherlands 1998	Cohen et al[133]	Cohort too small (13 patients)
42. Spain	Larru et al[134]	Limited to patients whose conditions failed to respond HAART
43. Spain 2006, 2004	Resino et al[135,85]	Calendar study
44. Spain 2003	Sanchez et al[136]	Overlap with Larru et al[134], Kaplan-Meier survival
45. Spain	Guillen Martin et al[137]	Epidemiology/immigrant study, no post-HAART outcomes reported
46. Switzerland	Steiner et al[138]	Overlap with Nadal et al[78]/Rudin et al[79] excludes patients with <72 wk follow-up, growth study,
47. UK, Ireland	Gibb et al[91]	Overlap with PENTA,[82] calendar study
48. UK, Ireland	Doerholt et al[89]	Age limited to <12 mo
49. 9 countries	Newell et al[139]	Overlap with PENTA[82]/Scherpbier et al[74], results combined HAART- and non–HAART-treated patients
50. Europe 2009	Goetghebuer et al[140]	Limited to infants followed from birth
51. US 2001	Abrams et al[141]	Calendar study
52. US 2003	Benjamin et al[142]	PACTG 300 mono/dual treatment, growth study
53. US 2004	Berrien et al[143]	Adherence study, post-HAART outcomes not reported
54. US 2001	Blazevic et al[144]	Cohort too small (11 patients)
55. US 2000	Borkowsky et al[145]	Overlap with PACTG 338 reports, data not used in analysis
56. US 2010	Brady et al[146]	Calendar/birth-cohort study
57. US 2005	Brogly et al[147]	Overlap with PACTG 219C reports, calendar study, <24 y of age
58. US 2004	Brundage et al[148]	Overlap with PACTG 382 reports, data not used in analysis
59. US 2001	Buchacz et al[149]	Overlap with PACTG 219 reports, growth measures not comparable
60. US 2003	Caudill et al[83]	Results combined HAART- and non–HAART-treated patients
61. US 2005	Chadwick et al[150]	Age limited between 4 wk and 24 mo
62. US 2008	Chadwick et al[151]	Age limited to <6 mo
63. US 2001	Chougnet et al[152]	Overlap with Mueller et al[168,169], excluded patients with clinical/immune decline
64. US 2002, 2004	Church et al[153,9]	Cohort too small (14 patients), Enfuvirtide study
65. US 1999	Essajee et al[154]	Limited to severely immunocompromised patients
66. US 2004, 2007	Flynn et al[155]	Age limited to 8–22 y

APPENDIX Continued

Country	Author	Reason for Exclusion
67. US 2007	Glikman et al[157]	Cohort too small (9 patients), adherence study
68. US 2006	Gona et al[158]	Overlap with PACTG 219, calendar comparison, opportunistic-infection study
69. US 2001	Gortmaker et al[2]	Overlap with PACTG 219, calendar study
70. US 2001	Jankelevich et al[159]	Excluded patients with follow up at <96 wk
71. US 2001	Johnston et al[160]	Immune-reconstitution study
72. US 2009	King et al[161]	Age limited to 10–18 y, pharmacokinetic study
73. US 1998	Kline et al[162]	Cohort too small (12 patients)
74. US 2006	Lee et al[163]	Overlap with PACTG 219, quality-of-life study
75. US 2000	Lindsey et al[84]	Meta-analysis included mono/dual/HAART
76. US 1997, 2004	Luzuriaga et al[164,165]	Age limited between 2 wk and 24 mo
77. US 2005	McConnell et al[166]	Calendar study
78. US 1997	Melvin et al[167]	Cohort too small (9 patients)
79. US 1998, 1998	Mueller et al[168,169]	Follow-up included 16 wk of monotherapy and only 12 wk on HAART, overlap with Jankelevich et al[159]
80. US 2000	Nachman et al[170]	Overlap with PACTG 338, data not used in analysis
81. US 1999	Palumbo et al[171]	Mono and dual therapy study
82. US 2008	Patel et al[172]	Overlap with PACTG 219, CD4% comparison between patients with and without HAART initiation
83. US 1999	Pelton et al[86]	Results combined HAART- and non–HAART-treated patients
84. US 2005	Pelton et al[173]	Overlap with PACTG 338, data not used in analysis
85. US 2001	Polis et al[174]	Overlap with Mueller et al[168,169], monotherapy
86. US 2000	Reddington et al[175]	Overlap with PACTG 219 is unclear, adherence study
87. US 2008	Robbins et al[176]	Limited to patients whose conditions failed to respond to HAART therapy, pharmacokinetic study
88. US 1997	Rutstein et al[177]	Results combined HAART- and non–HAART-treated patients
89. US 2005	Storm et al[178]	PACTG 219, cross-sectional quality-of-life study
90. US 2002	Van Dyke et al[179]	Overlap with PACTG 377, adherence subset, data not used in analysis
91. US 2004	Viani et al[180]	Calendar comparison
92. US 2007	Wiznia et al[181]	Required HAART for 4 mo before study initiation, Enfuvirtide study
IAS Abstracts 2009		
93. Kenya	Ayaya et al[182]	Results combined HAART- and non–HAART-treated patients
94. Kenya	McGrath et al[183]	Growth study comparison of children <3 y/>3-y patient outcomes
95. Kenya	Owiso et al[184]	Calendar-study comparison
96. Kenya	Wamalwa et al[185]	Overlap with published study, data not used in analysis
97. KwaZulu Natal	Ndirangu et al[186]	Overlap with Reddi et al,[26] growth study
98. Malawi	Braun et al[187]	Limited to "infant" cohort, age not specified
99. Malawi	Dow et al[188]	Age limited to <6 wk
100. Malawi	Kabue et al[189]	Limited to patients failing first line HAART
101. Malawi	Kabue et al[190]	Limited to "infant" cohort age not specified
102. Swaziland	Chouraya et al[191]	Age limited to <12 mo
103. South Africa	Colvin et al[192]	Mortality not reported
104. South Africa	Coovadia et al[193]	Post-PMTCT study
105. South Africa	Fatti et al[194]	Overlap with Eley,[36] data not used in analysis
106. South Africa	Fenner et al[195]	Comparison of <5 y/>5-y patient outcomes
107. South Africa	Kaplan et al[196]	Overlap unclear, hospital not listed
108. Uganda	Kekitiinwa et al[197]	Limited to malnourished children
109. Cambodia	Augustinova et al[198]	Age limited to <18 mo
110. Cambodia	Isaakidis et al[199]	Cross-sectional survey
111. Cambodia	Sophan et al[200]	Limited to patients whose conditions failed to respond to first-line HAART
112. Indian	Pandian et al[201]	Overlap with published study, data not used in analysis
113. Thailand	McConnel et al[202]	Overlap with Puthanakit et al[51]
114. Brazil	Rezende et al[203]	Overlap with Romanelli et al[52], limited to patients with follow-up at >48 wk
115. Multiple	Carter et al[204]	Comparison of children <12 mo/>12 mo
116. Multiple	Hansudewechakul et al[205]	Overlap multiple studies
117. Southern Africa	Davies et al[206]	IeDEA, virologic failure study, does not report virologic suppression
118. US	Palumbo et al[207]	IMPAACT trial, age limited to <36 mo
119. Unspecified	Bognon et al[208]	Results combined HAART- and non–HAART-treated patients
CROI 2010		
120. South Africa	Venkatesh et al[209]	Limited to infants followed from birth
121. Uganda	Achan et al[210]	Outcomes reported virologic failure
122. Southern Africa	Becquet et al[211]	Survival study, not HAART-focused
123. India	Pandian et al[212]	Overlap with Rajasekaran et al[47]
124. Thailand	Sudjaritruk et al[213]	No mortality reported, hospitalization study
125. Spain	Palladino et al[214]	Fosamprenavir study, experimental
126. US	Nachman et al[215]	Cohort too small (10 patients)

PENTA indicates Paediatric European Network for Treatment of AIDS; PACTG, Pediatric AIDS Clinical Trial Group; IAS, International AIDS Society; PMTCT, prevention of mother-to-child transmission; IeDEA, International Epidemiologic Databases to Evaluate AIDS; IMPAACT, International Maternal Pediatric Adolescent AIDS Clinical Trials Group; CROI, Conference on Retroviruses and Opportunistic Infections.