Adherence to antiretroviral therapy in adolescents living with HIV: systematic review and meta-analysis

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Objective: Adolescent and young adult (AYA) populations (12–24 years) represent over 40% of new HIV infections globally. Adolescence is sometimes characterized by high-risk sexual behaviour and a lack of engagement with healthcare services that can affect adherence to antiretroviral therapy (ART). Despite adherence to ART being critical in controlling viral replication, maintaining health and reducing onward viral transmission, there are limited data on ART adherence amongst AYA globally. We undertook a systematic review and meta-analysis of published studies reporting adherence to ART for AYA living with HIV.

Design and methods: Searches included Embase, Medline and PsychINFO databases up to 14 August 2013. Eligible studies defined adequate adherence as at least 85% on self-report or undetectable blood plasma virus levels. A random effects meta-analysis was performed and heterogeneity examined using meta-regression.

Results: We identified 50 eligible articles reporting data from 53 countries and 10 725 patients. Using a pooled analysis of all eligible studies, 62.3% [95% confidence interval (CI) 57.1–67.6; I^2: 97.2%] of the AYA population were adherent to therapy. The lowest average ART adherence was in North America [53% (95% CI 46–59; I^2: 91%)], Europe [62% (95% CI 51–73; I^2: 97%)] and South America [63% (95% CI 47–77; I^2: 85%] and, with higher levels in Africa [84% (95% CI 79–89; I^2: 93%)] and Asia [84% (95% CI 77–91; I^2: 0%].

Conclusion: Review of published literature from Africa and Asia indicate more than 70% of HIV-positive AYA populations receiving ART are adherent to therapy and lower rates of adherence were shown in Europe and North America at 50–60%. The global discrepancy is probably multifactorial reflecting differences between focused and generalised epidemics, access to healthcare and funding.

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Introduction

Into the third decade of the HIV/AIDS epidemic, there are 34 million people living with HIV in the world, of whom five million are aged between 15 and 24 years [1]. Adolescence is a period of mental, physical and emotional maturation wherein commonly individuals undergo behavioural experimentation, identity formation, risk taking and face difficult choices on romantic relationships, sexual behaviour and alcohol and recreational drug use [2,3]. Furthermore, young people often have poorly developed life skills and are often lacking in worldly knowledge and financial autonomy [4]. They also have limited access to health facilities and are prone to sexual coercion and peer pressure [4]. Adolescents have been described as the 'fulcrum' and the 'centre of the epidemic' [5], with 42% of new HIV infections occurring in this age group in 2010 [1]. For all of these reasons, adolescents have been frequently recognized as a vulnerable group to becoming infected

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and to being marginalized from mainstream healthcare provisions [6].

Despite the dramatic improvement in survival and marked reduction in transmission through antiretroviral therapy (ART), a sustained effect depends on high levels of adherence (>95%) to daily oral dosing [7,8]. Poor ART adherence increases the risk of viral drug-resistance, limits treatment efficacy, leading to disease progression, and reduces future therapeutic options [9] as well as increasing the risk of transmission due to unsuppressed viral replication [10].

Following the publication of the HPTN052 study [10] and the accompanying paradigm shift in HIV prevention approaches to using ART strategically for all people living with HIV to significantly reduce the risk of onward viral transmission, successful viral suppression amongst core risk-taking groups, which include Adolescent and young adult (AYA) living with HIV, has a renewed focus. Mathematical models have explored the potential elimination of HIV transmission with a universal HIV testing approach accompanied by immediate ART for all HIV-positive individuals, but this must include AYA if it is to confer a population-level effect. The few studies on adherence show that access to antiretroviral and adherence is lower in adolescents than in the adult population [11–16]. There has been one previous review of ART adherence among HIV-infected youth [2], which showed adherence rates ranging from 28.3 to 69.8% in the USA. This review aims to update the findings of the previous review and quantifying adherence in AYA at a global level.

Materials and methods

Search strategy and selection criteria
We followed the PRISMA guidelines in carrying out this research [17]. Articles were identified through searches conducted on Medline, Embase, HMIC, Maternity and Infant Care, and PsychINFO up to 14 August 2013 using combinations of keywords such as 'adolescent', 'young adult', 'adherence', 'patient compliance', 'antiretroviral therapy' and 'antiretrovirals' as MESH headings and free-text terms. Bibliographies of potentially eligible full-text publications were also searched and when necessary, authors of relevant studies were contacted for clarification and for additional information. Potentially eligible studies were downloaded into EndNote, and titles and abstracts were searched according to the predefined inclusion and exclusion criteria.

We included quantitative studies reporting original data on medication adherence among HIV-infected youth (ages 12–24 years). Studies that included participants outside this age range were included where the median age of participants fell within the 12–24 year range.

Studies were included if adherence was measured by subjective measurement (self-reported adherence), pharmacologic measurements (pill count, pharmacy refill records) or physiological methods (viral suppression). Despite being a subjective measure, self-report is non-invasive, easy to administer and has been shown to correlate with objective measures such as pill counts [18,19]. Although viral load is an indirect measure, many studies have indicated that high adherence (>95%) is needed to maintain adequate virologic suppression [20–22].

Studies were included if they defined adherence as 100%, more than 95%, more than 90% and more than 85% of the medication taken correctly for a defined period in the study, or viral suppression as the lower limit detectable at the time and location defined by the authors (range <50 to <500 copies/ml). The studies also had to show the proportion of their population that was adequately adherent according to the study definition rather than reporting mean adherence. All study designs were included except for guidelines, reviews and case studies. The length of follow-up was left undefined and the studies were only considered if published after 1996 (the designated start of highly active ART era). Only English publications were included. Finally, studies were excluded if the population was deemed unrepresentative of the general adolescent population living with HIV (e.g. containing experimental interventions to promote adherence, financial incentives).

Study selection and data extraction
Two investigators (S.K., S.M.G.) conducted the search, reviewed all abstracts and full-text articles independently, with final inclusion decided through consensus with verification with senior study authors when needed. We extracted the data independently and in duplicate. The country, study year, sample size, age, sex, methods of adherence measurement and outcomes were extracted from each study. When more than one adherence measurement was used, data on all measures were extracted and the most objective method was chosen for the analysis (e.g. viral suppression). When a study examined the effect of an intervention on medication adherence, only the adherence data for the control group were extracted and analysed. Information on disease state, type of antiretroviral regimen, the time the individuals were on treatment for and socio-economic status were not abstracted due to large heterogeneity of each study population. For all studies, ART was taken as potent standard triple therapy.

Data analysis
Point estimates and Clopper–Pearson confidence intervals (CIs) [23] were calculated and the transformed data were pooled using DerSimonian–Laird [24] random effects model, as large heterogeneity was anticipated considering the varied populations, healthcare systems and the nature of the epidemic. We explored potential sources of heterogeneity with univariate, random-effects

meta-regression using continents, measures of adherence, thresholds of adherence, percentage of women in the study, study year (pre-2005 and 2005 onwards) and age of participants (<20 vs. $\geq$ 20years) as variables because they were identified as potential factors that might explain the heterogeneity observed in the analysis. We did analyses using Stata version 11 [25].

Forest plots were created for each region that showed individual study proportions meeting the threshold for appropriate adherence (as defined by the original study) with Clopper−Pearson CIs, the overall DerSimmonian−Laird pooled estimate and the I^2-value for heterogeneity. Results are reported as combined adherence proportions with 95% CIs.

Results

Fifty-one studies published between 1999 and 2013 passed the full-text screening and reported adherence rates for 10 725 patients in 53 countries. Seven studies were reported in national or international conference abstracts [26−30]; the rest as full-text articles. A flow diagram of studies included in the analysis is detailed in Fig. 1, with characteristics displayed in Table 1 [31−73] grouped by geographical region. Studies reported similar thresholds for adherence monitoring (e.g. 100%, >95%, >90% and >85%) and viral suppression was most commonly defined as less than 400 copies/ml. Pooled adherence rates across all studies are summarized in

Table 2 with forest plots by region in Fig. 2. Adherence was estimated at 62% (95% CI, 57−68; I^2, 97%) overall and this varied by region as summarized in the Table 2; it was lowest in North America (53%) and highest in Africa and Asia (84%). There was considerable heterogeneity between studies as shown by large I^2 values. We used meta-regression to examine the impact of continent, adherence measure, adherence threshold (100%, $\geq$95%, $\geq$90%, $\geq$85%), sex (<50% or $\geq$50% women), age group (<20 or $\geq$20 years old) and study year (before 2005 or after/including 2005) on this heterogeneity (Table 3); however, none of the variables fully explained the between-study heterogeneity.

Studies conducted after 2005 showed higher adherence rate (74%) than conducted pre-2005 (59%). The majority (98%) of the studies used either viral suppression ($n = 36$) or self-report ($n = 13$) as the adherence measure. Other measurements included pharmacy refills. Nine American studies measured adherence by self-report, but only two South American, one Asian study and one African study measured using self-report. On the contrary, viral suppression was a more common form of measurement outside North America, with 13 of 22 studies in North America, all 12 in Europe, three of five in South America, six of eight in Africa and two of three in Asia. Nine studies had multiple measures.

In order to assess whether the measure of adherence used by the different studies had an impact on the prevalence of adolescent adherence, we ran additional and separate meta-analyses for those studies that had viral suppression
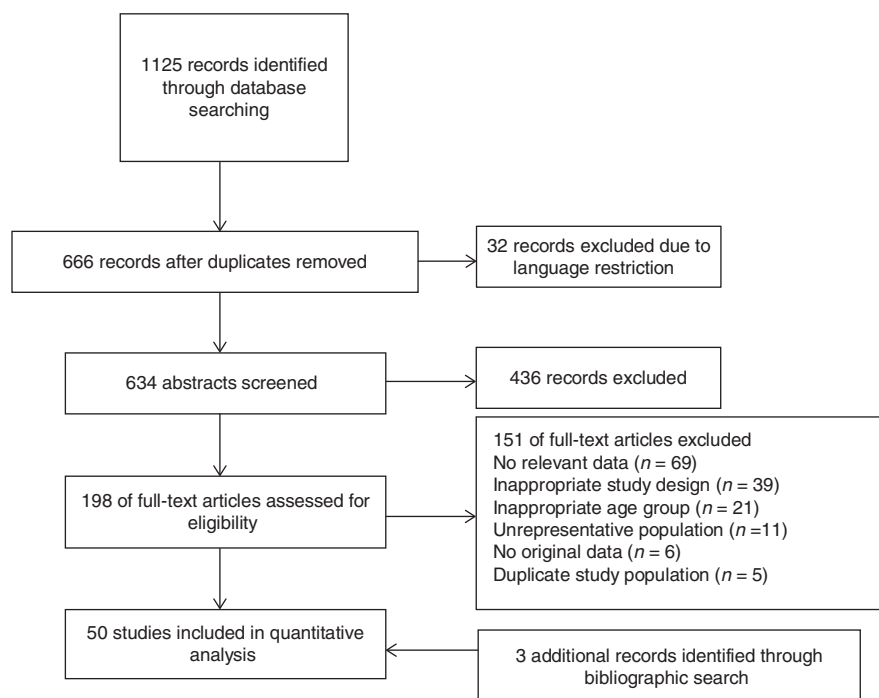

Fig. 1. Study selection process.

Table 1. Characteristics of studies included by global region.

Source	Study year	No of participants	Female %	Race/Ethnicity	%	Age (years)	Assessment of adherence	Adherence, % threshold for measurement	No adherence (%)
North America (n = 22 studies)									
Belzer et al. [34]	1997–1998	31	36	Hispanic	42	13–24	Patient	90; doses in the past 3 months	19 (61)
Buchanan et al. [35]	2000–2007	120	46	Black Black Hispanic	39 55 28	8–18 Median: 12.8	VL Patient	<400 copies/ml 100; based on past 1 month	72 (60) 54 (45)
Calabrese et al. [36]	2003–2005	25	48	Black	69	11–18	VL	<50 copies/ml	7 (28)
Chandwani et al. [37]	2003–2005	107	54	Hispanic	24	13–21 Mean: 16.4	Patient VL	100; based on past 3 days <400 copies/ml	68 (65) 30 (28)
Charles et al. [14]ᵃ	2003–2005	79	66			13–25	VL	<50 copies/ml	39 (49)
Comulada et al. [38]	1999–2000	136	29	Hispanic	60	14–29	Patient	90; based on past 3 months	85 (63)
Flynn et al. [39]	1999–2001	118	51	Black Nonhispanic black Hispanic	47 71 22	Mean: 22.9 8–22	VL Patient	<400 copies/ml 100; doses and study visits in past 3 days	69 (59) 32 of 120 (27)
Garvie et al. [40]		57	47	Nonhispanic white Black Hispanic	7 90 3	16–23 Mean: 19.9	VL Patient	<400 copies/ml 100; based on past 3 days	39 (68) 47 of 60 (78)
Hosek et al. [41]		42	41	Black	66	16–25	Patient	95; doses taken in past 2 weeks	18 (43)
Marhefka et al. [42]		144	48	Hispanic Black Latino	12 58 28	Mean: 20 9–16	Patient	100; based on past month	62 (43)
Martin et al. [43]		24	46	Black White Hispanic Native American	46 42 4 8	Mean: 12.37 8–18 Mean: 13.9	MEMS VL	90; <50 copies	5 (21) 9 (38)
Martinez et al. [44]	2003–2005	60	100	Black Hispanic	73 21	15–24 Mean: 20.6	Patient	100; based on past 4 days	39 (65)
Mellins et al. [45]	2007–10	238	50	Black	73	10–16 Mean 13.7	VL Patient	<400 copies/ml 100; based on past 7 days	153 (64) 141 (59)
Murphy et al. [12]	1998–99	231	73	Black	50	15–22	VL	<10 copies/ml	158 (68)
Murphy et al. [46]		101	47			16–24	Patient	90; past 3d	34 (34)
Park and Nachman [47]	2007	18	39	Black	50	14–24	Patient	100; based on past 2 weeks	8 (44)
Rudy et al. [48]		368	55	White Black Hispanic	44 60 29	Mean 18.1	VL Patient	<400 copies/ml	11 (61) 274 (75)
Rudy et al. [49]		396	51	Black	67	12–24 Mean 16.4 Median 15.7	Patient	85; based on past 7 days	248 (63)
Ryscavage et al. [16]	2003–09	46	61	Black	54	12–24 Mean 21.6 Median: 22.1	VL	<400 copies/ml	27 (59)
Van Der Linden et al.ᵇ [50]	1998–2010	43	60			17–24 Median. 21.1 18.1	VL	<500 copies/ml	19 (44)
Wiener et al. [51]		34	37	White	77	11–21 Median 15.4	Patient	100; based on past 3 days	11 (32)
Williams et al. [52]	2000–2004	772	52	Black Hispanic	56 27	13–17 Median 14.4	VL	<400 copies/ml	336 (44)

Source	Study year	Country	No of participants	Female %	Age (years)	Assessor	Adherence, % threshold for measurement	No adherence (%)
African studies (n = 8)								
Bakeera-Kitaka et al. [53]	2004–2006	Uganda	118	64	10–19; Median: 13.6	VL	<400 copies/ml	93 (79)
Evans et al. [33]	2004–2010	S. Africa	1206	81	10–24	VL	<400 copies/ml	1054 (87)
Mutevedzi et al. [31]	2004–2010	S. Africa	808	87	16–24	VL	<400 copies/ml	660 (82)
Nabukeera-Barungi et al. [54]	2004–2005	Uganda	60		12–18	Pill count	95; unannounced	43 (72)
Nachega et al. [55]	1999–2006	Southern Africa	92	73	11–19; Median: 16.4	Pharmacy refills	100	17 of 82 (21)
						VL	<400 copies/ml	58 (63)
Nglazi et al. [56]	2002–2009	S. Africa	584	85	9–28	VL	<400 copies/ml	526 (90)
Van Cutsem et al. [30][c]	2000–2007	S. Africa	496	88	10–24	VL	<400 copies/ml	470 (95)
Wiens et al. [57]	2008–09	Uganda	15	40	Mean: 14	Patient	95	14 (93)
Asian studies (n = 3)								
Lee et al. [58]	1997–2010	Taiwan	7	10	16–20	VL	<400 copies/ml	5 (71)
Narkbunnam et al. [59]	2010	Thailand	81	51	12–18; Mean: 14.7	VL	<40 copies/ml	69 (85)
Rongkavilit et al. [13]	2004	Thailand	28	59	16–25; Mean: 22.8	Patient	95, based on past month	23 (82)
European studies (n = 12)								
Avettand-Fenoel et al. [60]	2007–2009	France	79	57	15–24	VL	<500 copies	59 (75)
Cairns et al. [61]	2012	UK	117		Median: 13.5; Mean: 17	VL	<50 copies/ml	113 (97)
De Mulder et al. [62]	1997–2011	Spain	243	56	17	VL	<50 copies/ml	128 (56)
Dima et al. [63]		Romania	162	53	18–24	VL	<400 copies/ml	91 (56)
						Pill count	>95%	97 (60)
Dollfus et al. [64]	2005–2008	France	172	49	10–17	VL	<50 copies/ml	87 (51)
Eisen et al. [27]	2000–2007	UK	17		15–17	VL	<400 copies/ml	8 (47)
Elgalib et al. [28]	2011–2012	UK	58	100	13–19	VL	<50 copies/ml	32 (55)
Ellis et al. [65]		UK	28	49	18–24	VL	<50copies/ml	18 (64)
Foster et al. [66]	1996–2007	UK&Ireland	396		10+; Median: 20	VL	<400 copies/ml	309 (78)
Funck-Brentano et al. [67]	1999–2003	France	29	63	12–17	VL	<200 copies/ml	11 (38)
Kline et al. [68]	2001–06	Romania	265	46	5–18; Median: 14.2	VL	<400 copies/ml	192 (73)
Sabin et al. [32]	1998–06	33 European cohorts	201	63	13–17; Mean: 13; Median: 16.5	VL	<50 copies/ml	92 (46)
South American studies (n = 5)								
Cruz et al. [69]	2002–2009	Brazil	9	100	13–19	VL	<80 copies/ml	6 (67)
de Matos et al. [70]	1993–2009	Brazil	30		11–19	VL	<50 copies/ml	10 (33)
Filho et al. [71]		Brazil	101	54	10–19	Patient	95; based on past 3 days	80 (79)
Santarem Ernesto et al. [72]	2008–2009	Brazil	108	44	7–19; Mean: 13	Patient	95; based on past 7 days	78 (72)
Souza et al. [73]	2006–2007	Brazil	49	74	10–19; Median: 13.22; Mean: 12.5	VL	<400 copies/ml	26 (53)
						Patient	100; based on past 3 months	34 (69)

MEMS, Medication Event Monitoring System; VL, viral load.

a Haiti.

b Canada.

c Further details were verified through personal correspondence with the author.

Table 2. Percentage adherence by subgroups.

	Number of studies	% adherence	95% CI
Overall	50	62.3	57.1–67.6
North America	22	52.7	46.5–59.0
Africa	8	83.8	78.9–88.7
Asia	3	83.9	76.8–91.0
Europe	12	62.0	50.7–73.3
South America	5	62.8	46.6–77.0
Sex			
≥50% female	27	65.6	58.8–72.4
<50% female	15	54.3	45.9–62.7
Age			
Adolescents [12–29]	34	60.1	53.3–67.0
Young adults [20–24]	10	67.9	58.6–77.3
Study year			
Before 2005	22	59.3	49.2–69.4
2005 onwards	16	77.0	72.0–82.0
Adherence measure[a]			
Viral load	36	62.2	56.0–68.4
Self-report	20	59.1	51.8–66.4

CI, confidence interval. If viral load (VL) is taken as the primary measure, adherence is as follows. VL 62% (95% CI 56–68), self-report 62 (95% CI 53–71) and pill count 72 (95% CI 60–84).
[a]Publications with multiple measures were included in this subgroup analysis.

as the marker for sufficient adherence and those that used self-report, regardless of the level of either of these measures. Viral suppression was used as a measure of adherence in 36 studies while self-report was solely or additionally measured in 19 studies. Overall, the prevalence of adherence when using viral suppression as a proxy for complete adherence was 62.2% (95% CI, 56.0–68.4) was comparable to the estimate provided self-report of 59.1% (95% CI 51.8–66.4%), which showed that the measure of adherence has a little effect on the adherence estimates as they are in agreement.
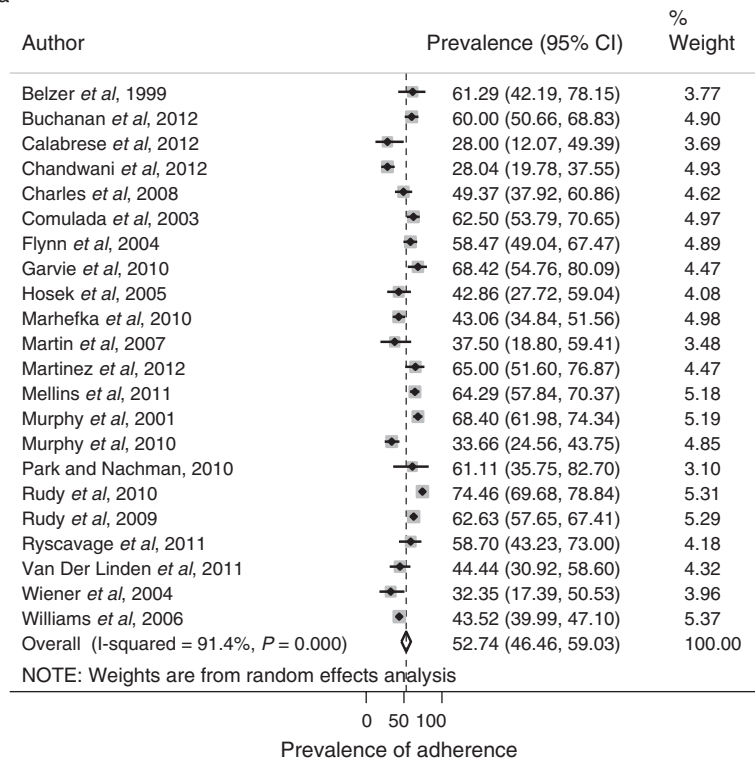
Discussion

The findings from this systematic review and meta-analysis showed that overall, from studies globally, 62% of adolescents and young adults were adherent to ART (as defined by >85%, 90%, 95%, 100%) during the time defined by the study or through viral suppression. There were differences between regions with lower adherence in Europe, South America and North America and higher levels in Africa and in Asia. There are no other global estimates of adherence in this group, although a meta-analysis of North American studies by Reisner and Mimiaga [2] reported rates between 28.3 and 69.8%. We have updated these figures by adding 13 additional studies in North America that were published after this review, which showed similarly disparate results (28.0–74.5%). Geographic variation in adherence has also been reported for adults. Mills et al. [74] carried out a meta-analysis of adult adherence to ART and found similar estimates both overall [64% (95% CI, 59–70; I^2, 99%)] and by region: they estimated adherence at 55% (95% CI, 49–62) amongst adults in North America and 77% (95% CI, 68–85) in Africa, similar to our findings of 53 and 84%, respectively. They did not include studies from other regions.

In contrast, our results suggest lower adherence in adolescents than adults for Europe; a multicentre prospective cohort study in 17 European countries with 1323 adult patients [75] showed 80% of its population achieving virological suppression (95% CI, 78–82), significantly higher than our adolescent estimate of 62% (95% CI, 51–73). Similarly, a Brazilian study with 1972 adult patients [76] with 75% of the study population achieving more than 95% adherence (95% CI, 73–77) is also higher than the adolescent population estimate for South America of 63% (95% CI, 47–77). There are fewer studies in Asian adults or adolescents: a study of 149 Thai adults showed 77% adherence (95% CI, 71–84) [77], comparable to the 83% (95% CI, 77–89) we found in adolescents.

Thus, in comparison with the adult levels, we have found lower adherence in adolescents in Europe and South America, while in North America and Africa and possibly Asia levels are comparable to adults. This is unanticipated given that many studies comparing viral suppression between adolescents and adults showed that adolescents are less likely to achieve viral suppression than the adult population [31,33,78,79]. Possible reasons could be either a selection from African, North American and Asian studies, as individuals enrolled in a study are more likely to be those who are more engaged in care, or a real difference due to variation in the meaning and experience of adolescence in different settings. It may be that in Africa and Asia, the population enrolled in the study have little differences than the adult population in the same setting culturally and socially, especially when they are a bit older (16–24 years). They are likely to have already worked and may have children of their own, compared with the adolescent population in Europe and South America where there are bigger differences in the adult and adolescent age groups.

The regional disparity in adherence, now documented in adults and adolescents, may reflect the significant differences in the healthcare systems between North America and Africa [5,80] and the different HIV epidemic, with Africa having a generalized epidemic in comparison with a focused epidemic in North America and Europe [5,81]. This observation is most likely multifactorial, but probably reflects the communities most affected by HIV as well as the different funding and accessibility of the healthcare services. For instance, in resource-poor regions with generalized epidemics, HIV testing and ART provision are widespread and can include house to house testing and care. In addition, it is usually free for eligible individuals [82] whilst in North America and Europe the HIV epidemic remains focused often being 'hidden' amongst certain vulnerable, core risk groups with less access to healthcare despite disproportionally richer resources [6]. The latest figures from North America show a high prevalence and incidence rates amongst MSM AYA of African and Hispanic descent [83], a group typically marginalized outside of healthcare

(a) North America

Author	Prevalence (95% CI)	% Weight
Belzer et al, 1999	61.29 (42.19, 78.15)	3.77
Buchanan et al, 2012	60.00 (50.66, 68.83)	4.90
Calabrese et al, 2012	28.00 (12.07, 49.39)	3.69
Chandwani et al, 2012	28.04 (19.78, 37.55)	4.93
Charles et al, 2008	49.37 (37.92, 60.86)	4.62
Comulada et al, 2003	62.50 (53.79, 70.65)	4.97
Flynn et al, 2004	58.47 (49.04, 67.47)	4.89
Garvie et al, 2010	68.42 (54.76, 80.09)	4.47
Hosek et al, 2005	42.86 (27.72, 59.04)	4.08
Marhefka et al, 2010	43.06 (34.84, 51.56)	4.98
Martin et al, 2007	37.50 (18.80, 59.41)	3.48
Martinez et al, 2012	65.00 (51.60, 76.87)	4.47
Mellins et al, 2011	64.29 (57.84, 70.37)	5.18
Murphy et al, 2001	68.40 (61.98, 74.34)	5.19
Murphy et al, 2010	33.66 (24.56, 43.75)	4.85
Park and Nachman, 2010	61.11 (35.75, 82.70)	3.10
Rudy et al, 2010	74.46 (69.68, 78.84)	5.31
Rudy et al, 2009	62.63 (57.65, 67.41)	5.29
Ryscavage et al, 2011	58.70 (43.23, 73.00)	4.18
Van Der Linden et al, 2011	44.44 (30.92, 58.60)	4.32
Wiener et al, 2004	32.35 (17.39, 50.53)	3.96
Williams et al, 2006	43.52 (39.99, 47.10)	5.37
Overall (I-squared = 91.4%, P = 0.000)	52.74 (46.46, 59.03)	100.00

NOTE: Weights are from random effects analysis

0   50 100
Prevalence of adherence

(b) Africa

Author	Prevalence (95% CI)	% Weight
Bakeera-Kitaka et al, 2008	78.81 (70.33, 85.80)	11.80
Evans et al, 2013	87.40 (85.39, 89.22)	16.20
Mutevedzi et al, 2011	81.68 (78.84, 84.29)	15.80
Nabukeera-Barungi et al, 2007	71.67 (58.56, 82.55)	8.38
Nachega et al, 2009	63.04 (52.34, 72.88)	9.66
Nglazi et al, 2012	90.07 (87.35, 92.37)	15.92
Van Cutsem et al, 2010	94.76 (92.41, 96.55)	16.13
Wiens et al, 2012	93.33 (68.05, 99.83)	6.10
Overall (I-squared = 93.0%, P = 0.000)	83.78 (78.85, 88.72)	100.00

NOTE: Weights are from random effects analysis

0 25 50 75 100
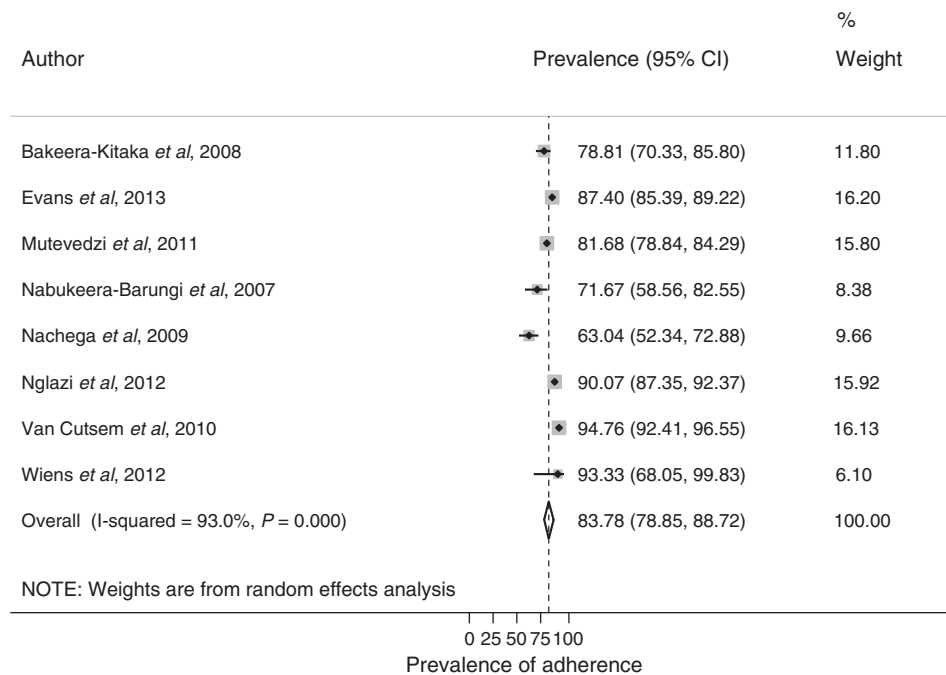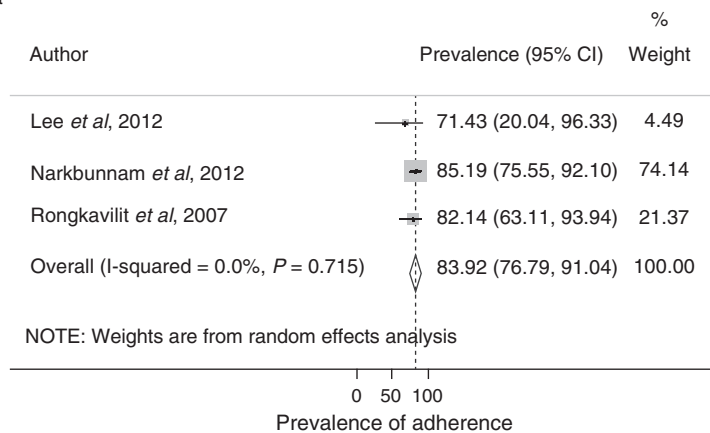Prevalence of adherence

Fig. 2. Pooled proportion of patients adhering to antiretroviral therapy by global region. (a) North America, (b) Africa.
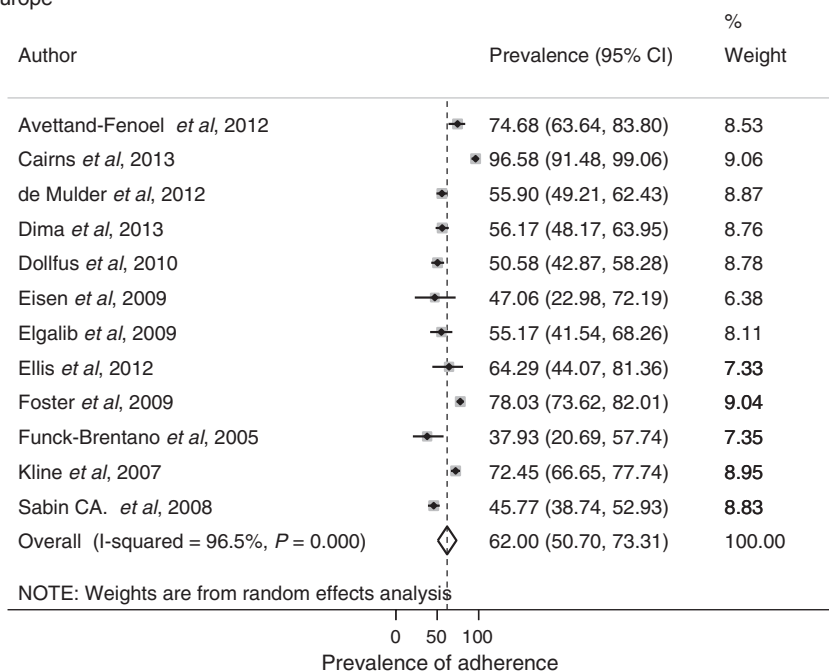
provision with high rates of incarceration, which is also linked with poor ART adherence [84]. In the UK, a disproportionate number of 'late presenters' to healthcare come from Black African communities [85].

Furthermore, in sub-Saharan Africa where HIV incidence and prevalence globally is highest, AYA women are likely to become pregnant in the second decade of life [86]. In order to achieve the IAS goals of an HIV-free
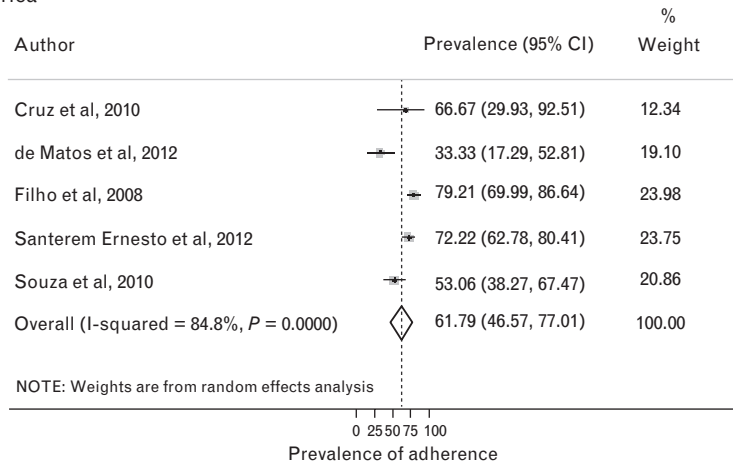
(c) Asia

%

Author	Prevalence (95% CI)	Weight
Lee *et al*, 2012	71.43 (20.04, 96.33)	4.49
Narkbunnam *et al*, 2012	85.19 (75.55, 92.10)	74.14
Rongkavilit *et al*, 2007	82.14 (63.11, 93.94)	21.37
Overall (I-squared = 0.0%, *P* = 0.715)	83.92 (76.79, 91.04)	100.00

NOTE: Weights are from random effects analysis

0 50 100
Prevalence of adherence

(d) Europe

%

Author	Prevalence (95% CI)	Weight
Avettand-Fenoel *et al*, 2012	74.68 (63.64, 83.80)	8.53
Cairns *et al*, 2013	96.58 (91.48, 99.06)	9.06
de Mulder *et al*, 2012	55.90 (49.21, 62.43)	8.87
Dima *et al*, 2013	56.17 (48.17, 63.95)	8.76
Dollfus *et al*, 2010	50.58 (42.87, 58.28)	8.78
Eisen *et al*, 2009	47.06 (22.98, 72.19)	6.38
Elgalib *et al*, 2009	55.17 (41.54, 68.26)	8.11
Ellis *et al*, 2012	64.29 (44.07, 81.36)	7.33
Foster *et al*, 2009	78.03 (73.62, 82.01)	9.04
Funck-Brentano *et al*, 2005	37.93 (20.69, 57.74)	7.35
Kline *et al*, 2007	72.45 (66.65, 77.74)	8.95
Sabin CA. *et al*, 2008	45.77 (38.74, 52.93)	8.83
Overall (I-squared = 96.5%, *P* = 0.000)	62.00 (50.70, 73.31)	100.00

NOTE: Weights are from random effects analysis

0 50 100
Prevalence of adherence

(e) South America

%

Author	Prevalence (95% CI)	Weight
Cruz et al, 2010	66.67 (29.93, 92.51)	12.34
de Matos et al, 2012	33.33 (17.29, 52.81)	19.10
Filho et al, 2008	79.21 (69.99, 86.64)	23.98
Santerem Ernesto et al, 2012	72.22 (62.78, 80.41)	23.75
Souza et al, 2010	53.06 (38.27, 67.47)	20.86
Overall (I-squared = 84.8%, *P* = 0.0000)	61.79 (46.57, 77.01)	100.00

NOTE: Weights are from random effects analysis

0 25 50 75 100
Prevalence of adherence

Fig. 2. (*Continued*): (c) Asia, (d) Europe, and (e) South America.

Table 3. Odds ratios from meta-regression results of all studies (*n* = 50).

	Category	*n* Studies	Univariate analysis	
			OR (95% CI)	*P*
No covariate				
Sex	≥50% female	27	1	
	<50% female	15	0 6 (0.4–1.1)	0.13
Continent	North America	22	1	
	Africa	8	2.3 (1.1–5.0)	0.04
	Asia	3	0.8 (0.3–2.8)	0.78
	Europe	12	1.7 (0.9–3.3)	0.11
	South America	5	1.8 (0.7–4.6)	0.24
Age	12–19	34	1	
	20–25	10	0.73 (0.4–1.4)	0.35
Study year	Pre-2005	16	1	
	2005 onwards	22	2.4 (1.3–4.4)	<0.01
Adherence measure	Viral suppression	36	1	
	Self-report	13	0.9 (0.5–1.7)	0.74
	Pill count	1	1.9 (0.3–13.4)	0.50
Adherence thresholds	100%	11	1	
	≥95%	4	1.7 (0.7–3.7)	0.21
	≥90%	8	0.9 (0.3–2.5)	0.84
	≥85%	2	2.6 (0.7–9.4)	0.13

CI, confidence interval; OR, odds ratio.

generation, prevention of mother-to-child-transmission through ART and adherence is critical and AYA-focused appropriate care needs to be reflected in ART delivery and retention programmes.

Our study found that studies that were conducted from 2005 onwards showed higher adherence rate (74%) than studies conducted before 2005 (59%). This is consistent with the fact that in earlier studies, the participants would have had more complicated treatment regimes, higher pill burden and experienced greater toxicity from ART and thus are more likely to have been nonadherent to treatment.

The strengths of this systematic review include explicit eligibility criteria, conduct of a comprehensive search and the usage of random-effects model to pool proportions in keeping with the large heterogeneity. The main limitation is in the quality of the studies. Accurate measurement of adherence has been a challenge to researchers and there is little consistency in adherence classification [87]. Patient recall and pill counts have inherent biases in their measurement [88] such as self-enhancement bias and recall bias, in addition how representative individuals who enrol into adherence studies are of the general populations from which they are drawn in unknown. Furthermore, as studies included were observational studies, some heterogeneity may have been introduced to our study due the lack of standardisation and variations in measuring adherence despite no significant differences between the measures of adherence and the thresholds for adherence were shown in the meta-regression (Table 1). With such high levels of heterogeneity in this study, the results should be interpreted with caution.

Due to the paucity of longitudinal studies, our study only looked at the cross-sectional adherence data, meaning

that we were unable to explore the sustainability and dynamics of adherence. Also, the heterogeneity of the information offered by individual studies meant that we were unable to examine the effect of adherence patterns, missed doses and treatment interruptions despite the possibility of these factors having a big impact on the treatment outcome such as immunological recovery and viral resistance to ART and these events tend to occur more frequently amongst AYA [89]. Furthermore, due to the nature of the studies, as with all meta-analyses of published data, we are not able to include data from AYA who, choose not to initiate medication despite eligibility, became lost to follow up or chose not to enrol into a study, or those deemed inappropriate for treatment by their physicians. Information on numerous contributing factors such as incentives and counselling as well as broader contextual factors such as political or socio-demographic status were not available in many studies that may have confounded the adherence level. However, although assessing the impact of all of the possible factors would be informative, it does not change the finding that nearly half of all HIV positive AYA population have suboptimal adherence rates that risks the development of drug resistance, disease progression and transmission to others.

The literature search did not yield studies from Australasia and only three studies from Asia. Moreover, countries such as Brazil, South Africa and United States were overrepresented meaning that these results may reflect adherence rates overall. Finally, there is a possibility that this review has missed articles (unpublished) despite extensive searching, and the restriction to English language may have excluded key data.

Our findings have important implications. Although we were unable to take into account all the possible factors such as drug regimens and adherence dynamics that may affect the overall adherence, we have shown that almost 40% of adolescents with HIV who are eligible for and have started ART are nonadherent to treatment and this level of nonadherence requires action. These data are from a period before recent changes to national guidelines and WHO recommendations that expand eligibility and would initiate treatment at an earlier point in the disease.

We assume that the poor reported adherence is highly contextual and multifactorial, but on an individual level, healthcare and public health providers need to proactively engage with AYA to enhance adherence to ART for this vulnerable group. On a policy level, in areas where AYA ART adherence is lower than that of adults (South America and Europe as shown by this study), programmes with better understanding of culturally specific barriers to HIV medication targeting this age group may have the largest potential impact on future health and incidence of HIV. However, in Africa and Asia, where adherence levels in adolescents are relatively high, the exclusion of

high-risk youth from ART may risk preventing potentially adherent patients from lifesaving treatment [34], and although increasing the scale-up of ART coverage in Africa may be beneficial to all, it is critical to enhance access to AYA.

Provision of successful HIV care requires a test and treatment cascade with a potential for drop off at many levels [89,90] and linkage for re-engagement must be offered at every step [91] in order to retest those at risk, and support sustained adherence and retention. Although this analysis focuses only on the latter part of the cascade and only at a single time-point, it has shed light on key gaps in services that could better support AYA living with HIV. In particular, the wide discrepancy in reported adherence between HIV-positive AYA the different continents requires urgent action, especially in resourced settings wherein the delivery of services needs to be appropriately refocused.

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Conflicts of interest
There are no conflicts of interest.

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