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Adherence to antiretroviral therapy for HIV in sub-Saharan Africa and Asia: a comparative analysis of two regional cohorts

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Abstract

Introduction: Our understanding of how to achieve optimal long-term adherence to antiretroviral therapy (ART) in settings where the burden of HIV disease is highest remains limited. We compared levels and determinants of adherence over time between HIV-positive persons receiving ART who were enrolled in a bi-regional cohort in sub-Saharan Africa and Asia.

Methods: This multicentre prospective study of adults starting first-line ART assessed patient-reported adherence at follow-up clinic visits using a 30-day visual analogue scale. Determinants of suboptimal adherence (<95%) were assessed for six-month intervals, using generalized estimating equations multivariable logistic regression with multiple imputations. Region of residence (Africa vs. Asia) was assessed as a potential effect modifier.

Results: Of 13,001 adherence assessments in 3934 participants during the first 24 months of ART, 6.4% (837) were suboptimal, with 7.3% (619/8484) in the African cohort versus 4.8% (218/4517) in the Asian cohort ($p < 0.001$). In the African cohort, determinants of suboptimal adherence were male sex (odds ratio (OR) 1.27, 95% confidence interval (CI) 1.06–1.53; $p = 0.009$), younger age (OR 0.8 per 10 year increase; 0.8–0.9; $p = 0.003$), use of concomitant medication (OR 1.8, 1.0–3.2; $p = 0.044$) and attending a public facility (OR 1.3, 95% CI 1.1–1.7; $p = 0.004$). In the Asian cohort, adherence was higher in men who have sex with men (OR for suboptimal adherence 0.6, 95% CI 0.4–0.9; $p = 0.029$) and lower in injecting drug users (OR for suboptimal adherence 1.6, 95% CI 0.9–2.6; $p = 0.075$), compared to heterosexuals. Risk of suboptimal adherence decreased with longer ART duration in both regions. Participants in low- and lower-middle-income countries had a higher risk of suboptimal adherence (OR 1.6, 1.3–2.0; $p < 0.001$), compared to those in upper-middle or high-income countries. Suboptimal adherence was strongly associated with virological failure, in Africa (OR 5.8, 95% CI 4.3–7.7; $p < 0.001$) and Asia (OR 9.0, 95% CI 5.0–16.2; $p < 0.001$). Patient-reported adherence barriers among African participants included scheduling demands, drug stockouts, forgetfulness, sickness or adverse events, stigma or depression, regimen complexity and pill burden.

Conclusions: Psychosocial factors and health system resources may explain regional differences. Adherence-enhancing interventions should address patient-reported barriers tailored to local settings, prioritizing the first years of ART.

Keywords: HIV-1; antiretroviral therapy (ART); adherence; Asia; sub-Saharan Africa

To access the supplementary material to this article please see Supplementary Files under Article Tools online.

Introduction

The introduction of combination antiretroviral therapy (ART) has dramatically reduced morbidity, mortality and infectiousness of persons infected with HIV [1]. Of the estimated 17 million people receiving ART worldwide, about 12 million reside in sub-Saharan Africa and 2 million in Asia, the two regions most affected by the HIV epidemic [1].

Consistently high levels of adherence to ART are essential for sustained viral suppression, thus preventing drug resistance [2] and disease progression [3]. Reported correlates of adherence include patient-related factors (such as understanding the utility of ART and adherence, trust in the care provider, HIV-associated stigma), treatment-related factors (such as regimen complexity), psychosocial factors (such as depressive symptoms) and socioeconomic factors (such as financial constraints) [4,5]. These factors can differ greatly across regions and populations, due to variations in sociodemographics, culture and availability of resources.

The Joint United Nations Programme on HIV/AIDS (UNAIDS) 90–90–90 global treatment targets emphasize sustained viral suppression and therewith the need for optimal adherence [6]. Characterizing and understanding determinants of adherence in settings with the highest disease burden will be critical to attaining these targets. Despite favourable short-term data from low-resource settings [7–10], concerns remain that long-term adherence may be suboptimal because of multiple barriers including lack of basic health education and enrolment in massive ART programmes with limited capacity for patient monitoring and support.

Two meta-analyses identified a number of correlates/predictors and patient-reported barriers of adherence [4,5], but were hampered by large heterogeneity across studies in adherence method and study design [4] and limited data from developing world settings [5].

We, therefore, conducted a prospective analysis of ART adherence among HIV-positive adults receiving first-line ART in sub-Saharan Africa and Asia, who were enrolled in a bi-regional monitoring programme [11]. The use of a generic study protocol and standard self-report adherence measure allowed for a substantive assessment and comparison of the levels and determinants of long-term adherence between populations residing in culturally and economically diverse regions with the highest burden of HIV disease

Methods

Study design and population
The PanAfrican (PASER-M) and TREAT Asia (TASER-M) Studies to Evaluate Resistance-Monitoring are two parallel regional cohorts of HIV-1 infected adults (aged ≥18 years) receiving care at 13 clinical sites in 6 African countries (Kenya, Nigeria, South Africa, Uganda, Zambia and Zimbabwe) and 12 clinical sites in 5 Asian countries (Hong Kong SAR, Indonesia, Malaysia, Philippines and Thailand), sharing a generic study protocol, the same patient eligibility criteria and standard adherence measure, as previously profiled [11].

The present study included all cohort participants who initiated first-line ART and were followed up (time period: 2007–2013) in accordance with national guidelines, because of advanced immunodeficiency (defined by a CD4 cell count <200 or <350 cells/μl) or clinical disease (according to WHO or CDC classification) [12]. Previous use of any antiretroviral drugs to prevent mother-to-child transmission of HIV was not an exclusion criterion. We excluded persons who did not have at least one documented adherence assessment during the first 24 months on ART, or who were not retained in care for at least three months after ART initiation.

Participants provided written informed consent at enrolment. The study protocol was approved by the appropriate national and local research ethics committees at all collaborating sites.

Data collection and outcome measure
Participants received care in accordance with the local standard-of-care guidelines. Personnel at all sites had received training in adherence assessment and counselling. Self-reported drug adherence in the past 30 days was assessed at each follow-up clinic visit using the visual analogue scale (range 0–100%) [13,14]. Adherence outcomes were defined for six-month intervals (6, 12, 18, 24 months after ART initiation), allowing six-month time windows (3–9, 9–15, 15–21 and 21–27 months, respectively). If more than one adherence assessment was performed within a six-month interval, the mean was used. Adherence was classified as optimal (≥95%) or suboptimal (<95%) for each six-month interval [15–17]. For descriptive purposes, adherence levels were additionally categorized as <80, 80–94, 95–99 and 100%.

Follow-up time was measured from ART initiation and ended at the earliest of either last follow-up visit or 24 months after starting ART. The analysis was censored at time of death, transfer out, ART discontinuation, switch to second-line therapy because of treatment failure, or loss to follow-up.

Other collected data included pre-ART demographics, clinical information at each follow-up clinic visit, and annual plasma HIV viral load. Among African participants, patient-reported adherence barriers were recorded among those who reported missed pills using a standardized questionnaire.

Statistical analysis
We fit a multivariable logistic regression model to estimate the associations between several covariates and suboptimal adherence. Generalized estimating equations were used to account for the correlation of repeated measurements within participants [18], specifying a first-order auto-regressive variance-covariance correlation structure. The quasi-likelihood information criterion statistic was used to evaluate fit. To account for missing data, we did multiple imputations for independent variables (pre-ART viral load, CD4 cell count, concomitant medication; 11.7% of timepoints) and adherence (17.4% of timepoints), using the Markov chain Monte Carlo approach with 20 simulation datasets. We tested whether the missing data were missing at random (or at least approximately so), and concluded that use of multiple imputations was justified (Supplementary Table S1).

Main analysis
The main analysis was a model that incorporated the following a priori chosen variables: sex, age (continuous, per 10-year increase), HIV risk group (heterosexual contact, men who have sex with men (MSM), injecting drug use (IDU) or unspecified), pre-ART history of AIDS, pre-ART CD4 cell count (<50, 50–99, 100–199, ≥200 cells/μl), pre-ART viral load (<10,000, 10,000–99,999 or ≥100,000 copies/ml), type of ART regimen (non-nucleoside reverse transcriptase inhibitor (NNRTI) based or other), most recent CD4 cell count (continuous, per 100 cells/μl increase), use of any concomitant medication, public versus non-public sector health facility, and time on ART (6, 12, 18 or 24 months). If more than one measurement of CD4 cell count was available within a six-month interval, the mean was used. Because univariate analysis showed significant interaction between region and multiple independent variables, the main analysis was stratified for the African and Asian cohorts. All analyses were adjusted for calendar year of

ART initiation, number of adherence assessments, and clinic type (general hospital, HIV clinic, or teaching hospital).

Additional analyses
(1) We examined the association between suboptimal adherence and virological failure (plasma viral load ≥400 copies/ml) using multivariable logistic regression, for the 12 and 24 months intervals and for each region. (2) To assess the association between long-term ART duration and adherence, we repeated the analysis using the data of the 15 of 25 sites (5/13 in Africa and 10/11 in Asia) that had followed participants up to 36 months. (3) To assess the association between specific antiretroviral drugs and adherence, we repeated the analysis including only the participants on an NNRT-based regimen and adding two additional variables: type of nucleoside reverse transcriptase inhibitor (NRTI) backbone (containing zidovudine, tenofovir, stavudine or other) and type of NNRTI (efavirenz or nevirapine). (4) To investigate whether differences in adherence were attributable to resources available to the population at large, we repeated the analysis with the two regional cohorts aggregated into one model including a binary variable for country income status: low or lower-middle income (Indonesia, Kenya, Nigeria, Philippines, Uganda, Zambia and Zimbabwe) versus upper-middle or high income (Hong Kong SAR, Malaysia, South Africa, Thailand), based on 2013 World Bank definitions [19].

Sensitivity analyses
(1) To assess the robustness of our results, we modified the definition of the outcome measure, either using different cutoffs (<90% or <100%) to define suboptimal adherence, or using the lowest measured adherence level for each six-month interval (if >1 assessment was available) with a <95% cutoff – instead of mean adherence. (2) It could be argued that improving adherence with longer ART duration could be due to attrition (lost to follow-up, ART discontinuation, death or regimen switch). To investigate possible attrition bias, we performed a sensitivity analysis in which follow-up time for all participants was extended to 24 months regardless of their status, while imputing missing adherence assessments and time-changeable variables using last observation carried forward (LOCF) methods. Adherence was also filled backwards to earlier time intervals, if missing, using the first recorded data.

Results were expressed using odds ratios (ORs) with 95% confidence intervals (CIs) and two-sided *p*-values (*p* < 0.05 significant). All statistical analyses were performed with Stata version 12 (StataCorp LP, TX, USA).

Results
Study population
Of 4659 participants starting first-line ART, we excluded 430 (9%) because they had less than three months follow-up time and 295 (6%) because they did not have at least one recorded adherence assessments during 24 months of follow-up. The analysis included 3934 participants, 2424 (62%) from Africa and 1510 (38%) from Asia (Table 1). Countries of residence were Uganda (24%), South Africa (23%), Zambia (20%), Kenya (17%), Zimbabwe (9%), and Nigeria (7%) for Africa, and Thailand (57%), Malaysia (21%), Hong Kong SAR (11%), Philippines (9%) and Indonesia (2%) for Asia. 2030 (52%) participants came from low- or lower-middle-income countries, and 1904 (48%) came from upper-middle- or high-income countries. Most African participants were women (59%, 1441/2424), and most Asians were men (67%, 1008/1510). Advanced HIV before ART start was less frequent among the African than the Asian participants, with CD4 cell counts <100 cells/µl in 35% and 45%, respectively, and a history of AIDS in 15% and 51%, respectively. NNRTI-based regimens were predominant in both regions. All sites in Asia and 6 of 13 sites in Africa were public sector facilities.

Description of outcomes
After 24 months of follow-up, 3223 (82%) of 3934 participants were alive and retained on first-line ART; 80 (2%) died, 112 (3%) transferred out, 32 (0.8%) discontinued ART, 315 (8%) were lost to follow-up, and 172 (4%) were switched to second-line therapy (Supplementary Figure S1 and S2). Participant retention was similar in the African (81%, 1972/2424) and Asian cohorts (83%, 1251/1510). The proportions of participants with viral suppression (<400 copies/ml) at 12, 24 months and overall were 90% (1867/2073), 90% (1608/1792) and 90% (3475/3865), respectively, in the African cohort, and 94% (1072/1143), 96% (887/922) and 95% (1959/2065), respectively, in the Asian cohort (Africa vs. Asia, *p* < 0.001).

A total of 23,278 adherence assessments were performed, with a median number per participant of 7 (interquartile range (IQR) 6–7) in Africans and 8 (IQR 5–9) in Asians (Table 2). The proportion of suboptimal adherence was 6.4% (837/13,001) overall, 7.3% (619/8484) in the African cohort and 4.8% (218/4517) in the Asian cohort (*p* < 0.001) (Table 2). This regional difference was noted for each time point: 10.2% versus 7.5% for month 6, 7.8% versus 5.6% for month 12, 5.5% versus 3.6% for month 18, and 5.1% versus 2.3% for month 24, respectively.

The proportion of suboptimal adherence decreased over time, with relative reductions of 50% in the African cohort (from 10.2% to 5.1%) and 69% in the Asian cohort (from 7.5% to 2.3%) (Figure 1). Participants who reported adherence <80% were more frequent in Africa across all time points, compared with Asia. Conversely, participants with perfect (100%) adherence were more frequent in Asia across all time points, compared with Africa (Figure 2).

Patient-reported adherence barriers
Among the African participants, a total of 235 participants recorded to have missed one or more pills at 1045 clinic visits. The most frequently reported reasons were scheduling demands (such as conflicting work schedule or travel; 33%, 350), followed by pharmacy stockouts (30%, 317), forgetfulness (28%, 297), sickness

Table 1. Participant characteristics at ART initiation.

	Total	Africa	Asia	p-Value
	n = 3934	*n* = 2424	*n* = 1510	
Sex				<0.001
Female	1943 (49.4)	1441 (59.4)	502 (33.2)	
Male	1991 (50.6)	983 (40.6)	1008 (66.8)	
Age (mean, SD)	37.8 (9.3)	37.8 (9.0)	37.8 (9.8)	0.885
HIV risk group				<0.001
Heterosexual	2637 (67.0)	1631 (67.3)	1006 (66.6)	
MSM	392 (10.0)	4 (0.2)	388 (25.7)	
IDU	87 (2.2)	0 (0.0)	87 (5.8)	
Unspecified	818 (20.8)	789 (32.5)	29 (1.9)	
Previous antiretroviral use				0.825
None	3856 (98.0)	2375 (98.0)	1481 (98.1)	
PMTCT	78 (2.0)	49 (2.0)	29 (1.9)	
History of AIDS				<0.001
No	2801 (71.2)	2054 (84.7)	747 (49.5)	
Yes	1133 (28.8)	370 (15.3)	763 (50.5)	
Pre-ART CD4 cell count (median cells/µl, SD)[a]	134 (55–210)	141 (68–209)	119 (40–215)	0.027
<50	915 (23.5)	467 (19.4)	448 (30.3)	<0.001
50–99	607 (15.6)	387 (16.0)	220 (14.9)	
100–199	1238 (31.8)	857 (35.5)	381 (25.7)	
200–349	1061 (29.2)	680 (28.2)	381 (25.7)	
≥350	73 (1.9)	23 (0.9)	50 (3.4)	
Pre-ART HIV viral load (median $\log_{10}$ cps/ml, IQR)[b]	5.0 (4.4–5.5)	5.0 (4.3–5.6)	5.0 (4.5–5.4)	0.668
ART regimen				<0.001
NNRTI-based	3822 (97.2)	2418 (99.8)	1404 (93.0)	
Other[c]	112 (2.8)	6 (0.2)	106 (7.0)	
Calendar year of ART initiation				<0.001
2007	706 (18.0)	565 (23.3)	141 (9.3)	
2008	2000 (50.8)	1499 (61.8)	501 (33.2)	
2009	879 (22.3)	360 (14.9)	519 (34.4)	
2010	349 (8.9)	–	349 (23.1)	
Sector				<0.001
Non-public	1296 (32.9)	1296 (53.5)	–	
Public	2638 (67.1)	1128 (46.5)	1510 (100.0)	
Country income status				<0.001
Low/lower-middle income	2030 (51.6)	1873 (77.3)	157 (10.4)	
Upper-middle/high income	1904 (48.4)	551 (22.7)	1353 (89.6)	

ART, antiretroviral therapy; SD, standard deviation; IQR, interquartile range; MSM, men who have sex with men; IDU, injecting drug use; PMTCT, prevention of mother-to-child-transmission; NNRTI, non-nucleoside reverse transcriptase inhibitor.
All data are *n* (%), unless indicated otherwise.
[a]Data available for 3894 participants.
[b]Data available for 3890 participants.
[c]87 participants on protease inhibitor regimens and 25 participants on triple nucleoside reverse transcriptase inhibitor regimens.

or adverse events (13%, 135), psychosocial issues (such as stigma and depression; 8%, 88), regimen complexity (4%, 44), pill burden (3%, 35), and other (13%, 134); 35% (82) of participants reported two or more reasons.

Determinants of adherence
Main analysis
Table 3 shows the multivariable regression models stratified by region. In the African cohort, male sex (OR 1.3, CI

Table 2. Summary of adherence assessments.

	Total		Africa		Asia	
	n	(%)	*n*	(%)	*n*	(%)
Participants	3913	100	2424	61.6	1510	38.4
Adherence assessments	23,278	100	14,714	63.2	8564	36.8
Median (IQR) number of adherence assessments per participant	7	6–8	7	6–7	8	5–9
Mean adherence assessments	13,001	100	8484	65.3	4517	34.7
Suboptimal adherence	837	6.4	619	7.3	218	4.8

IQR, interquartile range.
Data are *n* (%) unless indicated otherwise.
Adherence assessments used the 30-day self-reported visual analogue scale.
Mean adherence was calculated if >1 adherence assessment was performed within a time interval, and classified as optimal (≥95%) or suboptimal (<95%).

1.1–1.5; *p* = 0.009), younger age (OR 0.8 per 10-year increase, CI 0.8–0.9; *p* = 0.003), any concomitant medication (OR 1.8, CI 1.0–3.2; *p* = 0.044), and attending a public facility (OR 1.4, CI 1.1–1.7, *p* = 0.004) were associated with suboptimal adherence. In the Asian cohort, compared to heterosexual exposure, MSM had a lower risk of suboptimal adherence (OR 0.6, CI 0.4–0.9; *p* = 0.029), and IDUs had a higher risk, but this did not reach statistical significance (OR 1.6, CI 1.0–2.6; *p* = 0.075). In both regions, the risk of suboptimal adherence significantly decreased with longer ART duration. Compared to the six-month time interval, participants in both cohorts were less likely to have suboptimal adherence at month 12, 18 and 24 (OR 0.8, 0.6 and 0.5, respectively, in Africa and OR 0.8, 0.6 and 0.4, respectively, in Asia). A higher recent CD4 cell count was associated with better adherence in both regions. Pre-ART HIV viral load, AIDS and CD4 cell count and the type of ART regimen were not associated.

Additional analyses

(1) Suboptimal adherence was strongly associated with virological failure, both at month 12 (OR 6.5, CI 4.7–9.0; *p* < 0.001) and 24 (OR 7.4, CI 4.7–11.5; *p* < 0.001), and both in Africa (OR 5.8, CI 4.3–7.7; *p* < 0.001) and Asia (OR 9.0, CI 5.0–16.2; *p* < 0.001) (Supplementary Table S2). (2) The long-term analysis up to 36 months of follow-up, including 2434 participants from 15 sites, found that the association between longer ART duration and higher adherence was sustained in both regions, supporting the findings from the main analysis. Compared to the six-month time interval, at month 36 participants from both cohorts were less likely to have suboptimal adherence (OR 0.1; CI 0.06–0.2; *p* < 0.001, in Africa and OR 0.2; CI 0.09–0.4; *p* < 0.001, in Asia). (Supplementary Table S3 and Figure S3.) (3) The by-drug analysis found that none of the individual NRTI or NNRTI drugs were significantly associated with adherence in either region (Supplementary Table S4). (4) In the country income analysis participants from a low- or lower-middle income were 1.6 times (CI 1.3–2.0; *p* < 0.001) more likely to have suboptimal adherence than those from an upper-middle- or high-income country.

Sensitivity analyses

(1) Varying the definition of suboptimal adherence yielded largely the same associations as found in the main analysis (Supplementary Tables S5, S6, S7). (2) Using LOCF, longer ART duration remained significantly associated with higher
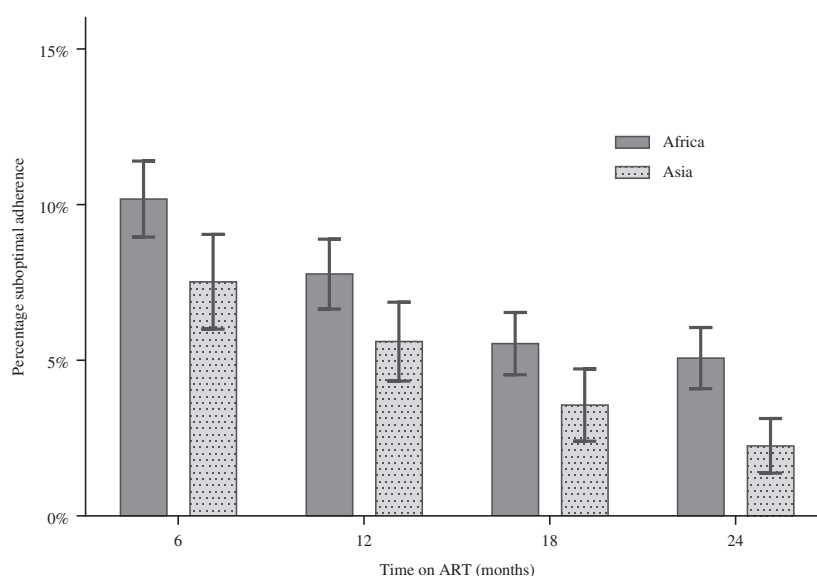
Figure 1. Proportions of suboptimal adherence over time in the African and Asian cohorts. Suboptimal adherence defined as a visual analog score of <95%. ART, antiretroviral therapy.
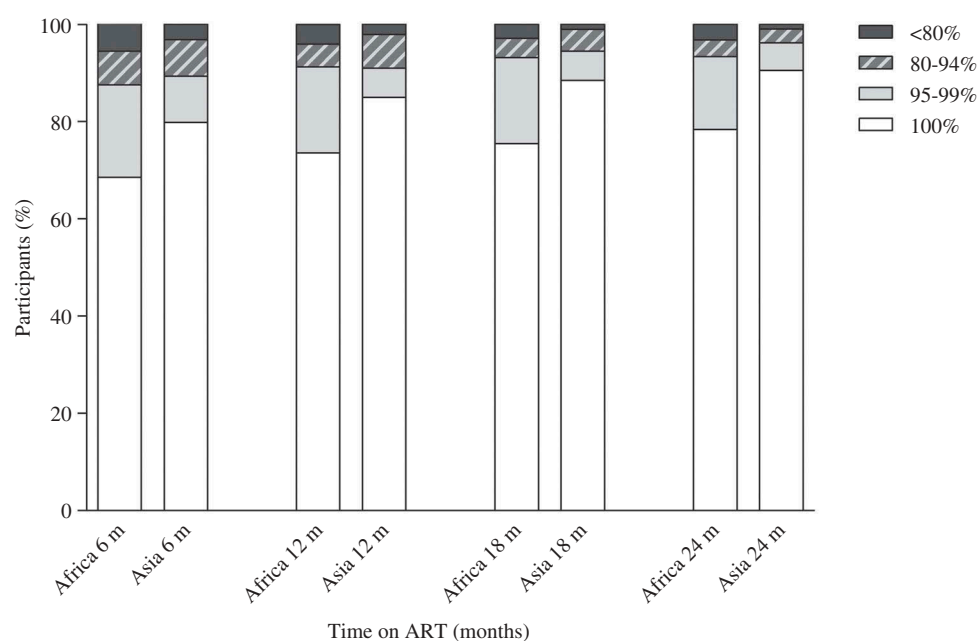
Figure 2. Categories of adherence levels over time in the African and Asian cohorts. Vertical bars represent 95% confidence intervals.

adherence in Africa, but not in Asia. Other associations remained largely similar to the main model (Supplementary Table S8).

Discussion

On the basis of 23,278 assessments in 3934 HIV-positive patients receiving first-line ART in sub-Saharan Africa and Asia, we observed high proportions of adequate self-reported drug adherence across both regions. During the first two years on ART, participants reported optimal adherence at 93% of clinic visits in the African cohort and 95% of follow-up clinic visits in the Asian cohort. This finding is consistent with two meta-analyses [8,9] and post-hoc analyses of two multi-country clinical trials [7,10] that reported favourable levels of adherence in low- and middle-income countries.

The 30-day VAS adherence measure was found to be strongly associated with virological outcomes in both regional cohorts, which corroborates the robustness of the observed associations. It needs to be recognized, however, that some studies have found self-reported adherence measures to be only moderately sensitive in predicting immunological or virological outcomes [20,21]. Recent WHO guidelines recommend viral load as the preferred monitoring strategy to assess ART effectiveness [22].

Despite overall high levels of adherence in the cohorts, we documented suboptimal adherence in a modest but relevant fraction of participants, which is a cause for concern. Participants in Africa reported lower adherence levels compared to their Asian counterparts. Correspondingly, viral suppression rates in the on-treatment populations were lower in the African cohort (90%), compared with the Asian cohort (95%).

We identified several determinants of suboptimal adherence, with some notable differences between the regions. First, a lower income status of the country of residence was found to be an independent risk factor of suboptimal adherence. Better adherence may partly be attributed to the resources available within a given national health system [23–25], or, more specifically, the ART site, for instance in terms of staff training levels, patient-staff ratios and patient monitoring strategies. In this respect, the Asian study sites were generally better resourced compared to their African counterparts. Our finding that in Africa adherence levels were lower in public facilities, which are typically less well-resourced, than non-public facilities, further supports this notion. Second, psychosocial and lifestyle differences between regions may play an important role. For instance, the subset of MSM participants in Asia reported higher adherence than heterosexuals, which expands on earlier reports of high adherence among MSM populations [9,26]. Among African male participants, MSM behaviour may be underrepresented (*n* = 4) due to stigma and associated limited access to HIV services [27]. Third, social desirability bias between the regions may have influenced the observed differences; however, given the corresponding regional differences in viral suppression rates, such an effect is likely to be limited.

Additional findings provide some relevant new insights. In both the African and Asian cohorts, drug adherence improved consistently over time up to at least three years of follow-up. Attrition rates in the early stages of ART in low- and middle-income countries are known to be high, because of early mortality and loss to follow-up [28]. In an attempt to account for potential attrition bias – by use of multiple imputations for missing data as well as a sensitivity

Table 3. Factors associated with suboptimal adherence, by region.

	Africa			Asia		
	OR	95% CI	*p*	OR	95% CI	*p*
Sex						
Female	1.00			1.00		
Male	1.27	1.06–1.53	0.009	1.12	0.78–1.61	0.537
Age						
Per 10-year increase	0.85	0.76–0.95	0.003	0.90	0.76–1.07	0.239
HIV risk group						
Heterosexual	1.00			1.00		
MSM [a]				0.59	0.36–0.94	0.029
IDU				1.58	0.95–2.60	0.075
Unspecified	0.76	0.70–0.82	<0.001	0.40	0.08–1.95	0.258
History of AIDS						
No	1.00			1.00		
Yes	0.97	0.76–1.24	0.816	0.85	0.60–1.21	0.371
Most recent CD4 cell count						
Per 100 cells/µl increase	0.89	0.84–0.95	<0.001	0.90	0.82–1.00	0.050
Pre-ART viral load (cps/ml)						
<10,000	1.00			1.00		
10,000–99,999	1.19	0.88–1.61	0.248	0.63	0.38–1.04	0.071
≥100,000	1.15	0.86–1.53	0.355	0.85	0.55–1.34	0.491
ART regimen						
NNRTI-based	1.00			1.00		
Other	1.49	0.31–7.07	0.615	0.31	0.08–1.22	0.093
ART duration						
6 months	1.00			1.00		
12 months	0.76	0.62–0.93	0.009	0.81	0.58–1.14	0.232
18 months	0.56	0.44–0.71	<0.001	0.56	0.38–0.84	0.006
24 months	0.51	0.39–0.65	<0.001	0.38	0.23–0.64	<0.001
Concomitant medication[b]						
No	1.00			1.00		
Yes	1.80	1.02–3.18	0.044	1.12	0.83–1.53	0.459
Sector						
Non-public	1.00			–[c]		
Public	1.39	1.11–1.74	0.004			

MSM, men who have sex with men; IDU, injecting drug use; NNRTI, non-nucleoside reverse transcriptase inhibitor, OR, odds ratio; CI, confidence interval.
This table shows results of multivariable logistic regression with generalized estimating equation and multiple imputations to model the probability that a participant was in the suboptimal adherence group. Therefore, an OR of >1 indicates an increased odds of suboptimal adherence, compared with the odds for the reference group. Models are adjusted for number of assessments, site type and calendar year of ART initiation. Pre-ART CD4 cell count was not associated in univariate analysis.
[a]MSM category in Africa was included in unknown category due to few observations (*n* = 4).
[b]Use of any other medication simultaneously with ART.
[c]All clinical sites in Asia were public facilities.

analysis using LOCF methods – adherence levels maintained their improvement over time in the African cohort; in Asia, however, improvement over time was no longer statistically significant in the LOCF analysis. These findings indicate that the significant effect of time was not entirely influenced by patient attrition, suggesting that patients who have been on ART for a longer period of time without defaulting may be more likely to be adherent. Patients may have become more adept at taking drugs on a daily basis, early side effects may have disappeared with time, or they may have received targeted adherence counselling and support. Our findings are in line with a UK study with nine years of

follow-up that found a consistent increase of 2% per year in adherence over time [29] and a French study with three years of follow-up that found that high early adherence was independently associated with a favourable long-term immunovirological response [30]. Our findings demonstrate that interventions to support adherence and reduce adherence barriers should be a priority in the early stages of ART.

Clarifying the reasons for missing pills can improve our understanding of the multifaceted challenges people encounter in maintaining life-long adherence to ART. The patient-reported barriers to adherence among the African participants varied considerably, and included scheduling demands, forgetfulness, sickness or adverse events, stigma or depression, regimen complexity, and pill burden. This reflects the diversity of the population affected by HIV and highlights the importance of tailoring adherence-support interventions to the individual and their sociocultural context [31,32]. Two recent meta-analyses of studies from sub-Saharan Africa summarized the available evidence of potential interventions that can promote ART adherence, suggesting that mobile phone text messages or other reminder devices, treatment supporters, education and counselling, and providing food supplements can be effective approaches in some settings [32,33]. Nonetheless, general limitations in available data emphasize that there is a need for more research to better examine the influence of sociocultural context and the content of potential adherence-support interventions that are relevant to local settings.

Furthermore, pharmacy drug stockouts were among the most frequently reported reasons for missing pills in Africa, illustrating deficiencies in service delivery rather than individual patients' lack of adherence. This finding endorses previous evaluations that identified important gaps in many procurement and supply systems of ART programmes in low- and middle-income countries [34]. These programmatic deficiencies need to be urgently addressed to preserve the durable effectiveness of first-line regimens and achieve sustained ART success.

This study found that use of individual NRTIs or NNRTIs were not associated with adherence, and that use of concomitant medication was associated with suboptimal adherence among the African participants. However, it needs to be recognized that this study was not able to fully assess the potential effects of pill burden, single-tablet or once-daily ART regimens [35]. Also, only few patients received a non-NNRTI-based regimen, which precluded a comparison with other regimens (e.g. protease inhibitor-based). Among the African participants, poor adherence was associated with younger age, concurring with several previous studies [7,29], and male sex. By contrast, in Asia, sex or age were not associated. A meta-analysis suggested that overall adherence levels may be higher in men than women, and that such sex differences could be attributable to several factors, such as – among men – being MSM or reporting no alcohol abuse, and – among women – having lower pre-ART CD4 cell counts, being a widow or residing in a low- or middle-income country [26]. Therefore, in the present study, it is

likely that additional unmeasured factors contributed to the observed regional differences.

The main strengths of the study were the prospective design with long-term follow-up and repeated adherence measurements, the large number of patients and clinical sites included in the aggregated analysis, and that we were able to correlate the self-report adherence measure with viral load outcomes. The outcome measure was robust in sensitivity analyses. The setting of routine ART programmes with wide geographic coverage enhanced the generalizability of the results, although the study population was not necessarily representative of all people with HIV/AIDS in the regions studied and caution is warranted when extrapolating results to different subpopulations or countries. The use of a common core study protocol with a standard, validated adherence measure across both regions added to the internal validity of our findings.

The study has some limitations. First, there was incomplete data ascertainment for a number of factors that can affect adherence both in terms of patient attributes (such as substance abuse and mental health), regimen characteristics (such as single-tablet regimens), and health-care-related factors (such as differences in health care models and policies to promote retention in care). The self-reported barriers to adherence (i.e. reasons for missed pills) among African participants underline the importance of including such factors in future research. Second, there are various sources of heterogeneity in the study population, both within and between the two regions studied, that could not be completely accounted for in the analysis, for instance differences in health care organization and human behaviour, which could have influenced the findings. Third, our findings mainly applied to patients who are severely immunocompromised (CD4 <200 cells/µl) at ART initiation, limiting generalizability to populations adopting a "test-and-treat" approach (who may be immunocompetent and therefore asymptomatic) in accordance with the latest WHO treatment guidelines [22]. Fourth, because of the observational design of the study, the associations found do not necessarily demonstrate causality. Also, despite our efforts to reduce attrition bias by applying multiple imputations and performing a sensitivity analysis, residual unmeasured confounding could have influenced some of the findings. Lastly, the analysis was limited to adults; ART-treated adolescents and children may face different adherence barriers to those identified in this study.

Conclusions

Comparing the determinants of suboptimal adherence to ART between the world's two most HIV-affected regions offered the potential to identify patients at risk, guide targets for developing interventions to enhance or maintain adherence, thus addressing the global challenge of providing effective long-term treatment to millions of patients in Africa and Asia. The study findings emphasized the influence of psychosocial factors and health system resources on ART adherence. Adherence-enhancing interventions need to address patient-reported barriers tailored to local settings, prioritizing the first years of ART. Improved drug

procurement and supply systems are required for sustained ART success in low-resource settings.

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Competing interests

All authors declare that they have no conflict of interest.

Authors' contributions

RB, AJ, RLH, AS and TFRW conceived the adherence study and developed the protocol. RB, AJ and TSB prepared the datasets for analysis. RB and RLH conceived, RB conducted, RLH checked and FWW supervised the statistical analyses. RB drafted the manuscript, with assistance from RLH. All authors provided valuable input to interpretation of the data and critically reviewed the paper for important intellectual content. All authors reviewed and approved the final version of the manuscript.

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