

Adherence/Compliance to HIV-1 Treatment Regimens in South Africa — a Targeted Literature Review

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Background

- Human deficiency virus 1 (HIV-1) infections has been on the rise over the years facilitating the transmission of the HIV epidemic.^{5, 12} Patients with HIV-1 have lower CD4+ T-cell count less than 200 cells per μL .³ There are many treatment regimens available to patients of which adherence/compliance from patients is essential to treatment effectiveness.⁵
- Adherence/compliance involves patients beginning treatment, maintaining medical appointments and consistently taking HIV medications. There is uncertainty on patient's adherence/compliance levels, and there is further uncertainty around the factors that affect adherence as well as how adherence is measured in South Africa.

Objective

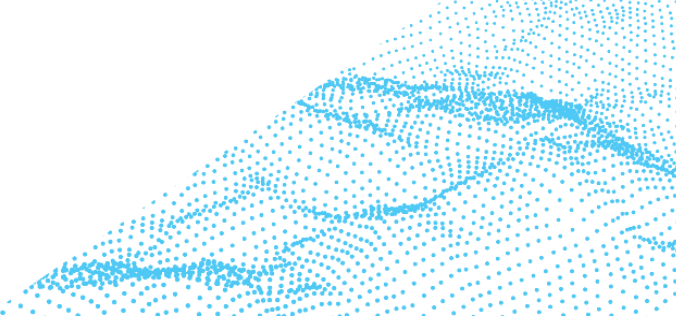
- This study aims to explore the adherence levels of patients with HIV-1 undergoing antiretroviral treatments (ART) and other treatments, and how this impacts treatment efficacy.

Key Results

- Twelve studies met the requirements for inclusion; 11 assessed ART (pooling multiple ART regimens), and one assessed an individual ART (Efavirenz-based) regimen. Adherence was measured differently across the studies using the following indicators: currently taking ART, drug detection in plasma, pill count adherence, and pharmacy refill data. General trends reported adherence levels (median/mean) of above 61%. Factors affecting adherence included secondary education, physical health, self-management, pregnancy status, viral load status, breadwinner status, HIV-RNA status, resistance mutation, workplace status, suboptimal baseline adherence, urban or rural resident status, and marital status. Effects of adherence on efficacy was reported in 8 studies ranging from mean to cumulative adherence. The evidence suggests that adherence was associated with increased level of efficacy.

Conclusion

- Most compliance/adherence studies generally reported sufficient data regarding general trends, as well as the variables impacting compliance/adherence and how compliance/adherence affects treatment efficacy.
- Adherence to ART by patients is dependent on several variables. Most cohorts in the included studies did not fully adhere to ART therapy. Various scales were used to measure adherence levels; however, the most appropriate measure is unknown.



Methods

Study design and search methods:

- Publications of interest were identified by searching databases available on Ovid platform based on a targeted search strategy.
- The search was conducted on November 28, 2021, in the MEDLINE® ALL database.
- The search was restricted to studies in South Africa.

Eligibility criteria:

- The identified publications were reviewed for relevance against the inclusion and exclusion criteria, defined by the PICOS criteria listed in **Table 1**.
- Data from included studies were extracted into a pre-defined Excel-based extraction template, ensuring that data were extracted uniformly and were comparable across studies.

Results

- The electronic database search yielded 219 studies. After screening through title and abstracts, 207 were excluded after title/abstract review as they did not meet the PICOS. A total of 12 studies were retained for extraction. A flow diagram of the selection process is illustrated in **Figure 1**.

Treatment

- The patient population in most studies (11/12) were those receiving antiretroviral therapy (ART) (a grouping of multiple ART regimens). One study (1/12) listed a single specific type of ART regimen - Efavirenz-based ART. This is presented in **Figure 2**.

Age

- Age: (11/12) of the studies reported the age groupings of the patient population as shown in **Figure 3**:
 - (6/12) targeted populations with mean/median ages between 13.6-4.3.
 - (3/12) targeted adolescent population living with HIV.
 - (1/12) does not report on the age of population.

Country

- All studies were conducted exclusively in South Africa (except for 2 studies which were conducted in both South Africa and Uganda). This is presented in **Figure 4**.

Measurement/definitions used

- Compliance/adherence was measured differently across the studies as follows:
 - Indicators of currently taking ART, drug detection in plasma, pill count adherence, and pharmacy refill data. One study did not report on how adherence was measured. Results is presented in **Table 2**.

General trends

- General trends found in (10/12) studies reported adherence levels (median/mean) of above 61%. Adherence definitions varied based on follow-up time, missed ARV treatment, treatment regimens, pill count, self reported, etc.
- (2/12) studies do not report on adherence trends. Results presented in **Table 3**.

Effect on efficacy

- Efficacy was evaluated in (8/12) studies based on:
 - Past week adherence, mean adherence, viral suppression, cumulative adherence, dose adherence, early adherence, virological failure, adherence monitoring device, pharmacy refill data (or data gaps), clinic-based pill count, and EFV concentration.
- (5/12) studies do not report on adherence or compliance efficacy. Results presented in **Table 5**.

Factors affecting adherence/compliance

- Factors affecting adherence (reported in 8/12) studies included:
 - Secondary education, physical health, self management, pregnancy status, viral load status, breadwinner status, HIV-RNA status, resistance mutation, workplace status, suboptimal baseline adherence, urban or rural resident status, and marital status.
- (3/12) studies do not explicitly report on the factors affecting adherence/compliance. Results are presented in **Table 4**.

Abbreviations:

AIDS, acquired immune deficiency syndrome; ART, antiretroviral treatments; ARV, antiretroviral; EFV, Efavirenz; HIV, human deficiency virus; HIV-1, human deficiency virus 1; HIV-RNA, human deficiency virus-Ribonucleic acid; LYs, life years gained; PICOS, patient/population, intervention, comparison and outcomes.

Figure 1. Flow diagram of study inclusion

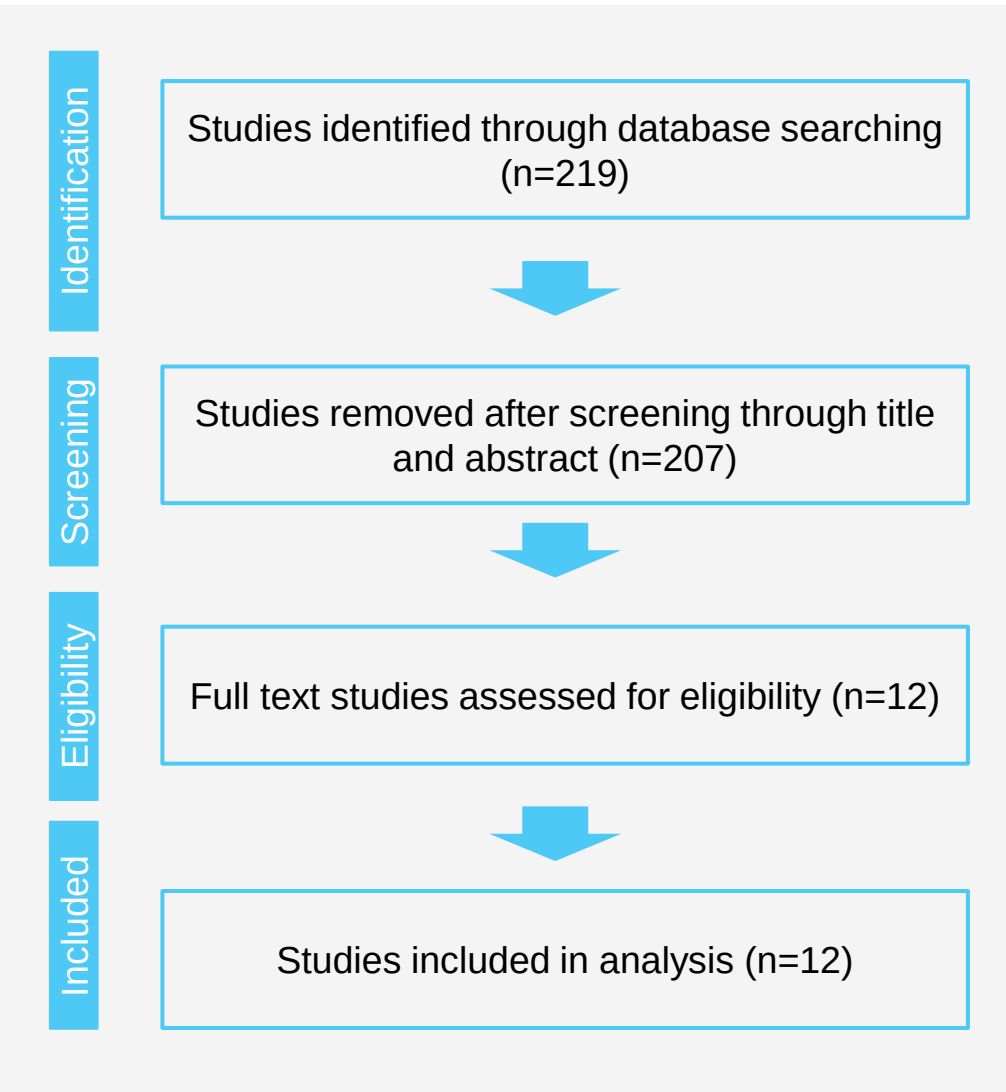


Figure 2. Treatment

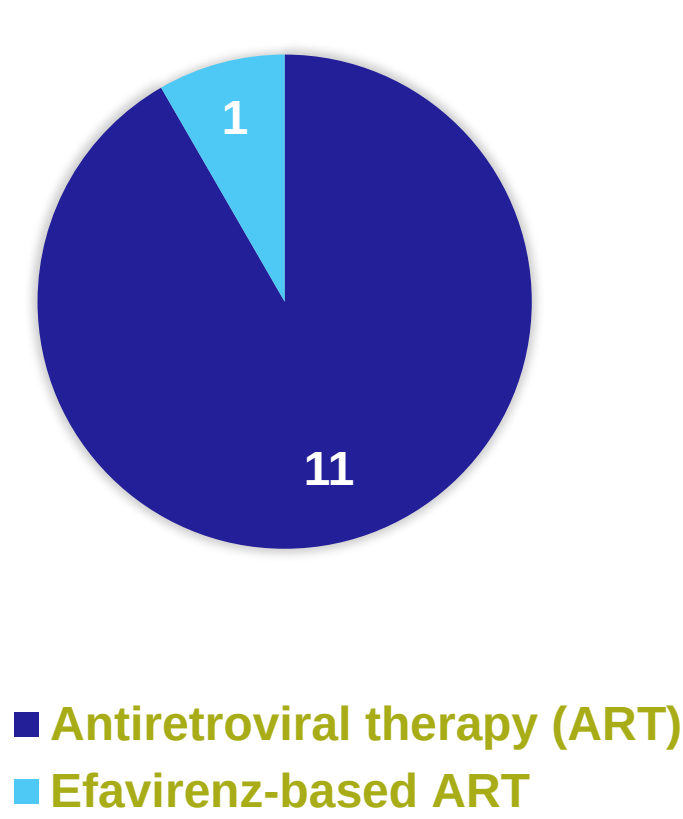


Figure 3. Age

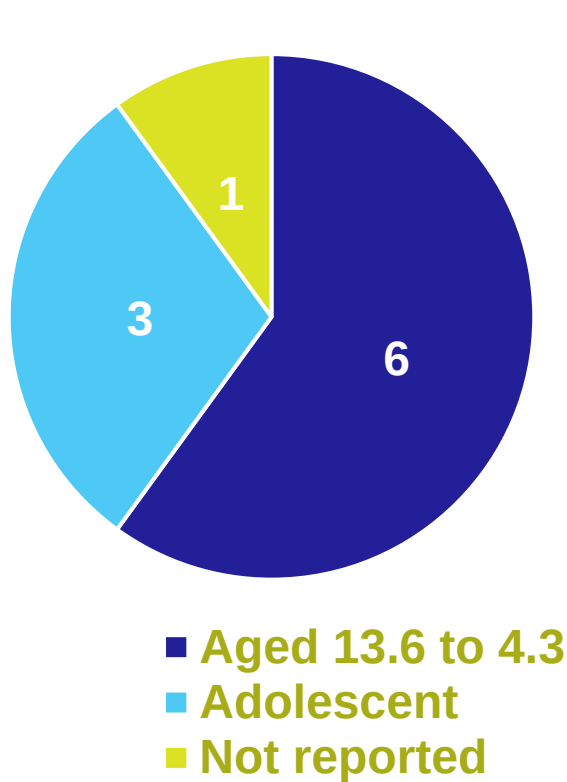


Figure 4. Country

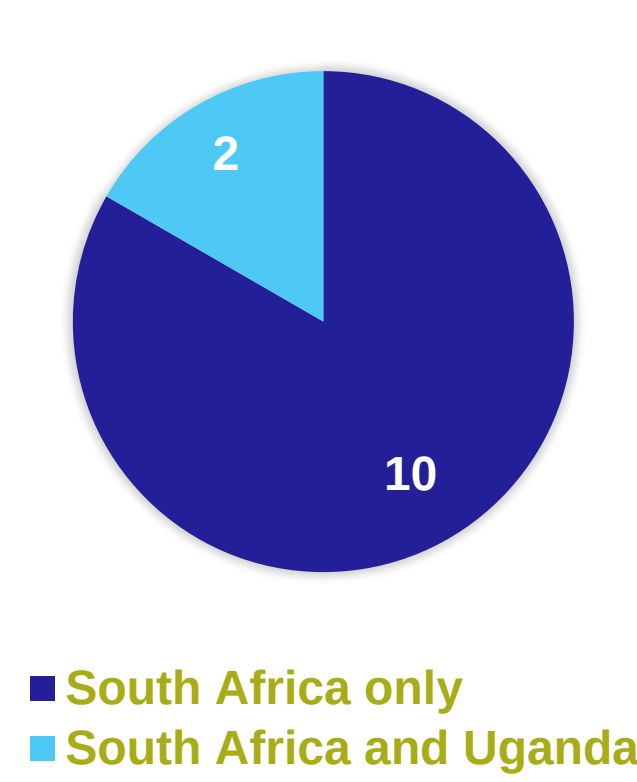


Table 4. Factors Affecting Adherence/Compliance

Study	Main Findings
Katz et al., 2021	Secondary education and higher physical health score protected against early gaps [adjusted odds ratio (aOR) 0.4, 95% confidence interval (CI): 0.2 to 0.8 and (aOR 0.93, 95% CI: 0.9 to 1.0), respectively].
Zhou et al., 2021	There were significant differences in sustained adherence by baseline age and the mode of HIV acquisition, but not the sex of the adolescents. Older age (106 [30.6%], p = 0.007) and horizontal transmission (55 [15.9], p = 0.002) were associated with inconsistent adherence over the three waves
Crowley et al., 2020	Adolescents who reported higher HIV self-management were more likely to be adherent to treatment (t = 4.435 [336], p < 0.01), virally suppressed (t = 2.376, p = 0.02).
Haberer et al., 2019	Adherence was higher in the early/non-pregnant group compared to the early/ pregnant or late/non-pregnant groups (76%, 37% and 52% respectively; p < 0.001 overall with p < 0.001 for 76% vs. 37%, p = 0.001 for 76% vs. 52% and p = 0.18 for 37% vs. 52%).
Myer et al., 2020	Pre-ART drug resistance mutations were approximately 1.5 times more frequent among women initiating ART who would go on to experience VEs (cases) compared to women who would maintain VS (controls) (adjusted OR, 1.5 [95% confidence interval (CI), 4–5.9]).
Moosa et al., 2019	Female gender (aOR = 1.33, 95%CI:1.05–1.67) and being a primary breadwinner (aOR = 1.32, 95%CI 1.02–1.72) were significantly associated with achieving optimal adherence.
Orrell et al., 2017	(12/14) participants whose HIV-RNA was >400 copies/ml at week 16 were successfully amplified when sent for HIV-1 resistance genotyping. Two participants had no major resistance mutations. Eight (66.7%) participants expressed the K65R mutation-conferring resistance to tenofovir, and three the M184 V mutation- conferring resistance to lamivudine/emtricitabine.
Kapiamba et al., 2016	Not reported
Johnston et al., 2012	Non-adherence was reported in a higher proportion of patients in the workplace, compared to the community programme (17.9% [workplace] vs. 1.4% [community]). In both programmes, of the 40 patients classified as non-adherent on second-line ART, 19% were identified through patient self-report and 83% through healthcare workers modification or interruption of ART for non-adherence.
Ncaca et al., 2011	Not reported
Peltzer et al., 2010	Both the VAS (198[38.3%], crude OR [2.78(1.60-4.83)] vs 319 [61.7%], crude OR [1.00] and the dose, schedule and food adherence(3.34 [2.13-5.25] vs 1.00) indicator found levels of adherence amongst urban residents to be almost 3 times greater than that of rural residents. The VAS indicator found greater adherence amongst those with lower levels of education (197[38.1%], crude OR [1.00] vs 320 [61.9%], crude OR [0.89(0.81-1.00)] vs amongst single, separated, divorced or widowed groups compared to those married and cohabiting (409[19.2%], crude OR [1.79(1.02-3.00)] vs 108 [20.9%], crude OR [1.00])
Ford et al., 2010	Not reported

Abbreviations: ART, antiretroviral therapy; aOR, adjusted odds ratio; CI, confidence interval; CPC, clinic-based pill count data; EAMD, electronic adherence monitoring device data; EFV, Efavirenz; HIV, human immunodeficiency virus; HIV-1, human immunodeficiency virus 1; HIV-RNA, human deficiency virus-Ribonucleic acid; VAS, visual adherence scale; VEs, virologic episode; VS, visual scale.

Table 5. Effect on Efficacy

Study	Main Findings
Katz et al., 2021	Not reported
Zhou et al., 2021	Past week adherence was associated with non-detectable viral load (aOR 1.72, 95%CI 1.14-2.59, P = 0.009).
Crowley et al., 2020	Not reported
Haberer et al., 2019	Not reported
Myer et al., 2020	Not reported
Moosa et al., 2019	Mean adherence to ART by pill count was 99.5% (overall 3- month ART) and Viral suppression rates were 87.4% 6 months after ART initiation. Adherence and viral load suppression in HIV-TB co-infected patients and patients on second-line ART 67% (±95%) mean adherence) and 100% > 400 copies/mL (6 months period before regimen).
Orrell et al., 2017	*Adherence quantified by EAMD, PR-average, PR-gaps, TR and log10 EFV concentration were all significantly predictive of resistance in both univariate and multivariable analyses at week 48. SR was non-significant in either model. Reduced age and decreased CD4 cell count at baseline significantly increased the odds of resistance in all multivariable models. While cumulative EAMD best predicted resistance with the narrowest confidence intervals (AUC ROC 0.92, 95% CI 0.87–0.97), it was not significantly better than either PR measure (PR-average AUC ROC 0.86, 95% CI 0.67–1.0, PR-gaps AUC ROC 0.83, 95% CI 0.65–1.00) at week 48. In contrast, only PR-average predicted resistance at week 16 (AUC ROC 0.72, 95% CI 0.57–0.90). Reduced age and decreased CD4 cell count at baseline significantly increased the odds of resistance in all multivariable models at week 1.
Kapiamba et al., 2016	50 (82%) of patients had adherence levels of 90% or above, 19 (38%) of these patients did not show any related viral suppression. A statistically significant relationship between adherence and viral suppression was not demonstrated.
Johnston et al., 2012	73.7% (N=179) of patients in the workplace and 84.4% (N=151) in the community programme were on second-line ART and had 48.3% (N=98) vs. 72.0% (N=152), respectively, viral suppression (p<0.01) by 15 months.
Ncaca et al., 2011	Median cumulative adherence was 97.8% for controls and 96.6% for failures. The majority (81.9%) of all study patients had a cumulative adherence ≥ 95%, whilst only 0.8% had a cumulative adherence below 80%. Ninety-six percent of controls had adherence ≥90%, compared to 86.3% of the failures.
Peltzer et al., 2010	Reported 30-day adherence using the visual adherence scale (VAS) was 82.9%. Self reported 4-day recall dose adherence was 84.5%.
Ford et al., 2010	Patients with adherence >95% by regimen EFV, NVP, and others were 81%, 15% and 4% respectively. Patients with adherence >95% by regimen EFV, NVP, and others were 79%, 20%, and 1% respectively

Abbreviations: ART, antiretroviral therapy; AUC ROC, Area Under The Curve, Receiver Operating Characteristics; aOR, adjusted odds ratio; CI, confidence interval; CPC, clinic-based pill count data; EAMD, electronic adherence monitoring device data; EFV, Efavirenz; HIV, human immunodeficiency virus; HIV-1, human immunodeficiency virus 1; HIV-RNA, human immunodeficiency virus-Ribonucleic acid; VAS, visual adherence scale; PR-average = average pharmacy refill data; PR-gaps = pharmacy refill gaps data; CPC = clinic-based pill count data; EFV = efavirenz mid-dosing interval data; SR = 3-day self-recall data

Limitations

- Studies that assessed self-reported adherence is subject to bias.
- Definitions of what constitutes adherence varied across studies and may not be generalizable.
- Two of the studies were retrospective observational studies and adherence monitoring may have limited the studies to correlation, not causation.
- The use of medical records in most studies caused missing data limitations.

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