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Adherence and retention in HIV care in resource-limited settings

By Theo Smart

Key points

- **Adherence to treatment and retention in care are important challenges for all HIV treatment programmes, especially where resources are limited.**
- **Retention in care after one year in many treatment programmes in sub-Saharan Africa is 60%, indicating that a lot of patients are being lost and a lot of time and money is being wasted preparing patients for treatment and treating them for a few months. Much less time and money is being invested in finding these patients once they fail to return to the clinic.**
- **More attention need to be given to finding the patients who don't return to the clinic, and finding the most cost-effective methods for doing so.**
- **At present defining a gold standard for adherence measurement tools is difficult; there are many tools and each has its advantages and disadvantages.**
- **Clinics that can dedicate more staff time to tracing defaulters, and going out into the community to do so, may have lower rates of loss to follow-up.**
- **The longer that a clinic leaves it to follow up a missing patient, the more likely they are to be permanently lost to follow-up.**
- **Retention of patients not yet on ART is important; patients lost to follow up before they are eligible for treatment could become late presenters who only turn up when seriously ill.**
- **Offering cotrimoxazole prophylaxis may improve retention in care for those not yet eligible for ART.**
- **ART preparedness counselling requirements may be onerous, and further work is needed to examine whether they are responsible for the disappearance of patients.**
- **Fast-tracking of patients of patients at high risk of serious AIDS-related illness should be a priority.**
- **Among those already on treatment, younger adults may need special attention to prevent loss to follow-up.**
- **Support groups and pill counts were associated with better adherence in a Nigerian study, but it may be the feeling of accountability of the patient to the health care worker, rather than the monitoring effect of spotting missed doses, that makes pill counting more effective.**

Ensuring good adherence and retention in care continue to be two of the biggest challenges facing antiretroviral treatment programmes as they scale up. Good adherence to medication, to clinic visits and to pharmacy visits are all critical in ensuring the best possible outcomes for patients.

Adherence and retention are also critical issues for treatment programmes from a cost-effectiveness point of view. As programmes seek to maximise the impact of limited resources, it is becoming apparent that failures in ensuring good adherence and lack of attention to loss-to-follow-up are costly.

Patients who do not adhere to treatment are more likely to develop drug resistance and require more expensive second-line treatment, or will fall ill as a result of treatment failure and require hospital care. Patients lost to follow-up will require tracing, and may reappear as hospital cases due to the interruption of their treatment.

Patients who disappear from care prior to starting ART may also turn up later, in need of hospital care, or may simply die before reaching the clinic again.

All of these outcomes place further stress on an over-burdened health system, as well as representing individual human suffering that ought to be preventable.

However, working out how to prevent these losses in the most effective and cost-effective way is a challenge for treatment programmes, and at last month's Conference on Retroviruses and Opportunistic Infections specialists from treatment programmes in sub-Saharan Africa reported on research designed to identify which measures might be most successful in ensuring good adherence and limiting loss to follow-up.

Insights from a themed discussion at CROI

"To be successful on ART, the patient needs to accept it, be adherent — and also needs to be retained in care," said Dr Jean Nachega, who is with both Johns Hopkins and Stellenbosch University.¹ "Our group has been able to show that we need to invest in learning how to monitor adherence and to improve adherence, because at the end of the day you are going to be saving money for the taxpayer. People who are poorly adherent cost a lot because of the high hospitalisation rate."

Dr Nachega was speaking as a co-moderator of a themed discussion on retention and adherence to care at this year's Conference on Retroviruses and Opportunistic Infections held in Boston, from February 27 - March 2, 2011. Dr Nachega gave an overview on this topic before introducing eight researchers who gave short descriptions of their recent work in the field, with a panel discussion moderated by Dr Wafaa El Sadr, of Columbia University and director of the International Center for AIDS Care and Treatment Programs (ICAP). While not a comprehensive review, the session did offer some useful insights, and can be viewed as a webcast [here](#).

A brief overview of adherence interventions

The evidence of the high cost efficiency for good adherence to which Dr Nachega was referring came from a recent cohort study with over 6800 patients conducted in South Africa. The study found that although some costs, such as those of medication, were higher in people with excellent adherence, they were more than offset by dramatically reduced hospitalisation costs as a result of maximally effective treatment of their HIV disease.² The same could hold true for many interventions to improve adherence and retention in care

– which appear to cost more upfront, but may wind up saving money in the end.

This has been demonstrated for the majority of adherence monitoring interventions, but as Dr Nachega illustrated with the following table, there is no gold standard tool to monitor adherence.

ART adherence monitoring tools: Identifying the elusive gold standard

ART Adherence Monitoring Tool	Validity	Detection of Adherence Patterns (Interruptions vs. Occasional missed doses)	Real-Time (Detection of adherence before virological failure)	Feasibility/Sustainability in routine practice	Cost Efficiency
Self-report	Specific, very insensitive	Yes	No	Yes	Yes
Pharmacy or Refill of Claim	Specific, Fairly Sensitive	No	Could be	Yes	Yes
Announced or Unannounced Pill Count	Fairly Specific, Fairly Sensitive	No	No	Yes	No
Electronic Pill-Container Caps (MEMS caps)	Specific, Too Sensitive	Yes	No	Yes	No
Electronic Web-Enabled Pill Box (Med-eMonitor, Wise Pill, etc)	Specific, Too Sensitive	Yes	Yes	Yes	Unknown
Directly Observed or Administration Therapy (DOT/DAART)	Specific, Specific	N/A	Yes	Feasible but not sustainable	Unknown
Monitoring of Antiretroviral Drug Concentration (Blood, Urine, Hair, etc)	Specific, Sensitive	Yes	Yes	No	No

“They all have their advantages and disadvantages,” he said, but he highlighted a couple. One involved a study his group also performed that was able to show that monitoring pharmacy refill closely can be better than CD4 monitoring for detecting breakthrough viraemia.³

He believes another major advance in the field may be real time monitoring tools.⁴ Some of these tools combine cell phone technology with an electronic pill box, which alerts a centralised web server whenever the pill box is opened. If the patient forgets to take

their medication, the web server sends their cell phones a text message. A number of these systems have been piloted recently, such as the [Wisepill](#) dispenser system in a small study in Uganda or the Med-eMonitor System.^{5 6} If scaleable, “and if we assume the cost is going to be going down, we’ll be able to make a really major advance,” Dr Nachega said.

If anything, though, data seem to suggest that adherence to ART in resource-limited settings is comparable if not better than in North America.⁷ Even so, challenges remain, including routine problems caused by alcohol or substance use, depression, side effects, pill burden/dosing frequency, memory, or adolescence. In addition, structural challenges need to be addressed such as the costs for the patient associated with transportation to the clinic, food insecurity, stock-out and substitutions and of course, stigma.

In terms of interventions to improve adherence, Dr Nachega highlighted two approaches. One, directly observed therapy (DOT) for ART, he said doesn’t appear to work well in the general population, according to a recent systematic review based on high quality evidence from randomised controlled trials, though the approach still might be useful in special populations.⁸

“But the most exciting data are on using cellphones in resource-limited settings. These cell phones are so popular, even grandma has her cellphone! We now have randomised controlled trials highlighting that this kind of approach may be of use, so we need now to think of how to implement it widely,” Dr Nachega said.^{9 10}

The other major issue addressed by the session was how to retain people under care, as highlighted by a systematic review by Rosen et al which found that by two years retention in most of the African programmes is only around 60%.¹¹ Loss to follow-up was the most common cause of attrition, followed by death.

Dr Nachega pointed out that one of the speakers in the session, Dr Elvin Geng (see below) had published work on the importance of accurately assessing survival among the losses to follow-up – since failure to do so may make it difficult to accurately identify modifiable risk factors for mortality in ART programmes. Without accurate information the programme’s response could fail. While tracking all the losses to follow-up could be difficult, the paper suggests that a sampling-based approach to account for losses to follow-up could be a feasible and potentially scaleable method of tracking and ascertaining causes of loss to follow-up.¹²

As for strategies to improve retention in care, Dr Nachega cited a recent paper from Professor Anthony Harries.¹³

“We need to try to set up and maintain simple standardised monitoring systems,” said Dr Nachega. These should track number of patients starting ART (every month or quarter) and avoid an overload of data. “We need to reduce indirect patient costs - all the structural barriers like transport to the clinic, perhaps through providing reimbursement for transport, or by delivering home-based care as in the trial from Jinja, Uganda,” he said.¹⁴

“Obviously, we need to try to prevent drug interruptions,” he said. Prof Harries’ paper stressed lessons learned from TB programmes, to ensure uninterrupted drug supplies by activating drug forecasting, securing drugs supplies and prioritising a few standardised regimens. In the case of ART, the regimens should be as simple and non-toxic as possible so that they are easy to administer, and can be given by paramedical staff. Treatment should of course be freely provided.

“Most importantly we need to decentralise ART clinics and reduce the frequency of visits,” said Dr Nachega. In other words, ART care needs to move beyond specialised facilities to rural

hospitals and health centres, with patient management tasks shifted to nurses and paramedical staff as much as possible.

Before introducing the session speakers, Dr Nachege stressed that the greatest threat to the retention in care of people living with HIV may be the international financial crisis.

“Some donors are stopping funding programmes in Africa, so that patients who are eligible are not likely to get started on ART,” he said. “We need to continue our advocacy to make certain that major donors, including PEPFAR, maintain their funding.”

After Dr Nachege spoke, a number of speakers followed. Notably, not all of their findings were consistent with each other or with published data. However, as Dr El Sadr noted, each programme can have its own approach to monitoring or to an intervention – and going forward, it will be important to characterise the activities in order to identify elements leading to their success or failure.

Not all the `lost to follow-up` are lost

“Loss to follow-up is common among ART programmes but it’s not consistently defined,” said Dr Aima Ahonkhai of Massachusetts General Hospital in Boston, who presented the findings of a large retrospective cohort study of adults initiating ART in the South African Catholics Bishops Conference and Catholic Relief Services HIV Treatment Programme between 2004 and 2008.¹⁵

The study’s objectives were to assess outcomes among different sub-groups often defined as lost to follow-up; to determine risk factors associated with these outcomes; and to evaluate trends in these outcomes over time. The analysis included 11,397 patients, with a median follow-up of 2.4 years. At study conclusion, 63% remained in care – however, not all were entirely lost to follow-up. Some clearly were, for instance, 9% of patients had died in the first seven months on ART, while 17% were lost to follow-up and missed all routine follow-up appointments in the first year on ART. But the remaining 11% of patients had only interrupted care. They missed all of their appointments in the first seven months on ART but returned to clinic before the year was over and resumed treatment.

“Patients with interrupted care had excellent clinical outcomes, upon return to clinic the median CD4 count increased to 257 cells and 84 percent had a viral load of less than 400 copies,” she said. On the other hand, patients who suffered early deaths, were the most ill at baseline, with a median CD4 count of 48 cells.

Compared to patients who remained in care, male sex predicted all other outcomes, but no other baseline risk factors or patient factors predicted, or differentiated between, interrupted care and loss to follow-up.

In contrast to some other expanding programmes, Dr Ahonkhai said that losses to follow-up have decreased over time. But she concluded that “because baseline risk factors do not distinguish interrupted care from lost to follow-up, more resources are needed for health information systems.”

Programme characteristics that impact retention in care

Factors such as having dedicated staff and vehicles to follow-up on patients, as well as the time interval to tracking down the patient may have a dramatic impact on retention in HIV care, according to analysis of programmatic data presented by Dr Paula Braitstein, of Indiana University School of Medicine and the USAID-AMPATH partnership in Eldoret, Kenya.¹⁶

The analysis was based upon data from IeDEA, the International Epidemiologic Databases to evaluate AIDS, a multi-regional consortium including 29 ART clinics around East Africa - Uganda,

Tanzania and Kenya. The programme level data for the analysis was drawn from two rounds of site assessments in 2007 and then by clinic self-report in 2009. Included in this analysis were all individuals aged at least 18 years and on ART at their last visit.

The primary outcome was lost to follow-up, defined as being absent from the clinic for at least 6 months. The Weibull survival model was used to model the time to lost to follow-up. A separate model was used for each of the outreach variables of interest: “basically,” she said, “who does the outreach; how do they do it; and when do they do it?” A random effect was included in the model to account for correlation among patients from the same site; and the model adjusted for patient age, sex, CD4 count at ART initiation and WHO stage at ART initiation.

The analysis involved 43,175 patients, 61 percent female; with a mean age of 38.4 years. The incidence of lost to follow-up was 16.5 per 100 person years to follow-up, but varied tremendously from site to site (from 1 to 79.5 per 100 person years).

The analysis looked at three programmatic characteristics, which Dr Braitstein said “brought it down to the lowest common denominators so that there was enough homogeneity within the groups to do the analysis properly.”

1) Did the clinic have dedicated staff for follow-up, or did they either not have dedicated staff or only use the telephone for follow-up (clinics with the latter two characteristics were more or less similar)? Using only the telephone or having no dedicated staff at all was associated with greater than 3-fold increased risk of patients lost to follow-up (adjusted hazard ratio 3.36, 95% confidence interval 1.72, 6.57) compared to clinics who had dedicated staff to do their outreach (p=0.001).

2) Did they only use public means, bicycle or walk to conduct follow-up, or did they also have access to a vehicle for follow-up? Compared to clinics who used all available means to go outreaching - which includes the use of a private vehicle - clinics that only use public means, bicycle or foot-power had a three-fold increase in the risk of patients lost to follow-up (3.12 adjusted hazard ratio, (95% CI 1.41, 6.88) p=0.009).

3) “And compared to going looking for patients within 30 days, clinics that wait more than 30 days to go looking for a patient were much more likely to have patients lost to follow-up,” Dr Braitstein said, (aHR 2.32 (95% CI 1.26, 4.24), p=0.011)

“There’s a lot of heterogeneity between all the different clinics as to what they do,” she said. “So for example at AMPATH in Western Kenya where I work, there’s a whole algorithm: If you are newly started on ART and you miss a visit, somebody tries to find you within 24 hours. If you’re stable on ARVs they wait a week. If you’re a child on ARVs, it’s 24 hours. Some clinics wait until people are lost to follow-up [> 6 months], before they actually go and look for them.”

However, Dr David Moore from Vancouver pointed out that all the programme characteristics that would seem to make a difference cost more money.

“So it would seem that there would be a general trend that better funded programmes actually perform better. So is it possible to actually tease out these specific characteristics of better funded programmes, from the overall effect of better funding for individual programmes?” he asked.

Dr Braitstein conceded that this question needs more examination, but went on: “Although some things are more costly, relative to the cost of losing all of these patients who you’ve already invested so much in, maybe it’s worthwhile to pay community health workers or peer outreach workers, thinking in terms of priorities and how to balance”.

She suggested that programmes need to look at the cost-effectiveness of providing cotrimoxazole prophylaxis or food aid in the context of the programme's ability to retain people in care.

Retention of patients not yet on ART

Are ART preparedness requirements leading to high loss to follow-up among people who qualify for ART but have not yet started?

Patients with CD4 counts of less than 250 require timely initiation of ART but structural, behavioural and psychosocial barriers may pose barriers to ART initiation. Losses to follow-up (i.e., unknown outcomes) at this stage are high and prevent complete observation of patients' outcomes, according to Dr Elvin Geng of the University of California, San Francisco.¹⁷ As already noted, Dr Geng has published on the use of sampling to try to ascertain what is going on with patients who are lost to follow-up, and has now expanded on his work with a study investigating the causes of loss to follow-up among people who qualify for ART but for one reason or another, do not start.

"We used a sampling-based approach which fills in outcomes through tracking a random sample of lost patients to evaluate ART initiation at a proto-typical, high-volume, semi-rural scale-up clinic in south-western Uganda and where two to three counselling sessions and a treatment supporter are typically required for ART initiation," he said.

In the study, over a three-year period 2369 ART eligible patients presented to the clinics. But by one year, 21% became lost before ART initiation - defined as being at least 60 days late for a return visit. In a random sample of lost patients, in which 82% of outcomes were ascertained, the one year mortality was 31%.

After incorporating outcomes among lost patients into the entire ART-eligible clinic population, Dr Geng and colleagues observed that over the first 90 days, the fraction starting ART rises quickly. But then at one year, only 69% of patients have initiated; 16% are waiting in care/for ART, but continued to visit a clinic - mostly at a different clinic than the original clinic; 7% are completely disengaged from care, meaning no visits to any clinic at all; and 9% of patients have died before ART initiation.

"The next question really is: why?" said Dr Geng. "The requirements for adherence counselling are an important aspect of care and are very widespread but perhaps their role in the time to ART initiation needs further evaluation."

"Make no mistake, I think that counselling has a tremendous causal effect in how well patients do after they start ART. But I think we need to ask ourselves - do we need to evaluate what kind of selection is going on at that point in time as well, and whether or not that selection precludes a decent chunk of patients from initiating ART?"

The requirements of adherence counselling include the need to make repeated clinic visits for counselling - which Dr Geng said in their clinic's protocol meant somewhere between two to four visits before being initiated on ART - as well as the need to designate a treatment supporter (who may also need to be trained). Other potential causes of failure to initiate could include distance to clinic and time off work or family duties required to make these visits.

"If these observations are true elsewhere, in the roll-out to date, potentially over one million ART eligible patients who have presented to care failed to initiate ART in a timely way. Strategies to engage ART eligible patients therefore represent a public health priority," he concluded.

Of particular concern are those patients who die before they can be initiated onto treatment, some speakers noted during the discussion section - so it may be best to fast track the most ill patients.

Dr Ahonkhai said that while she agreed about the importance of the pre-ART preparation, education and counselling, "I think in our cohort we found that the median time to ART initiation was 30 days in a very large multisite programme in South Africa - and the South Africa National Guidelines now recommend fast tracking. Fast tracking, particularly of patients who present with the most advanced disease, is another important programmatic uptake that can be [implemented]."

Dr El Sadr said that awareness needed to be raised among clinic staff about the urgency of getting this group of patients onto treatment, "Maybe by setting up something like a clock [or a timer]. The clock starts ticking from when the person is identified to be eligible so that there's an awareness that the clock is ticking [among] the clinic staff and they're trying to meet the deadline," she suggested.

"People can delay because they cannot afford travelling to facilities where ART can be found," said Dr Geng. "Lastly we need to remove stigma - to fight stigma - to actually ensure that stigma is not there because it contributes a lot to preventing people from accessing ART. They don't want to come forward for fear of being known by the community that they are HIV-positive."

Could providing preventive therapy retain people with HIV not yet on ART in care?

"I think all of us are aware that most of the data on retention and adherence have really focused on patients who have initiated ART. Until very recently the group that was in care, or pre-ART, has not been given enough attention. So that's kind of a group that is important to highlight, to try to find strategies to maintain these individuals in care so that they can initiate ART in a timely manner," said Dr El-Sadr.

One of the basic concerns regarding retention of patients in care before starting ART is creating incentives to remain engaged in care. After all, why should a patient give up time and money and travel a long distance to the clinic if there is no apparent health benefit and they feel well?

"Free cotrimoxazole significantly improves retention amongst ART ineligible clients in Kenya," said Dr Pamela Kohler of the University of Washington, Seattle, reporting on an analysis of data from a treatment programme in Nairobi.¹⁸ The aim of the study was to evaluate whether a programme change - which was offering free cotrimoxazole prophylaxis to all clients, regardless of CD4 count - was associated with improved retention in care among ART-ineligible clients.

The analysis included 1024 ART-ineligible clients who enrolled in the programme between 2005 and 2007. At that time, ART ineligibility was defined as having a CD4 count greater than 250, and WHO stage one or two disease. One-year retention in care among those enrolled was compared before (n=610) and after (n=414) free cotrimoxazole prophylaxis was offered. There were no significant differences in age, gender, TB status, BMI or CD4 count associated with time of access to care. However those lost to follow-up were significantly younger and had lower BMI than those who remained in care.

The analysis found that those who enrolled after the offer of free cotrimoxazole began had a significantly higher retention rate (84% versus 63%), $p < 0.001$, with a hazard ratio (adjusted for age, gender and CD4 count) of 2.64 (95 percent CI 1.95-3.57, $p < 0.001$).

In other words, those enrolled prior to implementation of free cotrimoxazole were more than two and a half times more likely to be lost to follow-up.

At the same time however, an analysis looking at retention in the same time periods among those treated on ART found no difference in the same time periods (89 and 88% retained in care) suggesting that overall temporal programmatic changes were not responsible for the difference seen in ART ineligible clients only.

"Although it's not clear from these data, possible mechanisms for this effect are decreased morbidity, perception of treatment, lower cost of care or perhaps establishment of care-seeking habits," said Dr Kohler. "The implications of this analysis is that today's ART ineligible lost to follow-up are quite possibly tomorrow's late presenters, and that losing these clients presents missed opportunities for timely initiation of ART and for messaging [to promote positive health dignity and prevention]."

This approach might work for other preventive care measures, such as isoniazid prophylaxis therapy to prevent TB (IPT), and more generally, the effect of pre-ART prophylaxis on retention in care needs to be evaluated in a variety of settings. Although uptake of cotrimoxazole is good in some countries among patients already taking ART or those on TB therapy, it continues to be an underused intervention among those ineligible for ART, despite WHO recommendations.

More services may be needed to retain younger adults on ART in care

Significantly worse retention in care was observed in younger adults on ART in Tanzania, according to a retrospective study presented by Dr. Geoffrey Somi of that country's National AIDS Control Programme.¹⁹

The study was conducted to assess the retention and the clinical response among patients enrolled in the national ART programme, through a clinic-based abstraction of six-monthly visit data. It utilised a retrospective cohort design with multi-stage random sampling to come up with a nationally representative sample out of 11 regions, 32 districts, 43 facilities, including a total of 2781 patients who were 15 years and above, and who started ART treatment between 2004 and August 2007.

Factors associated with advanced HIV disease at baseline and attrition at 12 months

Advanced HIV disease at baseline	AOR	95% CI	p-value
Under 30 years	1.63	1.35-1.97	<0.0001
Sex - Male	1.39	1.16-1.69	0.0004
Facility - Rural	1.72	1.13-2.63	0.01
Attrition at 12 months			
Under 30 years	1.64	1.25-2.17	0.0003
Sex - Male	1.7	1.32-2.18	<0.0001
Advanced HIV disease at baseline	1.61	1.15-2.27	0.005

The study found there were good clinical outcomes for those retained in care at 12 months in terms of CD4 gain, and weight gain. As for retention in care, at 12 months 63% were alive on ART, 8% reported dead; 4% were alive, ART status unknown, 25% attrition with an unknown cause. Retention and clinical outcomes did not vary significantly by ART initiation date across the study period.

However, retention was significantly worse in those with baseline CD4 cell counts below 50, males and those below 30 years.

"We concluded that good retention and response was maintained as client numbers rose by over 1600 percent, and the sites rose from 11 to 605. Young adults showed lower retention than older clients, and being a young adult was associated with having advanced HIV disease at baseline, suggesting that young adults are seeking care later," said Dr Somi. "Causes of attrition need to be identified and addressed - young adults appear to be a particular area of concern."

Adherence support

The value of peer counsellors and nurse-based care for ART adherence promotion

A task-shifting approach using peer counsellors and nurse based care may be just as effective at supporting adherence as standard clinic models, according to Dr Flavia Matovu, of the Mulago Hospital-Johns Hopkins Research Collaboration in Kampala, Uganda.²⁰

"Based on the urgent need for lower cost programmes aimed at achieving and maintaining higher levels of adherence to ART, we conducted a randomised non-inferiority intervention trial to assess the efficacy of peer counsellors and nurses in achieving/supporting adherence to ART among Ugandan patients attending the PMTCT clinic at the country's national referral hospital," she said.

Eighty-five participants were randomised to either of two HIV intervention models: the standard clinic-based model or a task-shifting intervention.

The standard clinic-based model promoted adherence through routine counselling by a certified counsellor, with care provided by a medical officer at each visit. This included shorter intervals between the visits, and all participants were started on ART provided through the PEPFAR programme by a hospital doctor.

The intervention model evaluated the effect of peer counsellors, and the effect of home visiting combined with a greater emphasis on nurses for routine visits, and also evaluated longer intervals between clinic visits.

The primary outcome was virologic suppression below 400 copies/ml. Secondary outcomes included a change in CD4 cell count, from baseline, change in weight and pill adherence.

"A high level of adherence was maintained in both models after adjusting for baseline viral load," said Dr Matovu. The task-shifting had similar outcomes and was not categorically inferior to the standard model that utilised doctors and counsellors. Essentially, there were no significant differences in viral load, CD4 cell count, pill adherence, or changes in weight over the 6 to 12 months follow-up period.

"These data are suggesting that ART adherence may be effectively supported using nurses and peer counsellors for follow-up care visits - a task shifting approach that may help deliver effective life-saving treatment to many more HIV-infected people in resource-limited settings," she concluded.

Adherence better in women who have started ART before pregnancy?

“Concerns have been raised in the literature regarding the impact of pregnancy on adherence to ongoing ART,” said Dr Rory Leisegang from the University of Cape Town, South Africa. “Previous studies have shown that adherence decreases post-partum; and that losses to follow-up for patients who’ve started ongoing ART while pregnant, have increased.”

To better understand the impact of pregnancy on adherence, a retrospective cohort analysis of women on ongoing ART in a South African private sector managed-care ART programme was performed. The control group included: 1) 4549 women on ART who were never pregnant, 2) 293 women who started ART upon learning they were pregnant (prevalent pregnant) and (3) 128 who became pregnant after starting ART (incident pregnant).

There were two key outcomes: ART adherence, from monthly refill data; and default on ongoing ART, defined as more than 6 months default on monthly prescription refills.

“The women were enrolled in a private sector programme and they received care through normal GPs. So they would have gone through the same process as any other person would go through during a pregnancy — there was no special care, no other special programme other than using the GPs with hospital services in the area,” said Dr Leisegang.

The key findings from the study were that median adherence was higher in the never pregnant, compared with the prevalent pregnant group: 79 percent vs. 54 percent ($p < 0.001$). Time to default was indeed higher in people who started antiretrovirals while pregnant, with the adjusted hazard ratio of 1.78 (95 percent CI 1.44 to 2.19). However, in the never vs. incident pregnant groups, higher adherence (by logistic regression) was associated with shorter time on ART (in other words, during the initial stages of ART), and with older age — also in the incident patients, during pregnancy and being 6 months post-partum.²¹

One member of the audience asked whether there was any variation during pregnancy — whether perhaps nausea and vomiting during the first trimester might be associated with worse adherence, but the study has not yet been able to show such effects. But another quandary was why adherence improved in incident pregnancy but not prevalent pregnancies.

“I think you have to think of them as two different groups. Women get screened when they are pregnant, and often they are starting antiretroviral therapy because someone has told them to start antiretroviral therapy [immediately],” said Dr. Leisegang.

“We won’t necessarily get people with higher CD4 counts onto programmes unless we can improve why people don’t take their antiretroviral therapy in cases where they may be well, or where there may be added stresses,” Dr Leisegang concluded.

Which components are most effective in a package of adherence interventions?

“I work in a facility that provides care to about 6,000 HIV patients with a very comprehensive programme to retain patients in care — both in the clinic, and as well as in the community component. But for us to be able to sustain PEPFAR programmes, we have to be able to identify which are the most efficient components of this programme,” said Dr Loice Achieng of AIC Kijabe Hosp, Kenya.²²

In order to determine which specific elements of their adherence programme contributed more to the success of ARV therapy, 301 HIV patients on ARVs were prospectively observed for participation in adherence activities within 6 months of initiating therapy. These included home visits by community health workers, support groups in the community, pill counts performed in front of the patient by

clinicians, post-pharmacy counselling after dispensing, and clinic visits. The primary endpoint was time to treatment failure defined as death, lost to follow-up or with a detectable HIV-1 RNA at one year as measured by Kaplan-Meier analysis.

Adherence was significantly different between those patients who either: had the correct number of clinic visits; who were involved in support groups; and who had pill counts performed by clinicians in front of the patients.

Comparison of Adherence in Success and Failures by Adherence Promoters

Factor	Days to Failure		Risk of Failure (Cox Model)
	Success	Failure	Hazard Ratio
Home visits	463	394	0.98
Support groups	480	425	0.54
Pill counts	481	355	0.57
Post pharmacy counselling	461	338	0.61
Made clinic visits	503	391	0.46

“We found that support groups and pill counts are associated with better adherence; clinic visits, and support groups and pill counts performed by clinicians are associated with the best time to treatment failure,” she said.

However, as some audience members pointed out, it is important to find out whether these findings are really generalisable.

One asked whether having the clinician count out pills is really practical when it comes to facilities with huge numbers of patients.

“Most of the patients come in, they’ve probably missed a few pills. It probably just takes a minute or two to actually count the pills with the patient in a clinic setting. And this is probably the cheapest intervention of all,” Dr Achieng responded. “Support groups involve a significant patient contribution, as well as being able to ensure the support groups run. The other things we analysed like home visits are quite expensive because you have to employ community health workers to take part in the home visits. Pill counts seem to be the cheapest and easiest to use in this setting.”

Why do pill counts appear to work?

“I think it’s a role of the clinician rather than any of the other providers, because in the same study you’ll find that post-pharmacy counselling [is being given] while the pharmacist’s at work,” said Dr Achieng. “Other studies have shown that when patients were talked to by the clinician, as opposed to by other members of the team, then they are more likely to adhere to treatment.”

In contrast, “directly observed therapy is difficult to perform, for many reasons: You have to have the patient, the patient has to be there with you. So that may not work just because of the logistics of having the patient there every day, several times a day.”

Dr Ahonkhai agreed that time with a clinician counting the pills might improve adherence, but was less convinced about pill counts themselves.

“Pill count is neither sensitive nor specific but is going to depend on who’s doing it, in which setting. Our experience about pill count overall has been very poor, and especially when you deal with large programmes i.e. Global Fund, PEPFAR with large numbers of people. So it’s not really perfect but [in fact] far from it. So in terms of measurement, there is intensive research to see how we can

combine measurement which is simple and practical to increase validity and reliability," she said.

Another audience member asked whether there might be early warning indicators of loss to follow-up like pharmacy refill visit intervals?

"The sector I work in is a managed care sector and we have a database and I work on a team that is trying to use multiple measures for tracking patients and then starting a phone call system which can use either a CD4 count, a refill or doctor [as a prompt]," said Dr Leisegang. "[With the] databases - it's extremely useful that you have a pop-up system that comes on for counsellors who then will phone patients and ask what's going on. That's often neglected because developing countries don't often have good databases. But where there is, that's what they do, they have a database automatically kicking up and telling us that there are patients that are missing their treatment."

Other panellists offered insights on potential early warning indicators in other populations.

"We're working on an analysis right now in children, looking at the relationship of missing visits and the risk of loss to follow-up. Because we think there's probably a strong relationship there," said Dr Braitstein. "And you might target more counselling around adherence to clinic visits, for example, or try to find out what's going on so that you increase the retention of the children who are particularly a vulnerable group. It's also worth looking at some of the risk factors that have been identified in the literature, like for example disclosure. So if somebody's never disclosed their HIV status, on some level it's a red flag that this patient is at high risk for becoming lost."

"Or men," she continued. "We found that males were at a much higher risk of becoming lost to follow-up, even after controlling for everything else. So we probably need some specific interventions to try and address that. Maybe it's weekend and evening clinics?"

"From our experience, in terms of patient preparation, the issues of disclosure that have been brought up; the issue of having a treatment buddy, using the refill history and clinic visit's - have been very good pointers," said Dr Matovu. "We have a good community network of community health workers, some of whom are actually patients, and these ones help us track the patients. One of the things we do is have a very clearly defined catchment area. Previously we have had programmes that had patients coming in from whichever place, and it's very hard to track these patients. When you have patients coming in from a well-defined catchment area, we are able to reach them; we know where each patient lives, or the community health worker in the area knows where each patient lives and you are able to look for all of the patients."

More research needed

Dr El Sadr offered some final words to conclude the discussion "There's tremendous interest and need for further research to try to really rigorously evaluate the effectiveness of well described interventions - not every peer programme is the same as the next peer programme; not every DOT programme is the same/similar to the other one. If we can learn not just what works but *why it works* in terms of well-defined programmatic characteristics and well-defined interventions; and then if we can demonstrate their effectiveness, I think then we'll be in a good position to try to replicate them and scale them up. So this is a very important area of research, and an important area of further enquiry."

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about HATiP

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