Cascade of care for HIV-seroconverters in rural Tanzania: a longitudinal study.

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Abstract

We examined the HIV care cascade in a community-based cohort study in Kisesa, Magu, Tanzania. We analyzed the proportion achieving each stage of the cascade - Seroconversion, Awareness of HIV status, Enrollment in Care and Antiretroviral therapy (ART) initiation- and estimated the median and interquartile range for the time for progression to the next stage. Modified Poisson regression was used to estimate prevalence risk ratios for enrollment in care and initiation of ART.

From 2006 to 2017, 175 HIV-seroconverters were identified. 140(80%) knew their HIV status, of whom 97(69.3%) were enrolled in HIV care, and 87(49.7%) had initiated ART. Time from seroconversion to awareness of HIV status was 731.3[475.5-1345.8] days. Time from awareness to enrollment was 7[0-64] days, and from enrollment to ART initiation was 19[3-248] days. There were no demographic differences in enrollment in care or ART initiation. Efforts have been focusing on shortening time from seroconversion to diagnosis, mostly by increasing the number of testing clinics available. We recommend increased systematic testing to reduce time from seroconversion to awareness of status, and by doing so speed up enrollment into care. Interventions that increase enrollment are likely to have the most impact in achieving UNAIDS targets.

Keywords: HIV Care Continuum, Linkage to care, Testing, ARV, Tanzania

Introduction

The target for antiretroviral therapy (ART) programs worldwide has been defined by the Joint United Nations Programme (UNAIDS) using the slogan 90-90-90 targets (UNAIDS, 2017). This aims to achieve 90% of people living with HIV (PLHIV) diagnosed (knowing their status), 90% of those diagnosed initiated on ART, and 90% of individuals on ART being virologically suppressed. Reaching the UNAIDS targets requires early diagnosis, effective linkage to treatment, and maintaining patients in care (Kunutsor et al., 2011; Ulett et al., 2009). Not only is it important to be aware of the presence and nature of obstacles to care, but identification of key factors associated with linkage to care are also needed to improve benefits of ART through the continuum of care (Nakagawa et al., 2012).

We used data from a community-based cohort in Tanzania to assess the spectrum of engagement in care of PLHIV in Northwest Tanzania and estimate the achievement of the 90-90-90 targets in this population.

Methods

Study population

The data for this paper is derived from a community-based cohort study in Kisesa, Tanzania, covering an area of about 115 km^2 with 35000 inhabitants residing in the study area (Boerma et al., 1999; Mwaluko et al., 2003, Kishamawe et al., 2015). Approximately every 3 years all residents aged 15 years or more are invited to a sero-survey to determine the health needs in the population, with the first in 1994, and the 8^{th} sero-survey finished in February 2016. All sero-survey participants were offered Voluntary Counseling and

Testing (VCT), and if found to be HIV-infected were referred to the main clinic in Kisesa for treatment. Dried blood spot samples (DBS) from all consenting participants, whether or not they had VCT, were tested for HIV-1 at the National Institute for Medical Research (NIMR) reference laboratory in Mwanza. We identified seroconverters from HIV testing of DBS between September 2006 (sero-survey 5) and February 2016 (sero-survey 8). Seroconverters were defined as those with at least one HIV negative test, and a subsequent HIV positive test, with the date of seroconversion defined as the mid-point between dates of the last negative test and the first positive test.

Three stages of the HIV care cascade were included in our framework:

1) Awareness of HIV status: defined as the awareness of positive HIV status either through VCT at the sero-survey, or through self-reported HIV Counseling and Testing (HCT) attendance or other proof of HCT (available in public health facilities unrelated to the sero-surveys). The date of awareness of HIV status was defined as the date the person first knew of his or her own HIV status.

2) Enrollment in HIV care: defined as completing and/or self-reporting at least 1 visit to a Care and Treatment Clinic (CTC). Those diagnosed with HIV through a positive HIV test at any of the HCT clinics, or through VCT in the sero-surveys, are referred to a CTC. The date of CTC enrolment was defined as the date of the first reported attendance at CTC.

3) ART initiation: defined as having a clinically confirmed ART initiation report and/or self-reported use of ART. The date of ART initiation was defined as the first reported date that ART was given to participants.

Follow-up

The follow-up period spanned from date of seroconversion to March 15th 2017, the date at which everyone who had not progressed to the next stage was censored. We searched for each seroconverter manually and via a record linkage computer algorithm using name, sex, date of birth, and place of residence in all the health clinics providing HIV care within a 10 km radius around the sero-survey catchment area. We additionally visited the two oldest and largest HIV clinics in the region (in Mwanza City, 20 km from the DSS) to search for seroconverters.

Statistical analysis

The proportion of HIV-positive persons achieving each stage in the cascade was calculated. Statistical inference for differences between levels of explanatory variables was based on a χ^2 test for categorical variables. We also used modified Poisson regression to estimate prevalence risk ratios (PRRs) and 95% confidence intervals (95%CIs) for enrollment in care and initiation of ART. All plausible variables were individually included into the model and model goodness-of-fit assessed. Data were entered into Microsoft Excel and all analyses were performed in STATA 14.1 (College Station, TX, USA).

Ethical considerations

Ethical approval for retrospective analysis of these data was obtained from Bugando Medical Centre in Mwanza (BREC/001/04/2011), the National Institute for Medical Research in Dar es Salaam (NIMR/HQ/R.8a/Vol.IX/1489), and Weill Cornell Medicine in New York (1108011883). Study participants provided consent at the time of enrollment into the cohort study in accordance with the approved procedures of the TAZAMA project (Boerma et al., 1999; Mwaluko et al., 2003).

Results

From September 2006 to February 2017, a total of 207 HIV-seroconverters were identified in the cohort. Among those, 175 HIV-seroconverters were available for follow-up. A total of 20 health facilities (HCTs and CTCs) contributed to the analysis.

The demographics of the HIV-seroconverters are presented by stage of the cascade in Table I. There was no difference in the proportions of HIV-seroconverters by area of residence.

Table I. Proportion of the 175 HIV-seroconverters engaged in each of the HIV care cascade stages by selected characteristics.

IQR=Interquartile range

Characteristic	HIV seroconverters	Aware of HIV status		Enrolled in care		Initiated ART	
		n (%)	p-value[a]	N (%)	p-value[a]	n/N	p-value[a]
Total	175	140 (80.0%)	-	97 (55.4%)	-	87(49.7%)	-
Sex							
Female	118 (67.4%)	93 (78.8%)	0.57	69 (58.5%)	0.24	63 (53.4%)	0.16
Male	57 (32.6%)	47 (82.5%)		28 (49.1%)		24 (42.1%)	
Occupation							
Farmer	142 (81.1%)	111 (78.2%)	0.42	74 (52.1%)	0.17	69/142 (48.6%)	0.77
Businessman	12 (6.9%)	11 (91.7%)		9 (75.0%)		6/12 (50.0%)	
Mix of farming and business	21 (12.0%)	18 (85.7%)		14 (66.7%)		12/21 (57.1%)	
		Median (IQR)	**p-value[a]**	**Median (IQR)**	**p-value[a]**	**Median (IQR)**	**p-value[a]**
Age							
Aware/enrolled/ initiated	36 (27-46)	36.5 (28-46)	0.46	35(27-43)	0.15	36.5 (27.5-48)	0.42
Not aware/ enrolled/initiated		34 (26-43)		37(28-52)		36 (27-45)	
Years of education							
Aware/enrolled/ initiated	7(2-7)	7(2-7)	0.75	7(0-7)	0.16	7 (3.5-7)	0.062
Not aware/ enrolled/initiated		7(0-7)		7(3-7)		7 (0-7)	

[a] Use of Chi-square test for categorical variables and rank-sum test for continuous variables.

As of March 2017, end of follow-up, 140/175 (80.0%) knew their HIV status, 97/175 (55.4%) were enrolled in HIV care, and 87/140 (62.1%) had initiated ART. The cascade of care is presented in Figure 1.

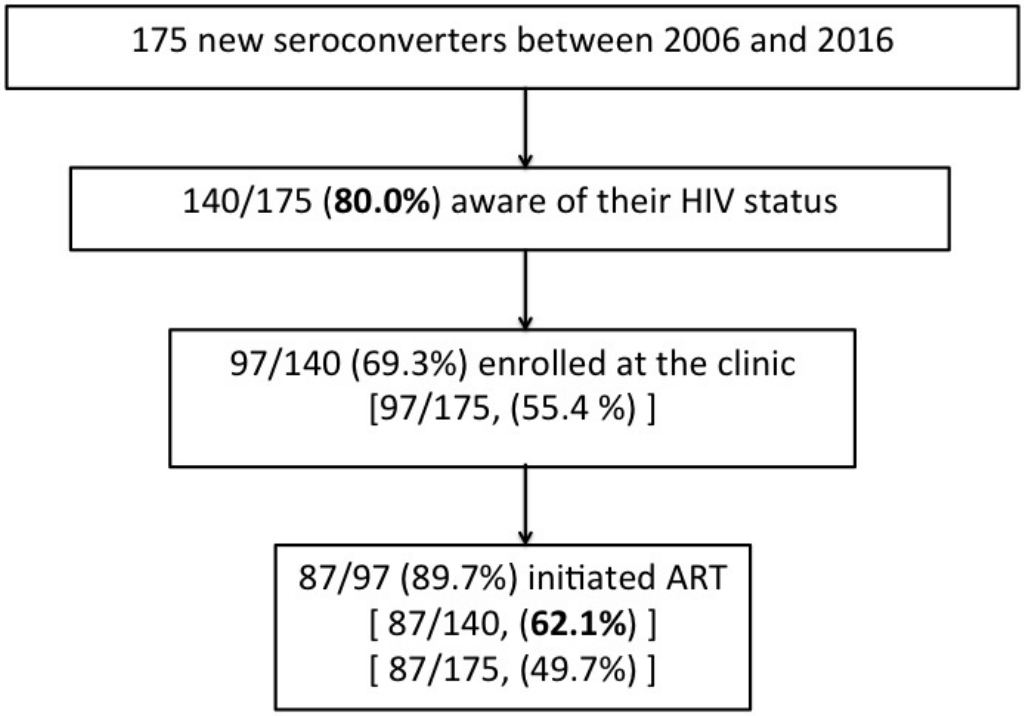

Figure 1. Cascade of care in the study population, Tanzania. The first two 90-90-90 targets are in bold.

Figure 1 depicts the cascade of care in our study population. 80% of HIV-infected people knew their HIV status and 62% of these were on ART.

The majority of the seroconverters learned about their positive status for the first time at the sero-survey (67/140, 47.8%), or at a HCT clinic (47/140, 33.6%). 20/140 (14.3%) of the seroconverters discovered their status via provider-initiated testing and 6/140 (4.3%) at Ante-Natal Care (ANC).

The median time from seroconversion to being aware of one's HIV status was 731.3[475.5-1345.8] days while time from awareness of HIV status to enrollment was 7[0-64] days. The overall median time from enrollment to ART initiation was 19[3-248] days. The key time variables are presented in Table II.

Table II. Key time variables (in days) for the 175 seroconverters

IQR=Interquartile range

Variable	Median	IQR	Minimum	Maximum	N
Time from seroconversion to awareness	731.3	475.5 - 1345.8	135.5	2889	140
Time from seroconversion to enrollment	965.5	511.5 - 1652.5	135.5	2889	93[a]
Time from seroconversion to ART initiation	1247.5	803.5 - 1867.5	206.5	3324.5	83[a]
Time from awareness to enrollment	7.0	0 - 64	0	2170	93[a]
Time from awareness to ART initiation	146.0	19 - 535	0	2989	83[a]
Time from enrollment to ART initiation	19.0	3 - 248	0	2988	83[a]
Time being followed-up at the clinic (up to March 15th 2017)	803.0	378 - 1646	64	3009	93[a]

[a] *4 people self-reported attending a clinic and initiation ART but did not provide us with exact dates.*

Time to ART initiation decreased sharply with the successive implementation of new guidelines. Time from awareness of HIV status to enrollment transiently increased with the creation of new clinics where old seroconverters who had not previously been enrolled in care could now enroll in care more easily. Throughout the study period, the time from awareness of HIV status to enrollment was longer for those receiving their results at sero-surveys than for those receiving their results at a clinic ($p<0.001$). These results are presented in Figure 2.

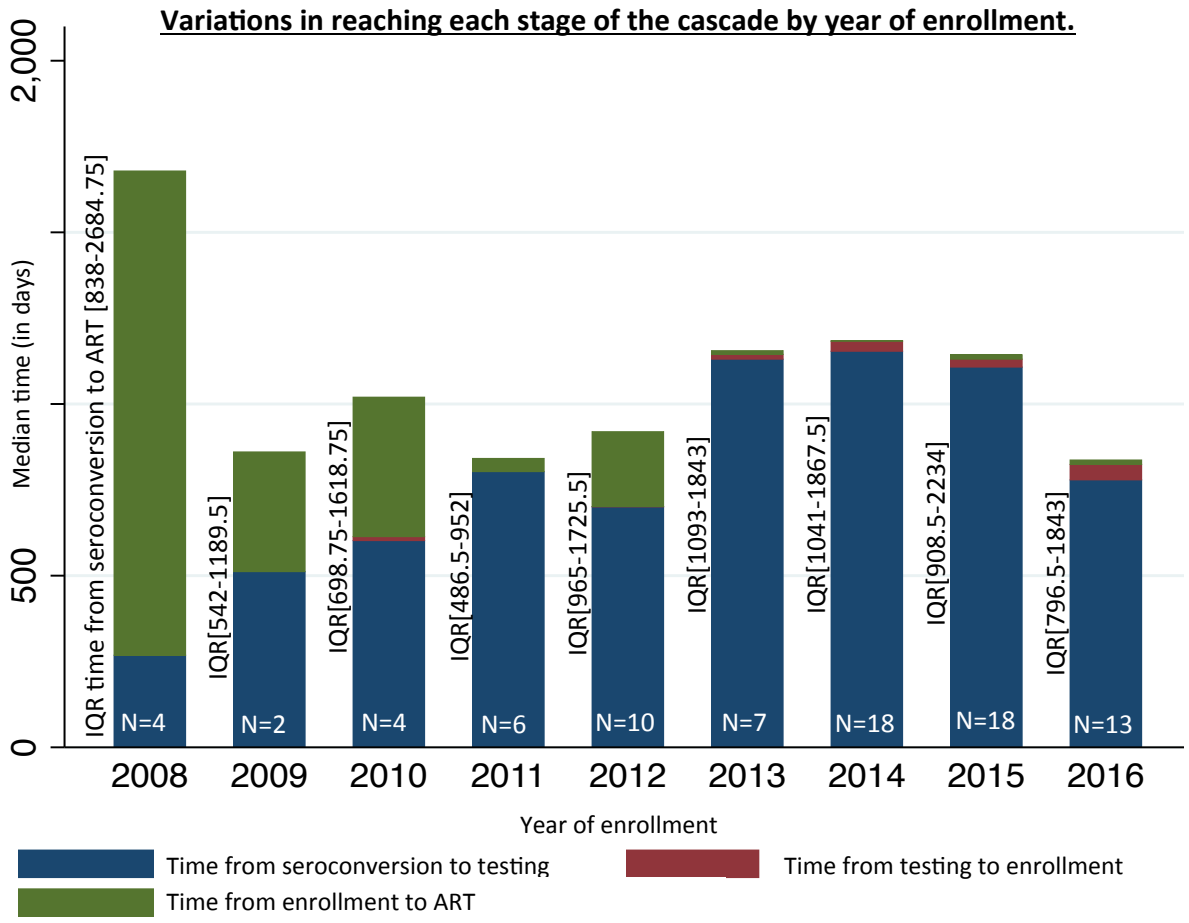

Figure 2: Variations in reaching each stage of the cascade by year of enrollment

Figure 2 shows the variation in key time variables over the years, following major HIV/AIDS testing and care interventions. Time to ART initiation decreased dramatically with the successive implementation of new guidelines while time from diagnosis to enrollment transiently increased with the creation of new clinics. The first sero-survey was conducted in 2006-2007 and is not represented on this figure.

There was no difference by sex in enrollment in care (adjPRR=0.85, 95%CI 0.61-1.17), and no other significant differences. There was also no difference by sex in ART initiation (adjPRR=0.75, 95%CI 0.51-1.08), and no other significant differences. There was no difference in occupation, age or years of education in any of the stages of the cascade of care.

Discussion

This is the first report, to our knowledge, on Tanzania's achievements regarding the 90-90-90 targets. This longitudinal study in Tanzania occurred at a unique time during which new HIV clinics were opening and ART eligibility was increasing. Our Tanzanian study population demonstrates some moderate successes, with 80% of HIV-infected people knowing their HIV status and 62% of these on ART. Routine viral load monitoring was not yet fully implemented at the time of our study and future studies will evaluate the 3rd target of the UNAIDS 90-90-90 goal.

The success in our rural study population is that the percentage of HIV-positive individuals knowing their status is high. This effect was largely driven by the recent strategy change of the final sero-survey in 2016, which provided opt-out HIV testing for all participants rather than requiring the person providing blood to take initiative to obtain their results. This highlights the need for more regular access to opt-out testing and a greater encouragement for uptake of HIV testing (Church et al., 2017). This would also help reduce time from seroconversion to awareness of HIV status, which is still the main reason for substantial delays in enrollment into care in our cohort. Due to the logistical

challenges and the expense of large-scale sero-surveys, provider-initiated testing might be more able to fit those criteria (Sanga et al., 2017).

Gender was not a predictive factor for initiating ART in our study population, which was unexpected and inconsistent with other studies (Hatcher et al., 2012; Lahuerta et al., 2014), as women have been accessing ART when pregnant, regardless of CD4 counts for the past 7 years. It could be explained by the fact that very few women in our study population received their HIV results through ANC. No other demographic factor predicted enrollment into care or initiation of ART, which strongly suggests that failure in linkage to care is inherent to the system, and not due to patient factors (Church et al., 2017 , Mshana et al., 2006). Integration of HIV care services remains a substantial problem in this setting, despite the availability of free services in close geographic proximity. Effective referral must be strengthened if linkage to HIV treatment is to be improved. More specifically, individuals who were diagnosed at a HCT clinic were more rapidly linked to CTC than those diagnosed at sero-surveys in our study population, as was shown in other regions of Tanzania as well (Sanga et al., 2017). This highlights the need for better integration of the sero-surveys into the HIV healthcare system and more efficient referral of the patients to the CTC clinics.

The target of 90% of the population diagnosed with HIV being on ART is still far from being achieved in our study population. This is likely due to both a low percentage of diagnosed individuals going into care and treatment and to changes in guidelines based on CD4 counts over the duration of our observational period.

The low percentage of diagnosed individuals going into care and treatment can be explained partially by the fact that not many easily accessible CTCs were opened until 2014. In fact, before 2014 there were only 5 CTCs in the region, and those were far away for the majority of the rural population, with over an hour of walk needed to reach the facilities. Thus the increasing time from seroconversion to enrollment in care over the years is indeed the result of more old seroconverters enrolling in CTCs as they open.

CD4-count based guidelines would be the second reason for low ART initiation. Until 2010, the criteria for ART initiation were a CD4 count ≤200 cells/mm3 or a WHO clinical stage of 4 for all adults. The criteria changed to ≤350 cells/mm3 from 2010-2012, ≤500 from 2013-2015, and all HIV-infected in 2016. (The United Republic of Tanzania. Ministry of Health, Community Development, Gender, Elderly and Children, 2017; The United Republic of Tanzania. Ministry of Health, 2005; The United Republic of Tanzania. Ministry of Health and Social Welfare., 2012, 2015).The WHO guideline of initiating ART for all HIV-infected people was issued in 2015 and has been rolled out gradually since then in Tanzania. Not only do the new patients now need to initiate ART immediately, but the older patients who had not gotten on ART based on previous guidelines still need to start ART. It will take a few years for each clinic to overcome the lag but this approach for treatment will ultimately lead to an ongoing and consistent improvement in the number of individuals on antiretroviral therapy.

Importantly, more CTCs continue to open in the region and the country and home-based testing is also currently being investigated in Tanzania (Lwezaula, 2012).

Both of these will likely serve as powerful resources to strengthen linkage of HIV-infected individuals to testing and care.

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Declaration of interest

The authors declare no conflict of interest. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Data availability

The data that support the findings of this study are available from the corresponding author, S.C., upon reasonable request.

Authorship

S.C. contributed to conception, design, acquisition of data, analysis, interpretation of data and wrote the original manuscript. R.M. and B.M. contributed to design and acquisition of data and reviewed the manuscript. P.L. contributed to acquisition of data and reviewed the manuscript, W.S. contributed to the interpretation of data and reviewed the manuscript, J.B. conception, design, analysis, interpretation of data and reviewed the manuscript, J.A.D. and J.T. contributed to design and interpretation of data and wrote the original manuscript, M.U. and J.C. supervised the study, contributed to conception and interpretation of data and reviewed the manuscript. All authors have read and approved the submitted manuscript.

References

Boerma, J. T., Urassa, M., Senkoro, K., Klokke, A., & Ngweshemi, J. Z. (1999). Spread of HIV infection in a rural area of Tanzania. *Aids*, *13*(10), 1233–1240.

Church, K., Machiyama, K., Todd, J., Njamwea, B., Mwangome, M., Hosegood, V., … Wringe, A. (2017). Identifying gaps in HIV service delivery across the diagnosis-to-treatment cascade: findings from health facility surveys in six sub-Saharan countries. *J Int AIDS Soc*, *20*(1), 21188. http://doi.org/10.7448/ias.20.1.21188

Kishamawe, C., Isingo, R., Mtenga, B., Zaba, B., Todd, J., Clark, B., … Urassa, M. (2015). Health & Demographic Surveillance System Profile: The Magu Health and Demographic Surveillance System (Magu HDSS). *Int J Epidemiol*, *44*(6), 1851–1861. http://doi.org/10.1093/ije/dyv188

Kunutsor, S., Walley, J., Katabira, E., Muchuro, S., Balidawa, H., Namagala, E., & Ikoona, E. (2011). Improving clinic attendance and adherence to antiretroviral therapy through a treatment supporter intervention in Uganda: a randomized controlled trial. *AIDS Behav*, *15*(8), 1795–1802. http://doi.org/10.1007/s10461-011-9927-9

Lwezaula, S. (2012). *Perceptions and attitude of the community members towards the uptake of home-based counseling and testing in Ilala district.* Muhimbili University of Health and Allied Sciences.

Mshana, G. H., Wamoyi, J., Busza, J., Zaba, B., Changalucha, J., Kaluvya, S., & Urassa, M. (2006). Barriers to accessing antiretroviral therapy in Kisesa, Tanzania: a qualitative study of early rural referrals to the national program. *AIDS Patient Care STDS*, *20*(9), 649–657. http://doi.org/10.1089/apc.2006.20.649

Mwaluko, G., Urassa, M., Isingo, R., Zaba, B., & Boerma, J. T. (2003). Trends in HIV and sexual behaviour in a longitudinal study in a rural population in Tanzania, 1994-2000. *Aids*, *17*(18), 2645–2651. http://doi.org/10.1097/01.aids.0000088225.55968.9d

Nakagawa, F., Lodwick, R. K., Smith, C. J., Smith, R., Cambiano, V., Lundgren, J. D., … Phillips, A. N. (2012). Projected life expectancy of people with HIV according to timing of diagnosis. *Aids*, *26*(3), 335–343. http://doi.org/10.1097/QAD.0b013e32834dcec9

Sanga, E. S., Lerebo, W., Mushi, A. K., Clowes, P., Olomi, W., Maboko, L., & Zarowsky, C. (2017). Linkage into care among newly diagnosed HIV-positive individuals tested through outreach and facility-based HIV testing models in Mbeya, Tanzania: a prospective mixed-method cohort study. *BMJ Open*, *7*(4), e013733. http://doi.org/10.1136/bmjopen-2016-013733

The United Republic of Tanzania. Ministry of Health, Community Development, Gender, Elderly and Children. (2017). *National guidelines for the management of HIV and AIDS 6th ed.*

The United Republic of Tanzania. Ministry of Health. (2005). *National guidelines for the clinical management of HIV and AIDS. National AIDS Control Programme 2nd ed.*

The United Republic of Tanzania. Ministry of Health and Social Welfare. (2012). *National guidelines for the management of HIV and AIDS. National AIDS Control Programme 4th ed.*

The United Republic of Tanzania. Ministry of Health and Social Welfare. (2015). *National guidelines for the management of HIV and AIDS. National AIDS Control*

Programme 5th ed.

Ulett, K. B., Willig, J. H., Lin, H. Y., Routman, J. S., Abroms, S., Allison, J., … Mugavero, M. J. (2009). The therapeutic implications of timely linkage and early retention in HIV care. *AIDS Patient Care STDS*, *23*(1), 41–49. http://doi.org/10.1089/apc.2008.0132

UNAIDS. (2017). 90-90-90 - An ambitious treatment target to help end the AIDS epidemic. Retrieved from http://www.unaids.org/en/resources/documents/2017/90-90-90