Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Havlir DV, Balzer LB, Charlebois ED, et al. HIV testing and treatment with the use of a community health approach in rural Africa. N Engl J Med 2019;381:219-29. DOI: 10.1056/NEJMoa1809866

HIV Testing and Treatment with the Use of a Community Health Approach in Rural Africa

APPENDIX: SUPPLEMENTARY MATERIALS

Contents

Investigators

University of California, San Francisco, School of Medicine, San Francisco, United States: Diane V. Havlir, MD, Edwin D. Charlebois, PhD, MPH, Tamara D. Clark, MPH, Teri Liegler, PhD, Gabriel Chamie, MD, MPH, Carol S. Camlin, PhD, MPH, Vivek Jain, MD, MAS, Theodore Ruel, MD, Starley B. Shade, PhD, MPH, Catherine Koss, MD, Lillian Brown, MD, PhD, Carina Marquez, MD, MPH, Craig R. Cohen, MD, MPH

Makerere University, School of Medicine, Kampala, Uganda: Moses R. Kamya, MBChB, MMed, MPH, PhD

University of California, Berkeley, School of Public Health, Berkeley, United States: Maya Petersen, MD, PhD, Mark van der Laan, PhD

University of Massachusetts, Amherst, School of Public Health and Health Sciences, Amherst, United States: Laura B. Balzer, PhD

University of Pennsylvania, Perelman School of Medicine, Philadelphia, United States: Harsha Thirumurthy, PhD

Infectious Diseases Research Collaboration, Kampala, Uganda: Dalsone Kwarisiima, MBChB, MPH

Kenya Medical Research Institute, Nairobi, Kenya: Elizabeth Bukusi, MBChB, MMed, MPH, PhD, James Ayieko, MBChB, MPH

San Francisco Department of Public Health, San Francisco, United States: Yea-Hung Chen, PhD

Data Safety Monitoring Board Members, Advisory Board Members, Other Scientific Advisors and Additional Supporters

Data and Safety Monitoring Board: Nicholas P. Jewell (Chair), Stephen Watiti, Dorothy Mbori-Ngacha, Carlos del Rio, Harriet Mayanja-Kizza

Uganda Country Advisory Board: Alex Opio (Chair), Elly Katabira, Emmanuel Luyirika, Edward Bitarakwate, Miriam Nanyunja, Joshua Musinguzi, Gerald Mutungi, Moses Kamabare, Jackie Calnan, Donna Kabatesi, Peter Okwero

Kenya Country Advisory Board: Peter Cherutich (Chair), William Maina, Ambrose Otieno Rachier, Jessica Cowden, Kawango Agot, Sirengo Wafula, Irene Mukui, A. D. Jack, Omondi Owino, Florence Manguyu, Nicholas Muraguri, Hellen Mutai, Katherine Perry, Clement Zeh, Lucy N Wanjiku, Margaret Makumi, Pacifica Onyancha, Patrick Mureithi, Peter Eerens, Kevin De Cock, Solomon Mpoke

Other Scientific Advisors: Haileyesus Getahun, Reuben Granich, Elvin Geng, Nancy Padian, Carl Dieffenbach

Additional Supporters: Daniel Mwai, C. Olwande, Rich Clark, Antonio Alvarez, Charles Muga, Patrick Oyaro, Gerald Aketche, Joel Gondi, George Agengo, Bishop Opira, Zachary Kwena, Bridget Nzarubara, Catherine Tugaineyo, Jerop Toroitich, Linda Nassaka, Irene Rwomushana, Sumaya Namukose, Phoebe Mercy Achieng, Faith Mukoya, Brian Kamugisha, Mitto Okal, Placide Ntwali Nsengiyumva, Charles Kavuma, Cylus Okongo, Irene Odongo, Edith Biira, Medius Teriyeitu, Lamek Ouma, Janet Otte, Miriam Kayendeke, Gordon Orori, Bruce Owakubariho, Calvin Obuya, Roland Namwanja, Winnie Nuwagaba, Sabina Ogachi, Flavia Najjuma, Wilson Opudo, Frederick Opel, Elly Assurah, Ronald Aine, Betty Mwebaza, Irene Maeri, Dennis Tumwebaze, Judith Namanya, Cecilia Akatukwasa, Samuel Okello Ngome, Paul Malagala, Ronald Kakuru, Fred Nyatika

Figure S1: Community Selection

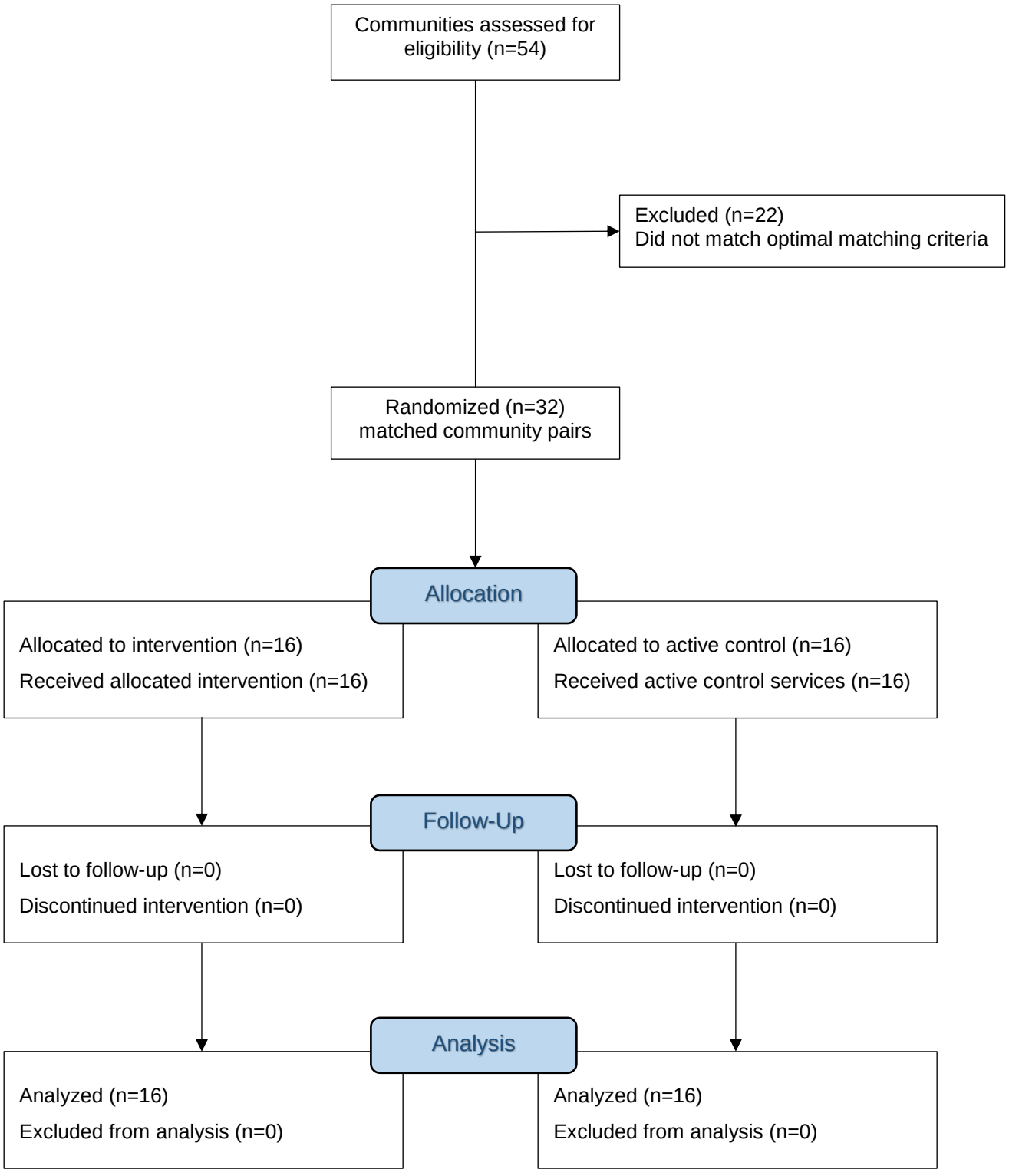
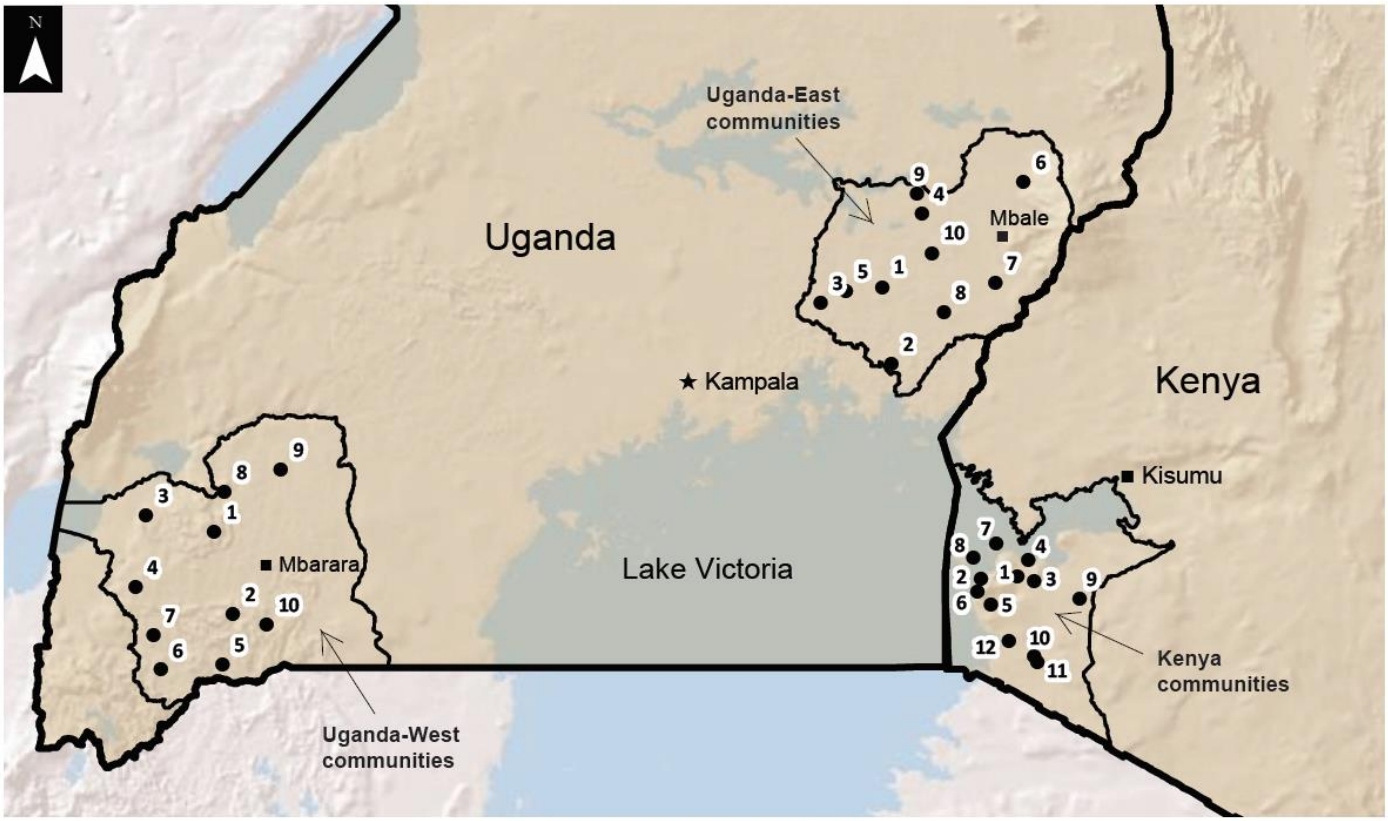


Figure S2: SEARCH Community Location

East Africa map of 32 communities in the SEARCH trial



The communities were within three regions: **Uganda-West** (study community names: 1=Nsiika; 2=Bugamba; 3=Rugazi; 4=Mitooma; 5=Kitwe; 6=Rubaare; 7=Rwashamaire; 8=Ruhoko; 9=Kazo; 10=Nyamuyanja); **Uganda-East** (1=Nsiinze; 2=Nankoma; 3=Kiyunga; 4=Kamuge; 5=Bugono; 6=Muyembe; 7=Merikit; 8=Kiyeyi; 9=Kameke; 10=Kadama), and **Kenya** (1=Nyatoto; 2=Nyamrisra; 3=Ogongo; 4=Kitare; 5=Magunga; 6=Kisegi; 7=Tom Mboya; 8=Sena; 9=Ongo; 10=Othoro; 11=Sibouche; 12=Bware).

Figure S3: Hypertension and Diabetes Treatment Algorithms

Figure S3a: Hypertension Management Algorithm

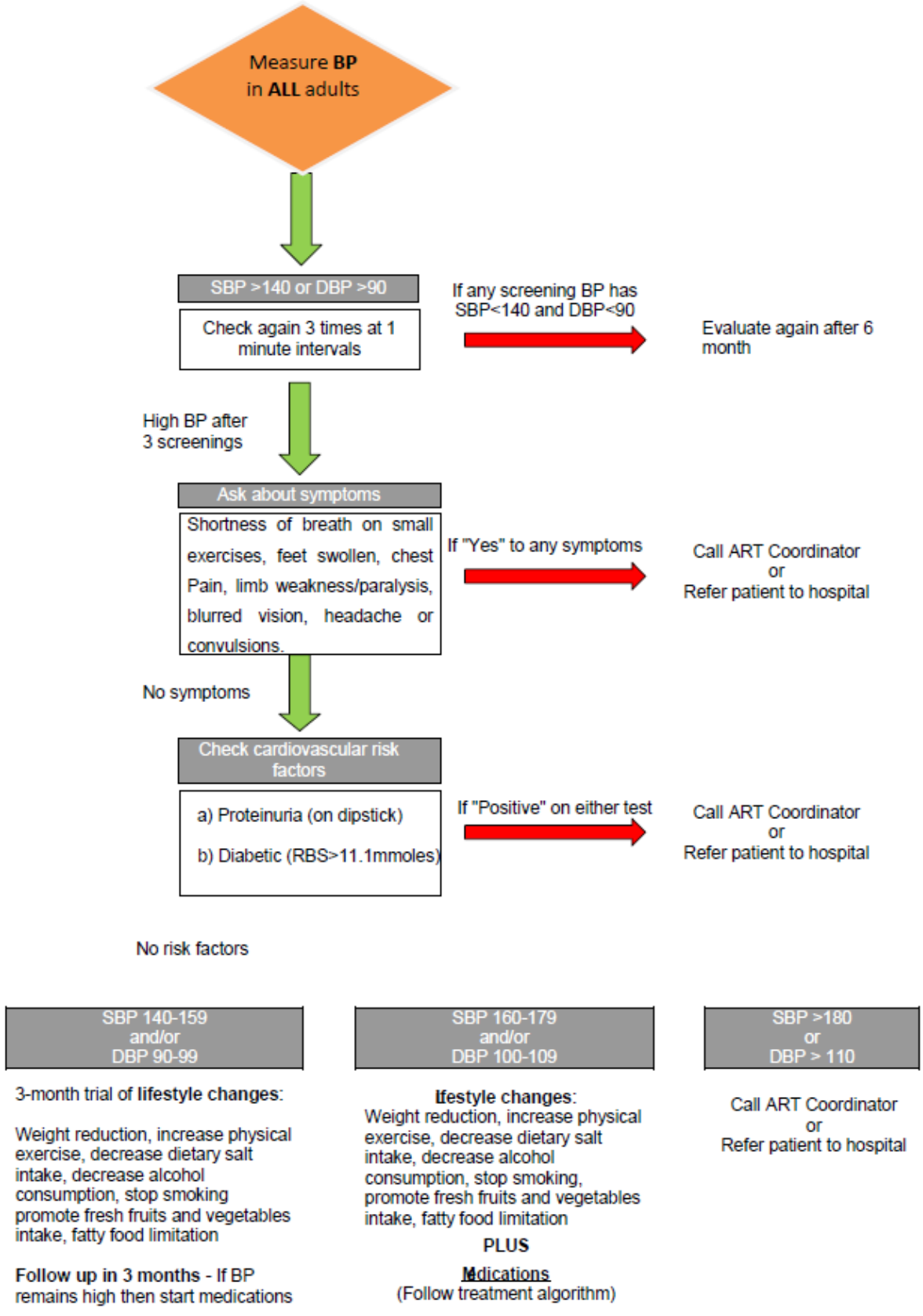


Figure S3b: Hypertension Drug Use Algorithm

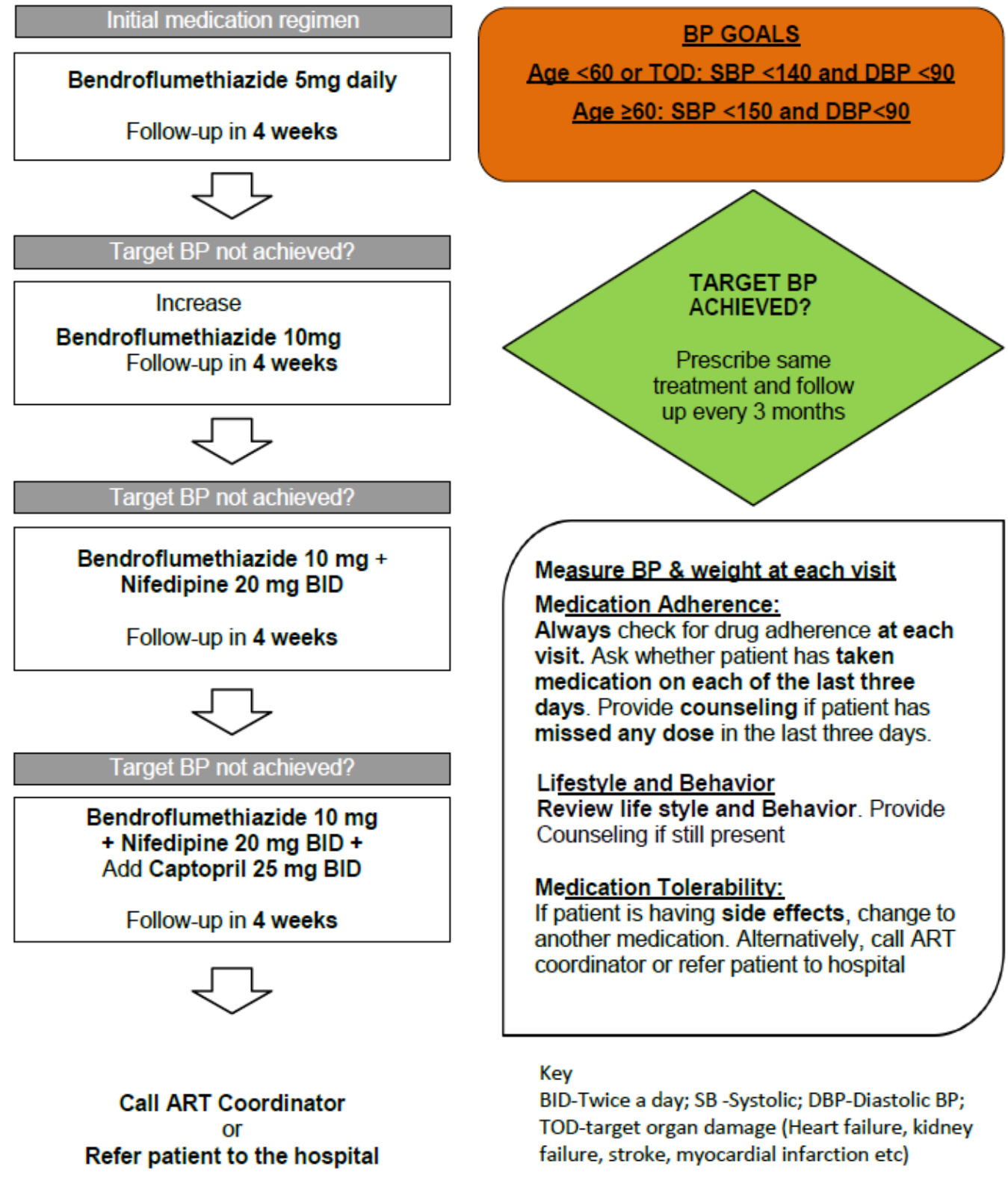


Figure S3c: Diabetes Management Algorithm

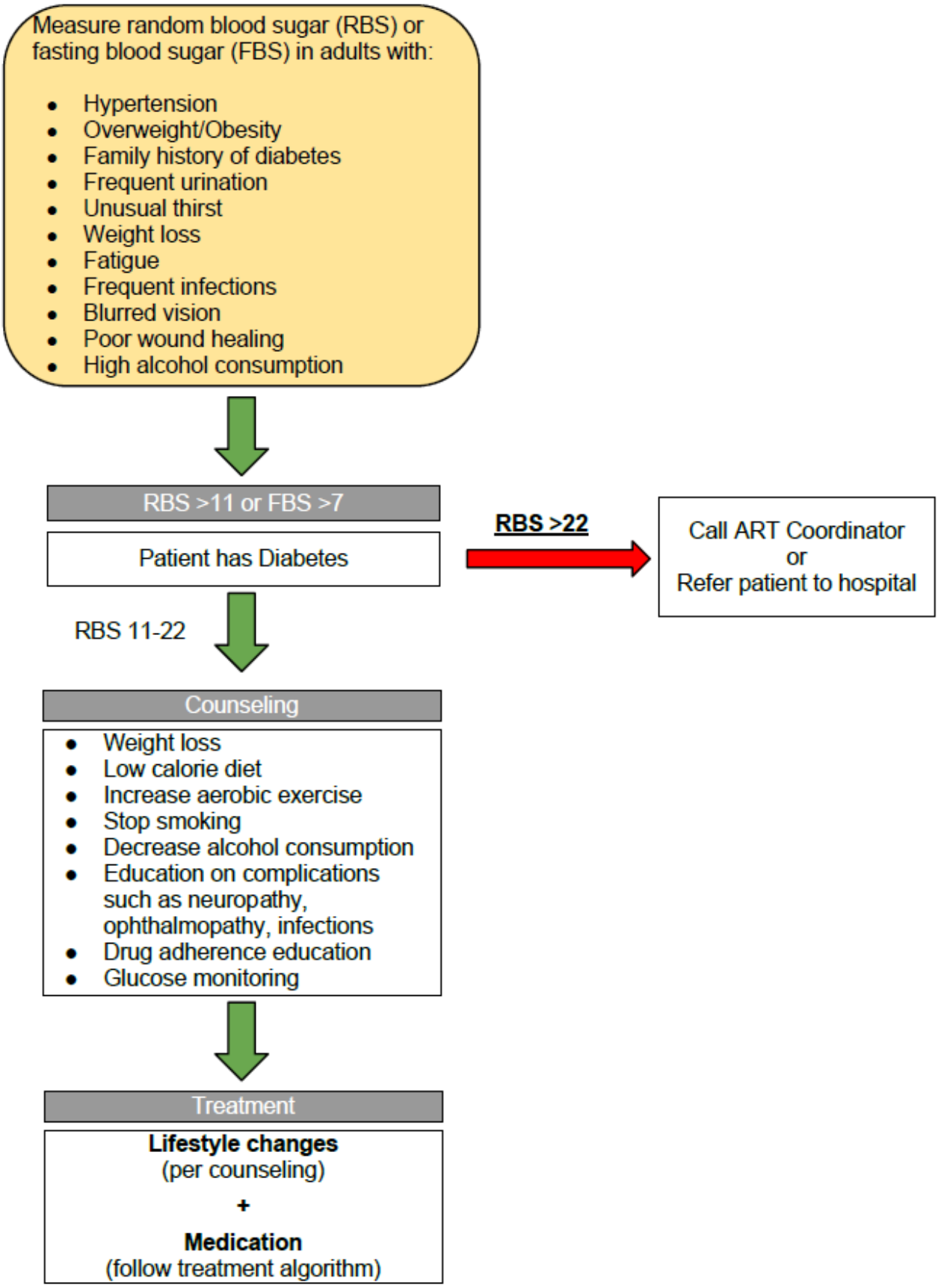


Figure S3d: Diabetes Drug Use Algorithm

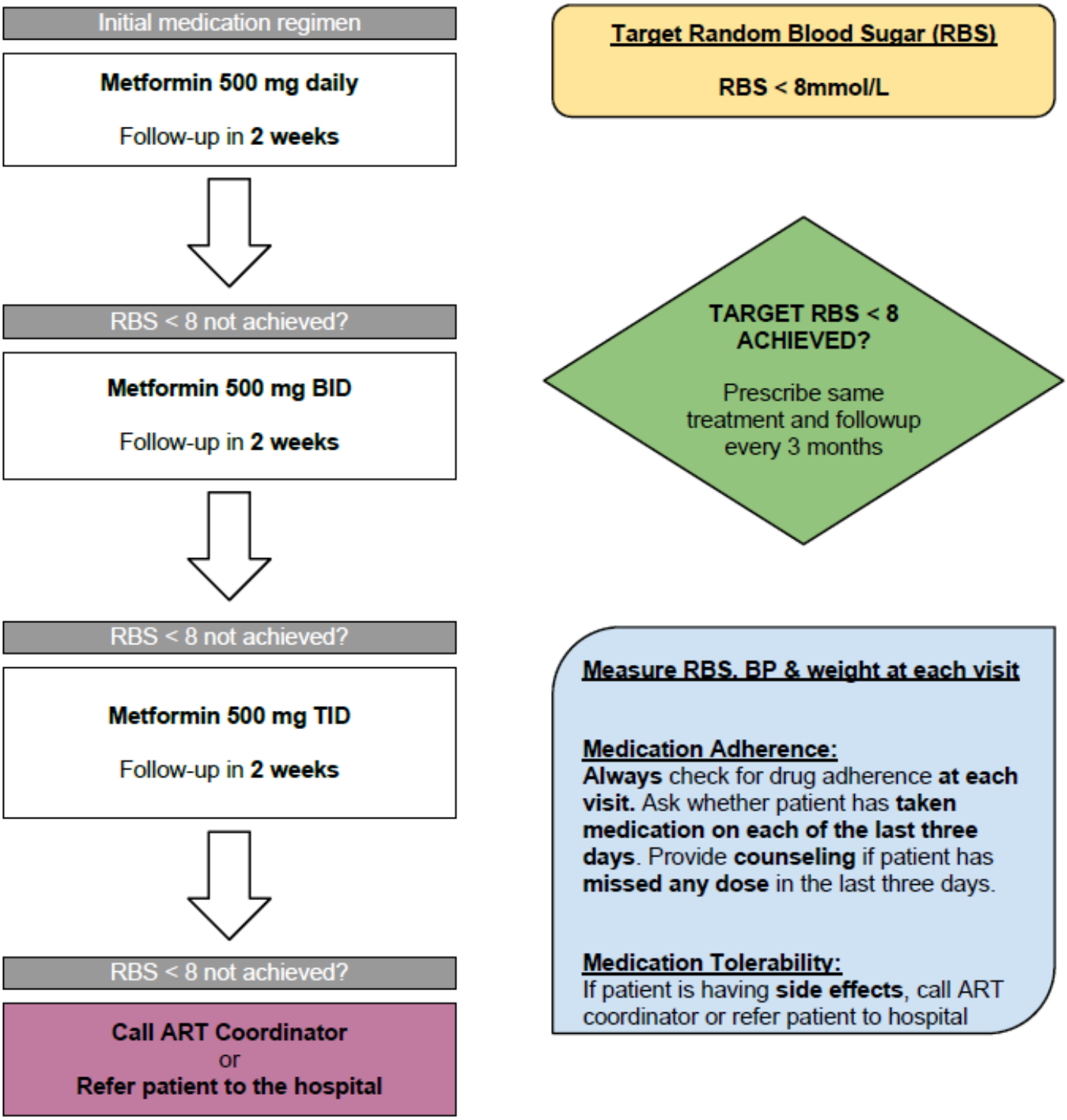


Figure S4: SEARCH Clinic Adaptation of HIV Treatment Guidelines

Figure S4a: Uganda-West

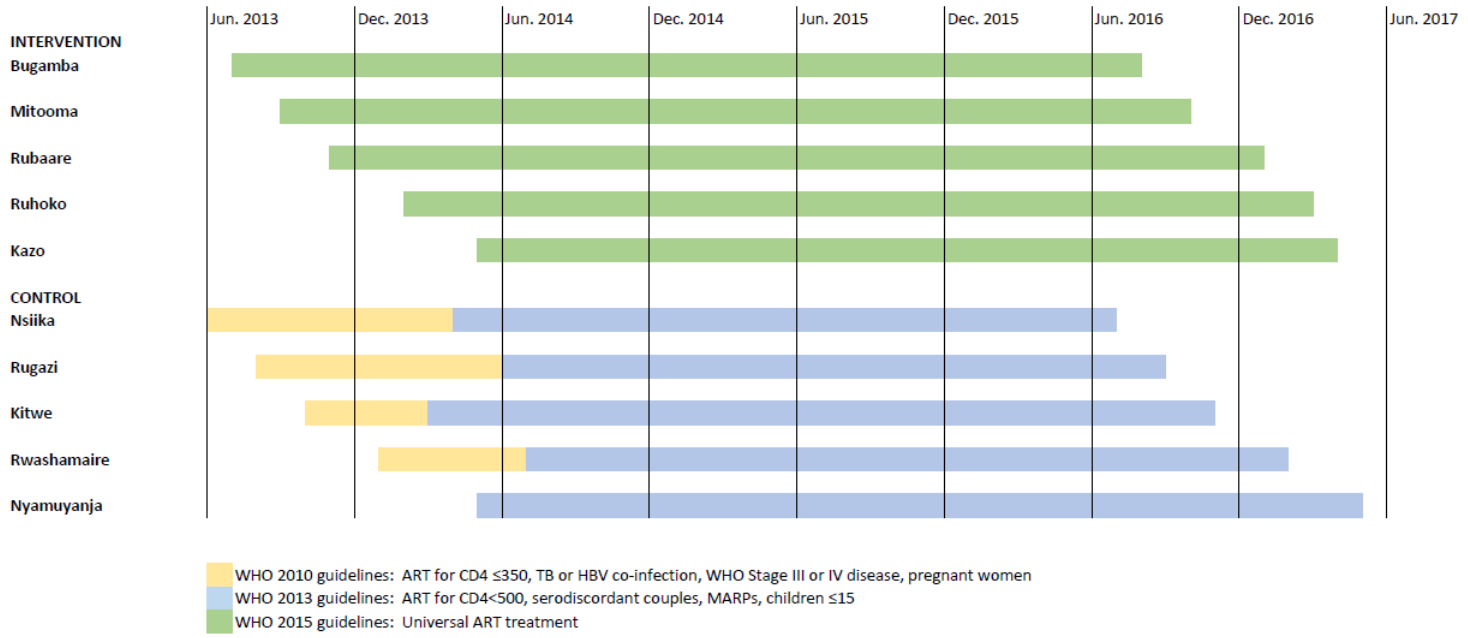


Figure S4b: Uganda-East

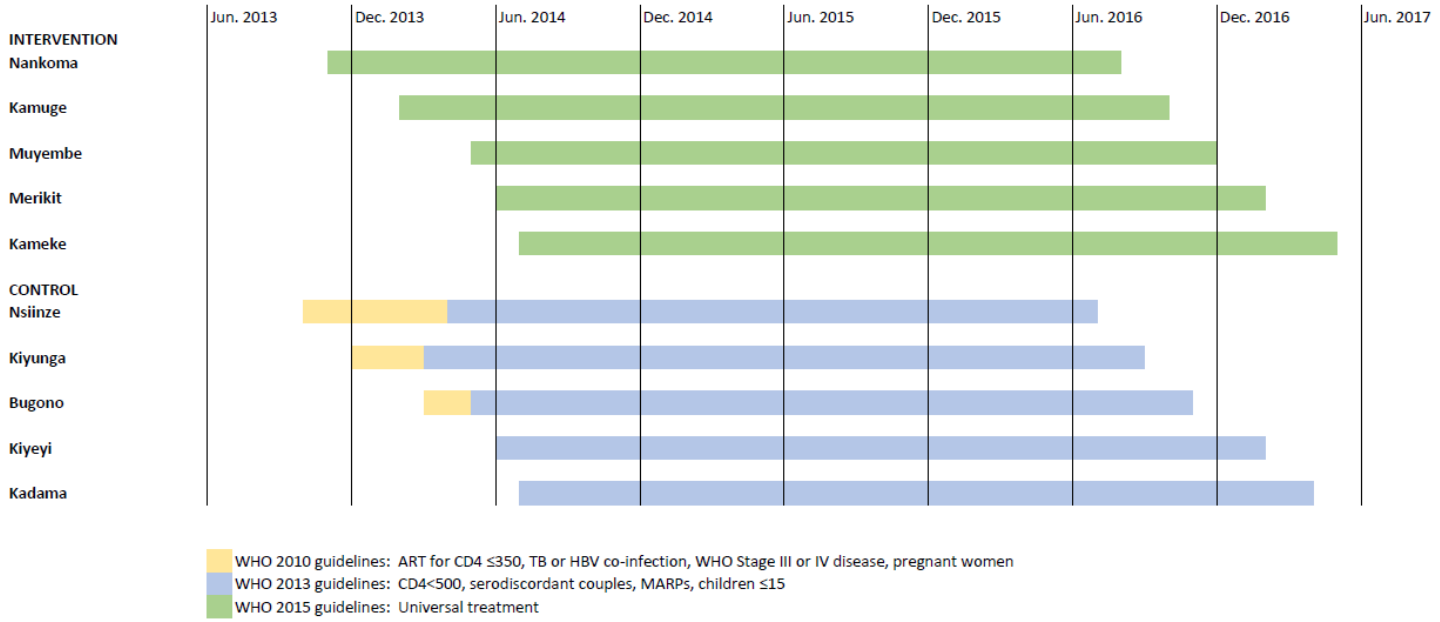


Figure S4c: Kenya

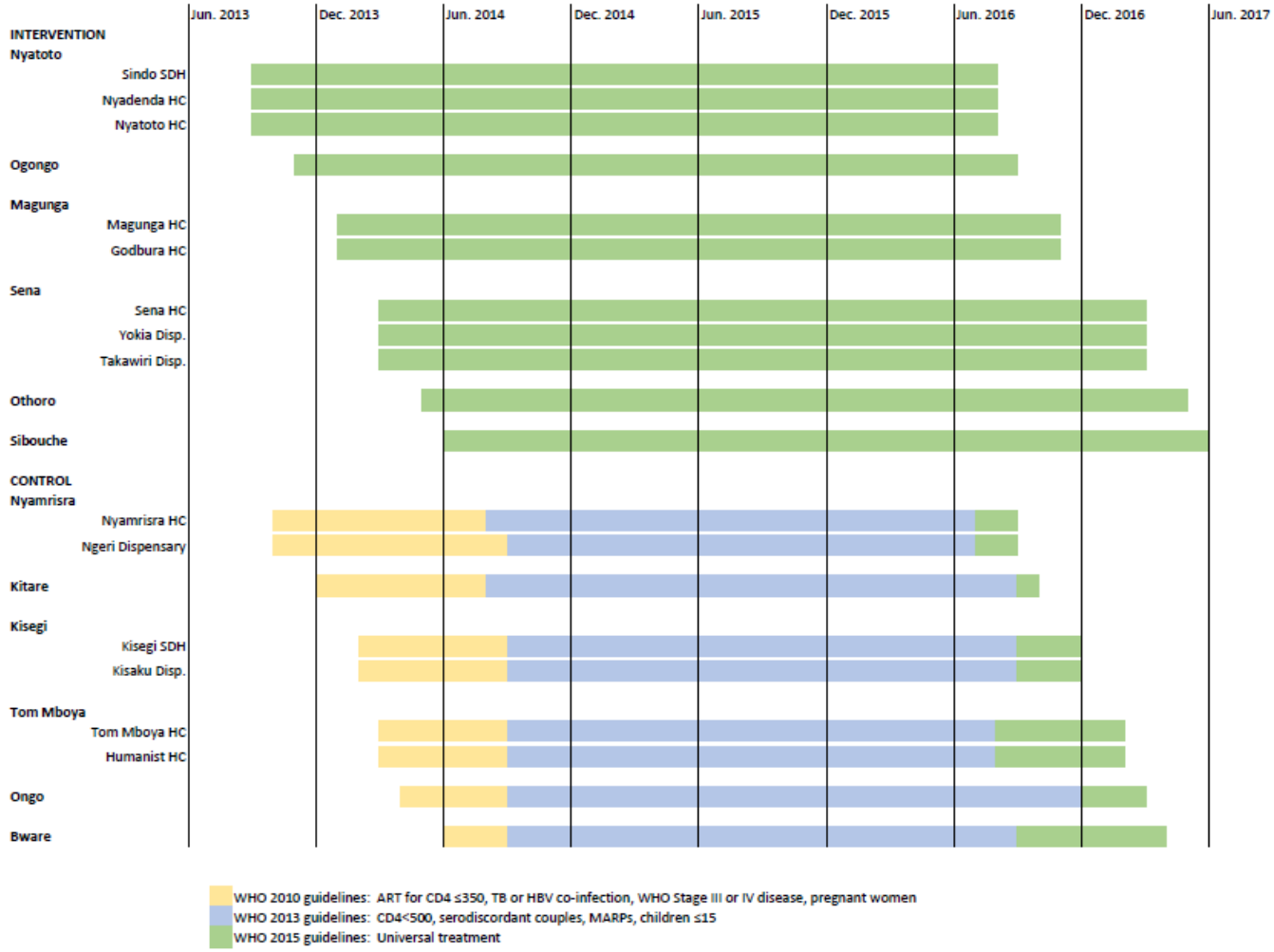
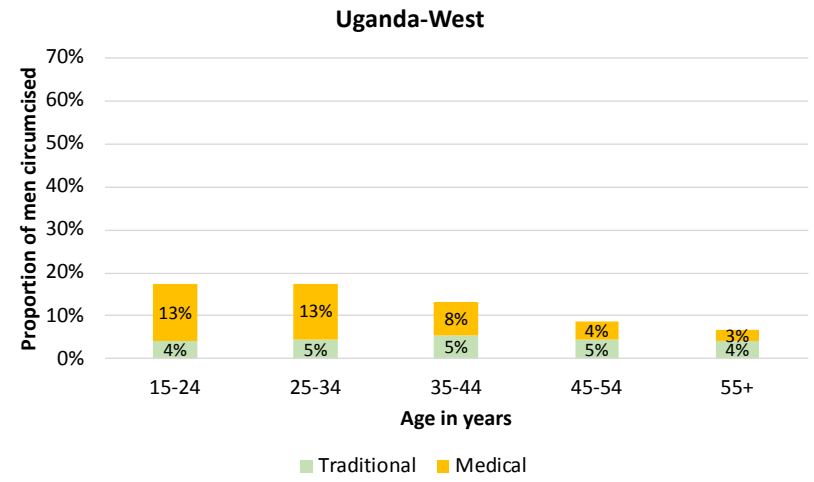
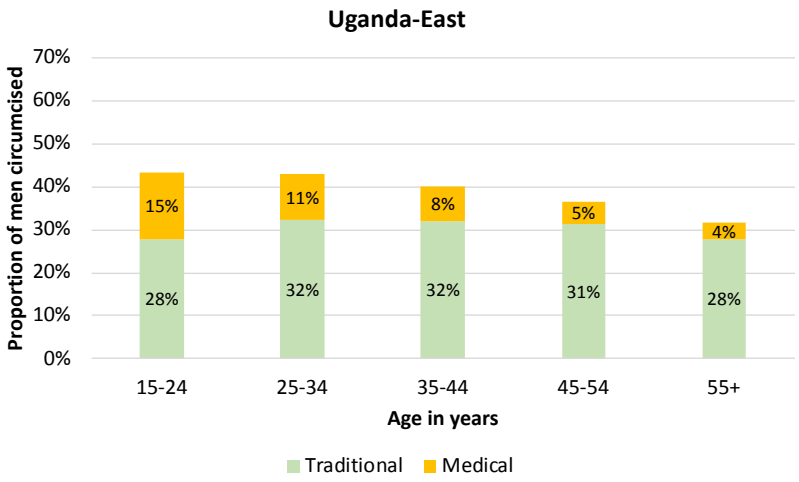


Figure S5: Baseline Male Circumcision by Age and Region. Proportion of male residents with medical and traditional circumcision at study baseline; 2,767 of 19,482 men (14%) circumcised in Uganda-West, 8,246 of 20,434 men (40%) in Uganda-East, and 9,584 of 20,763 men (46%) in Kenya.





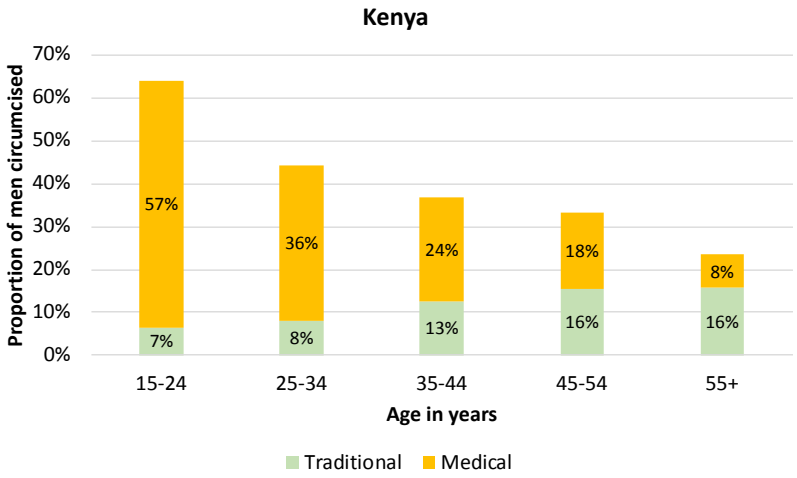


Figure S6: Baseline HIV Prevalence by Age, Gender and Region. Proportion of residents with known HIV status who are HIV-infected at study baseline (rapid antibody test or documented HIV+ from Ministry Record); 2,873/43,769 (7%) in Uganda-West, 1,590/44,764 (4%) in Uganda-East, 9,066/46,951 (19%) in Kenya.

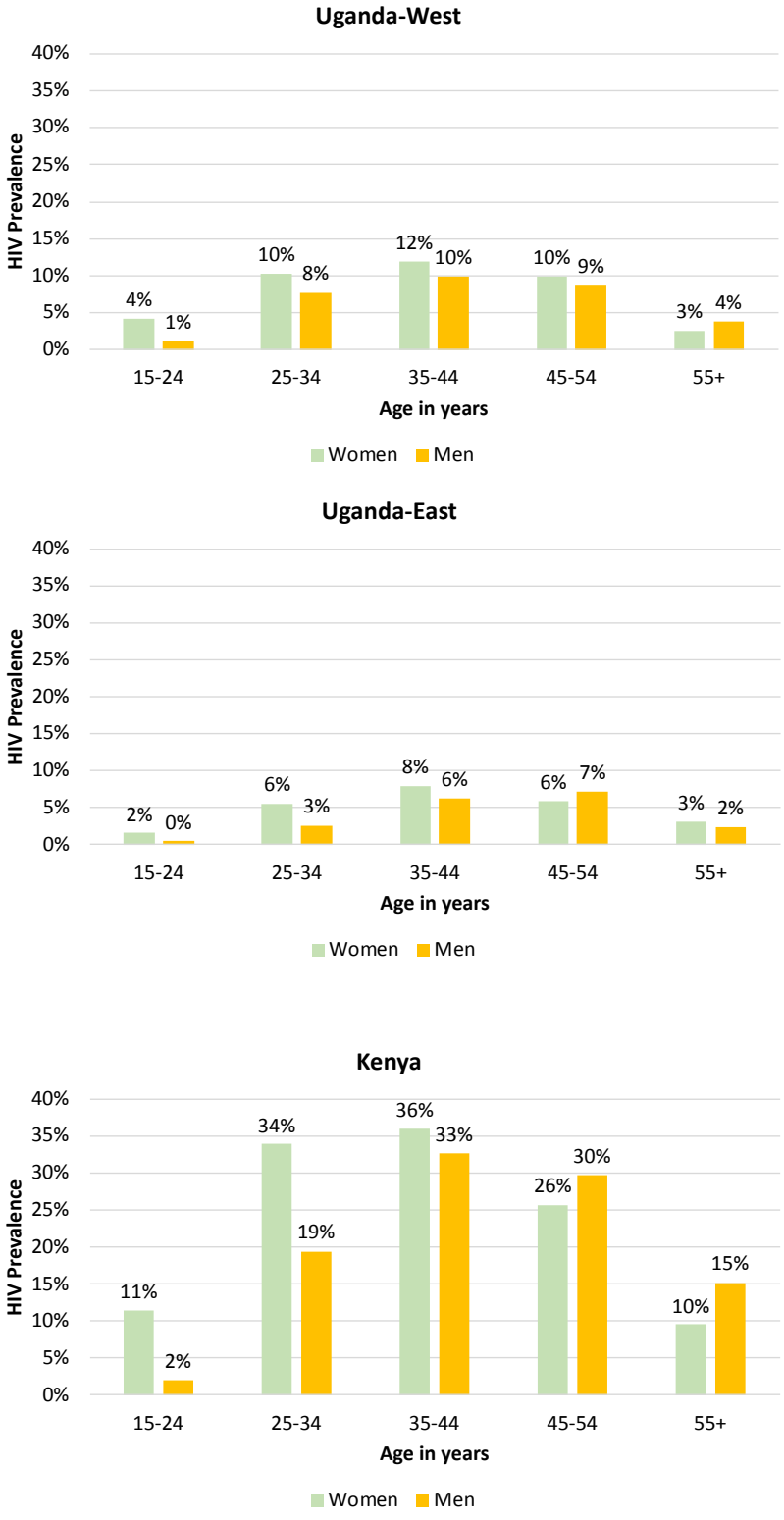


Figure S7: Antiretroviral Therapy Initiation Among HIV-Infected Persons Not on Therapy at Baseline by Baseline CD4+ Cell Count Strata. Among baseline residents with known HIV-infection at baseline, seen at baseline testing, and with no record of prior ART use; N=1,304 with CD4+ T cell count <350 cells/µl; N= 1,216 with CD4+ T cell count 350-500 cells/µl; N=2,786 with CD4+T cell count >500 cells/µl. Community-level estimates of probability of initiating ART by 6,12, 24 and 36 months based on Kaplan-Meier, censoring at death or outmigration.

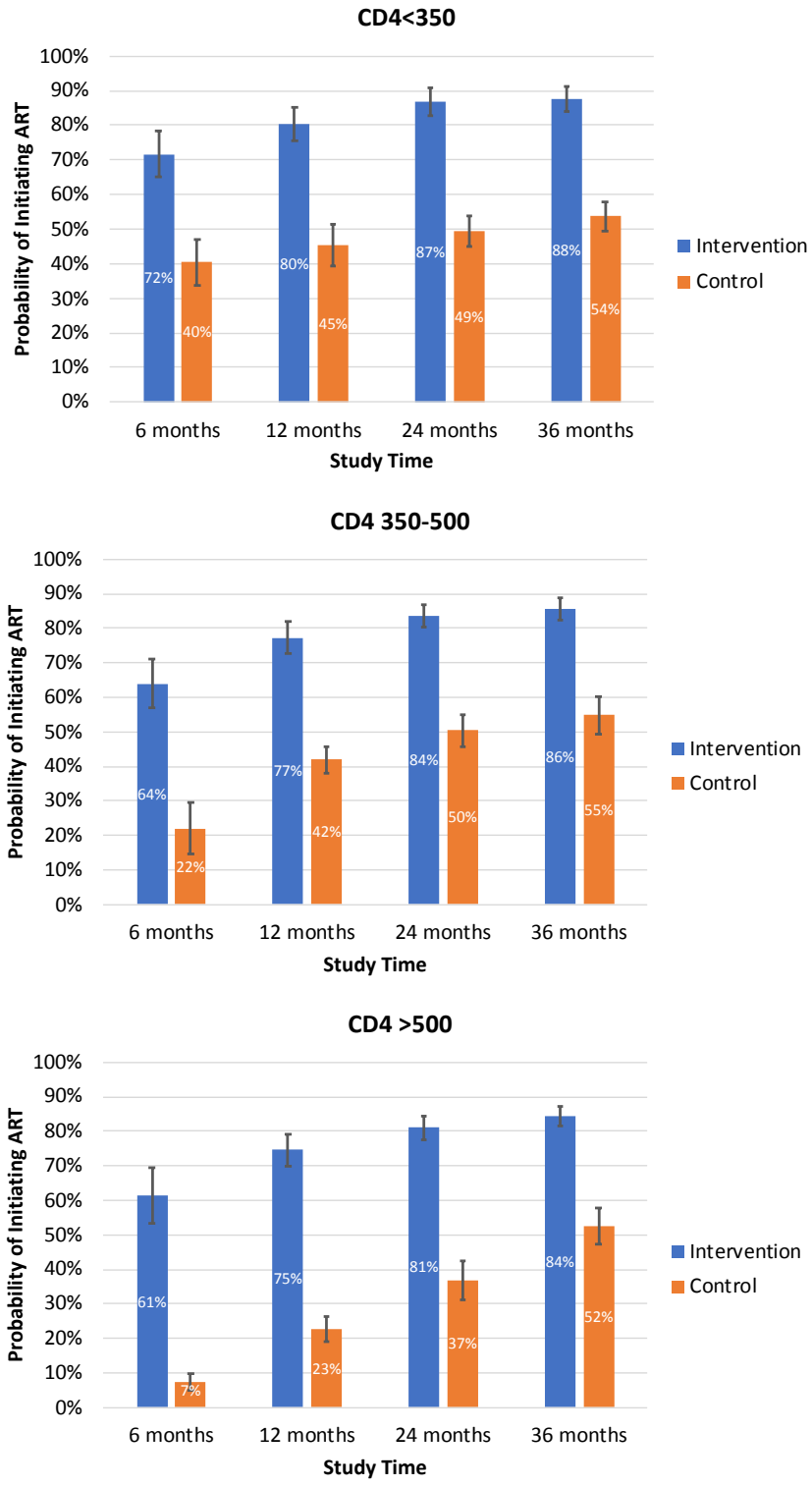


Figure S8: Population-Level HIV RNA Suppression at Year 3 by Gender and Age. Among all residents at Year 3 (including in-migrants identified through Year 3 re-census). Community-level estimates of suppression adjusted for incomplete measures of HIV serostatus and HIV RNA using individual-level TMLE; adjustment variables: sex (age-stratified estimates only), age group (sex-stratified estimates only), marital status, education, occupation, alcohol use, household wealth, mobility, prior HIV testing, and care status; comparison between arms based on community-level TMLE.

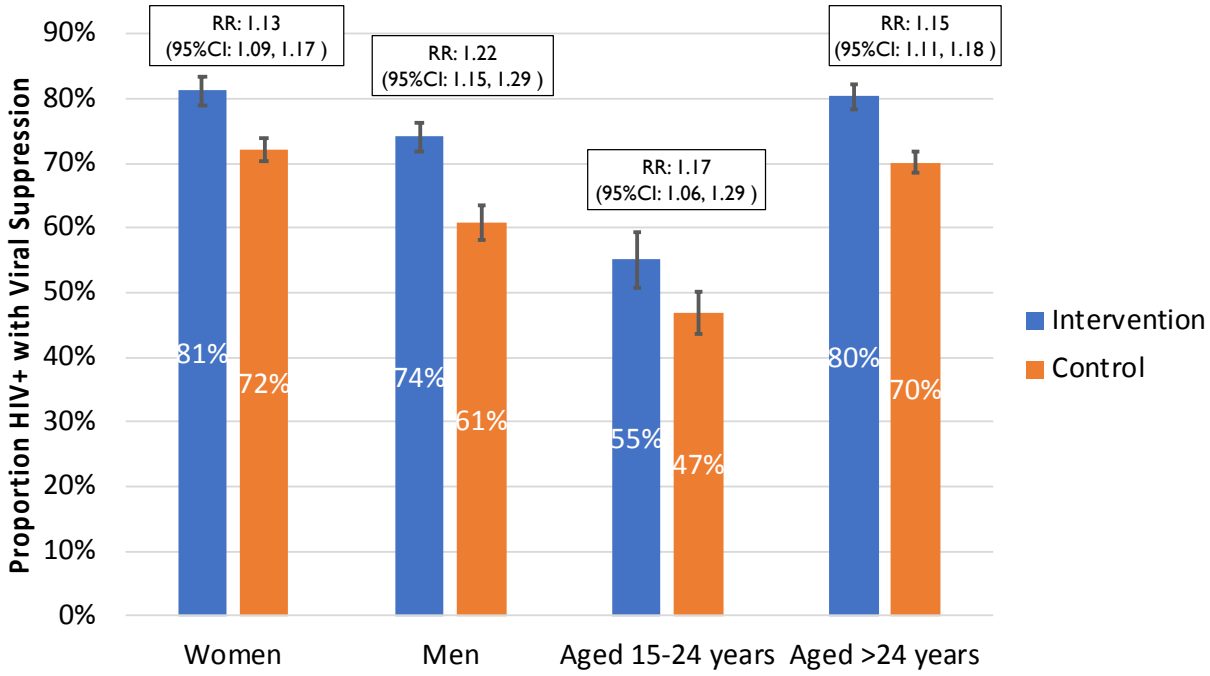
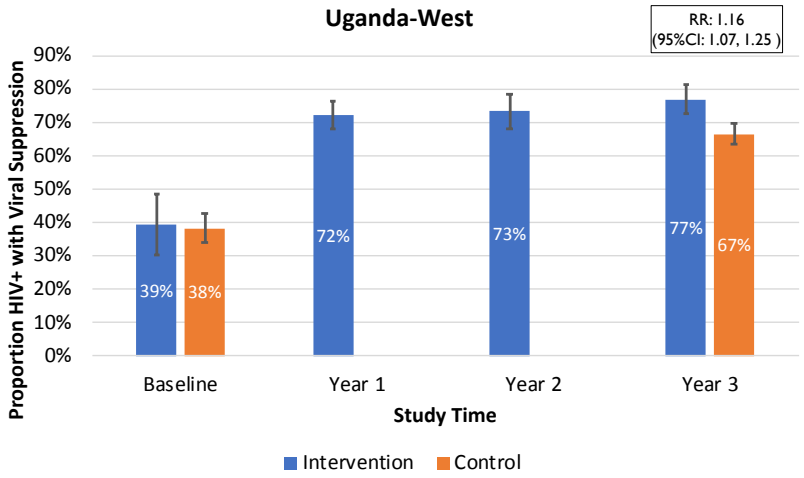
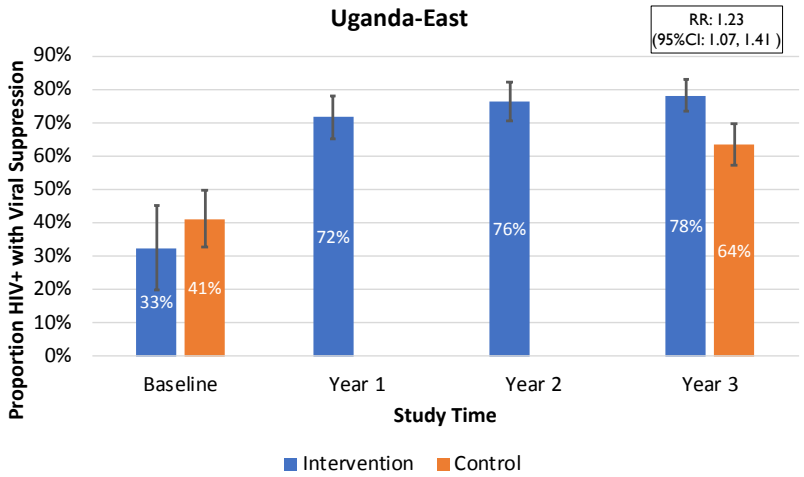


Figure S9: Population-level HIV RNA Suppression in HIV-infected Adults over Time by Region. Among all residents at Year 3 (including in-migrants identified through Year 3 re-census). Community-level estimates of suppression adjusted for incomplete measures of HIV serostatus and HIV RNA using individual-level TMLE; adjustment variables: sex, age group, marital status, education, occupation, alcohol use, household wealth, mobility, prior HIV testing, and care status; comparison between arms based on community-level TMLE.





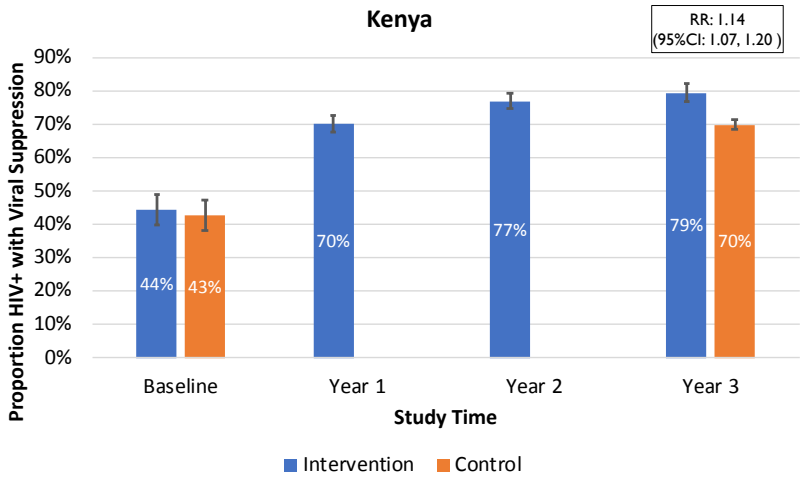


Figure S10: HIV RNA Suppression at Year 3 among Baseline HIV-infected Adults by Baseline HIV Care Status. Among baseline residents with HIV infection at study baseline. "No prior care at baseline" (N=4,315): no ministry record of prior HIV care; "Prior care no ART at baseline" (N=1,727): ministry record of prior care but absence of documented ART start date and HIV RNA level not <500 copies/ml; "ART, suppressed at baseline" (N=4,778): HIV RNA level <500 copies/ml; "ART, not suppressed at baseline" (N=768): ministry record of prior ART start and HIV RNA level ≥500 copies/ml. Community-level estimates of suppression censored at death and out-migration and adjusted for incomplete measures of HIV RNA using individual-level TMLE; adjustment variables: sex, age group, marital status, education, occupation, alcohol use, household wealth, mobility, prior HIV testing, and campaign attendance; comparison between arms based on community-level TMLE.

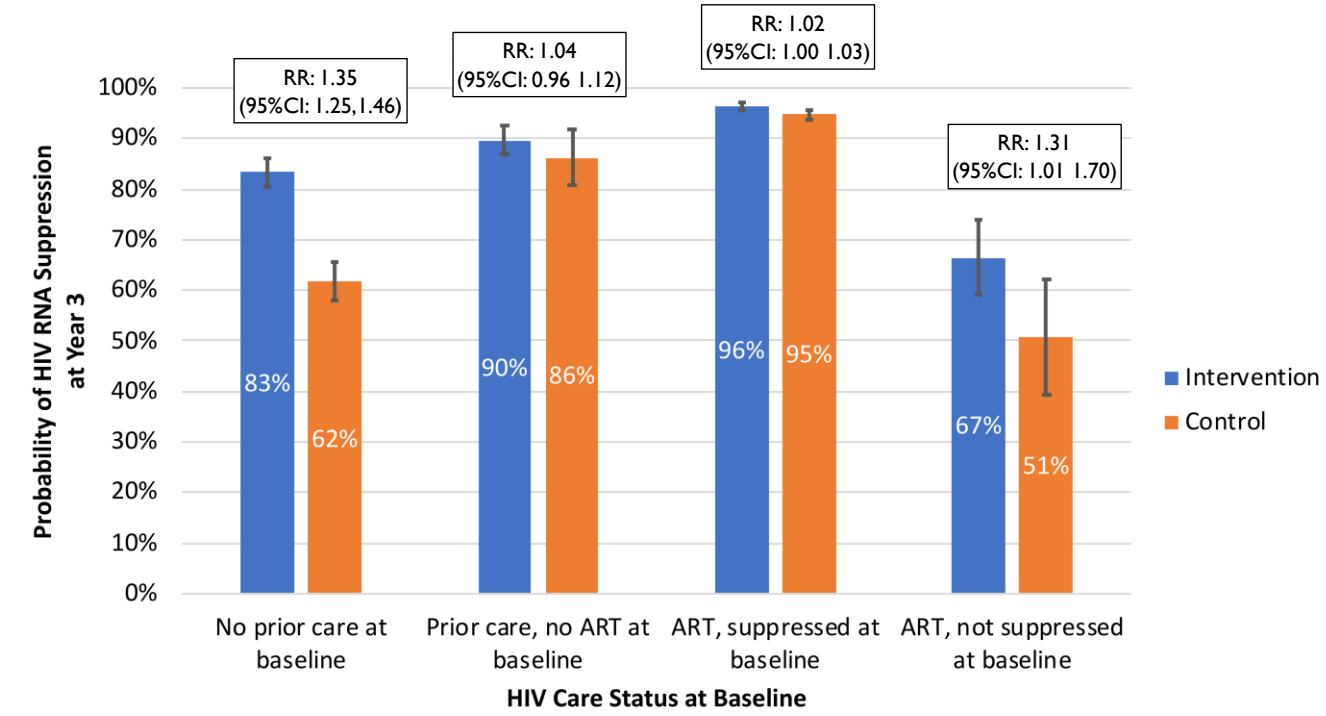


Figure S11: Measurement of Primary Endpoint: 3-Year HIV Cumulative Incidence. Patient flow by intervention versus control arm.

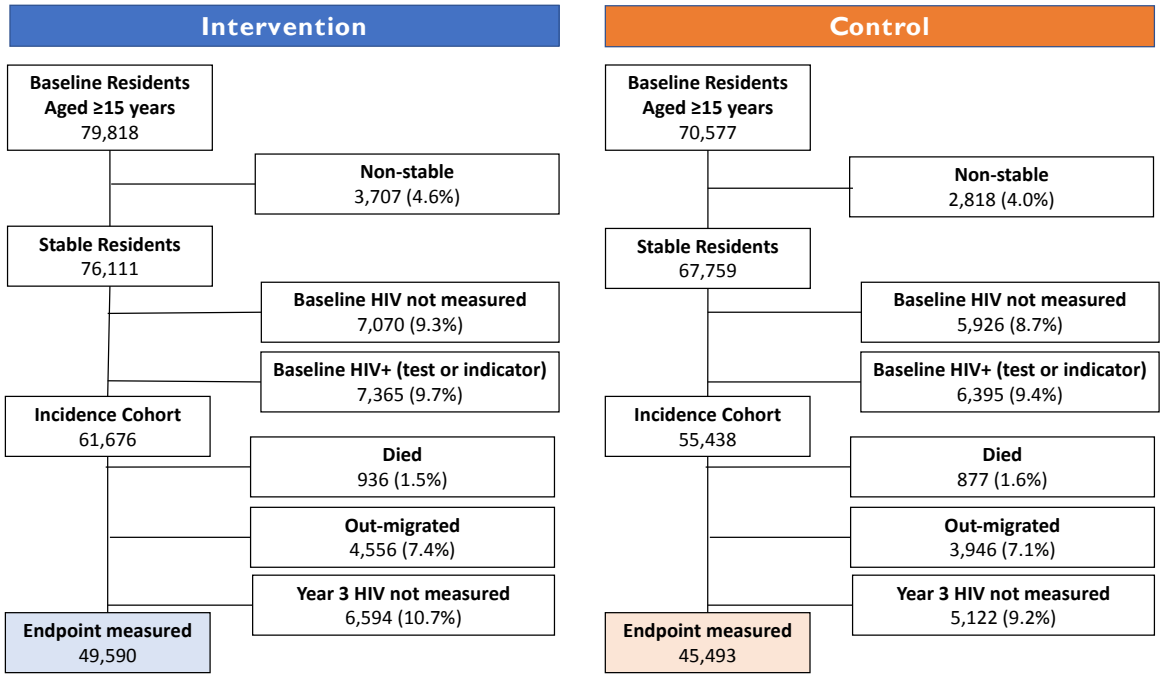


Figure S12: CONSORT Diagram for Primary HIV Incidence Endpoint. 3-year cumulative HIV incidence among baseline stable residents who were HIV-uninfected at baseline.

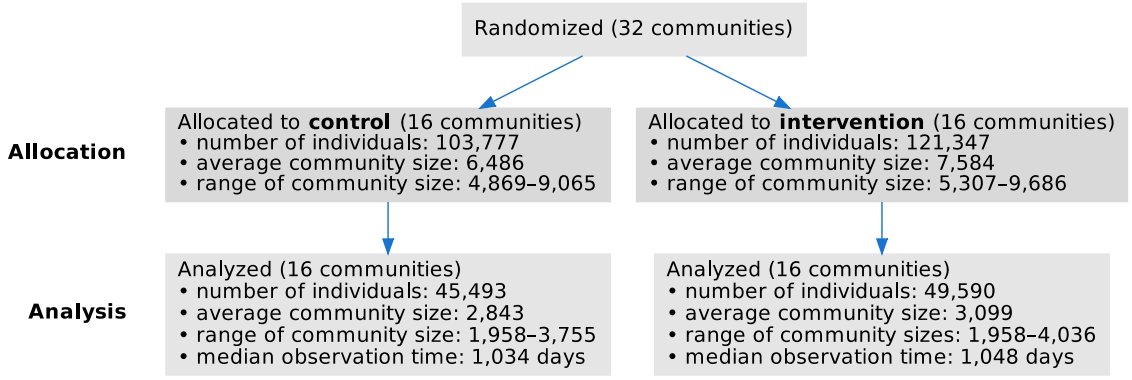


Figure S13: Three-year HIV Cumulative Incidence in Intervention vs. Control Arm Among Pre-specified Subgroups. Among incidence cohort of baseline HIV-uninfected stable residents who were alive, not out-migrated and with HIV serostatus measured at Year 3. Women: N=53,611; Men: N=41,472; Aged 15-24 years: N=30,361; Aged ≥25 years N=64,722; Non-mobile (<1 month in past year away from community): N= 87,068; uncircumcised men: N=27,747. Comparison between arms based on community-level TMLE.

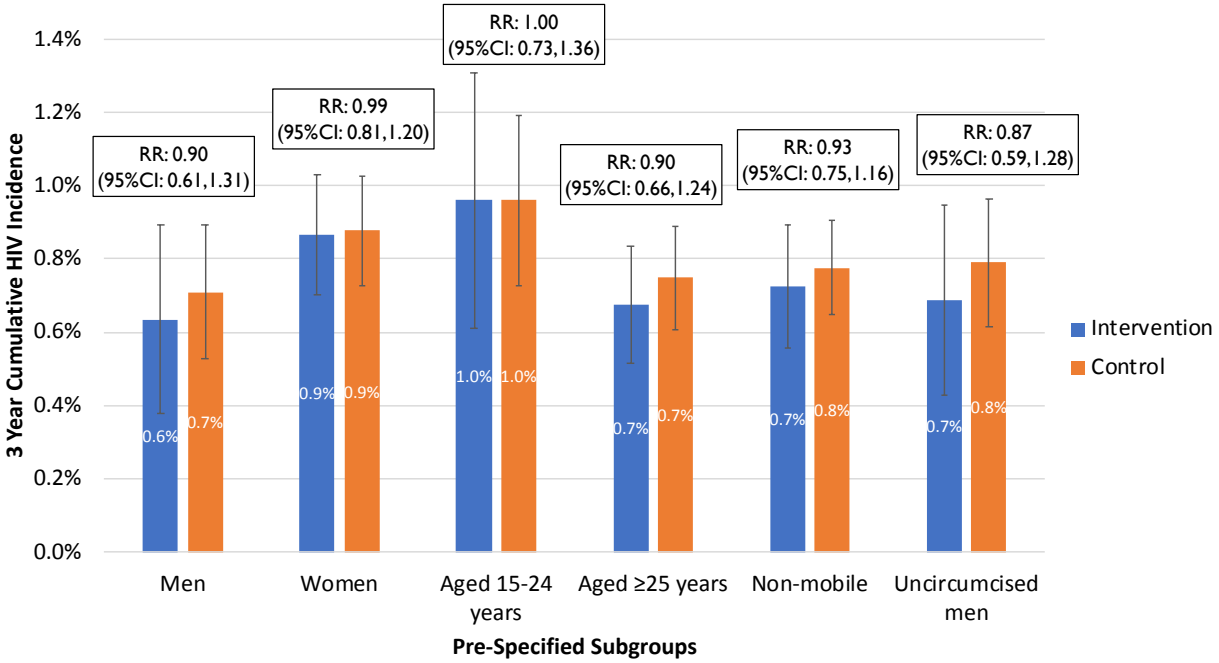


Figure S14: Three-year HIV Cumulative Incidence in Intervention vs. Control Arm by Region. Among incidence cohort of baseline HIV-uninfected stable residents who were alive, not out-migrated and had HIV serostatus measured at Year 3. Uganda-West: N= 31,633; Uganda-East: N= 33,916; Kenya: N= 29,534. Comparison between arms based on community-level TMLE.

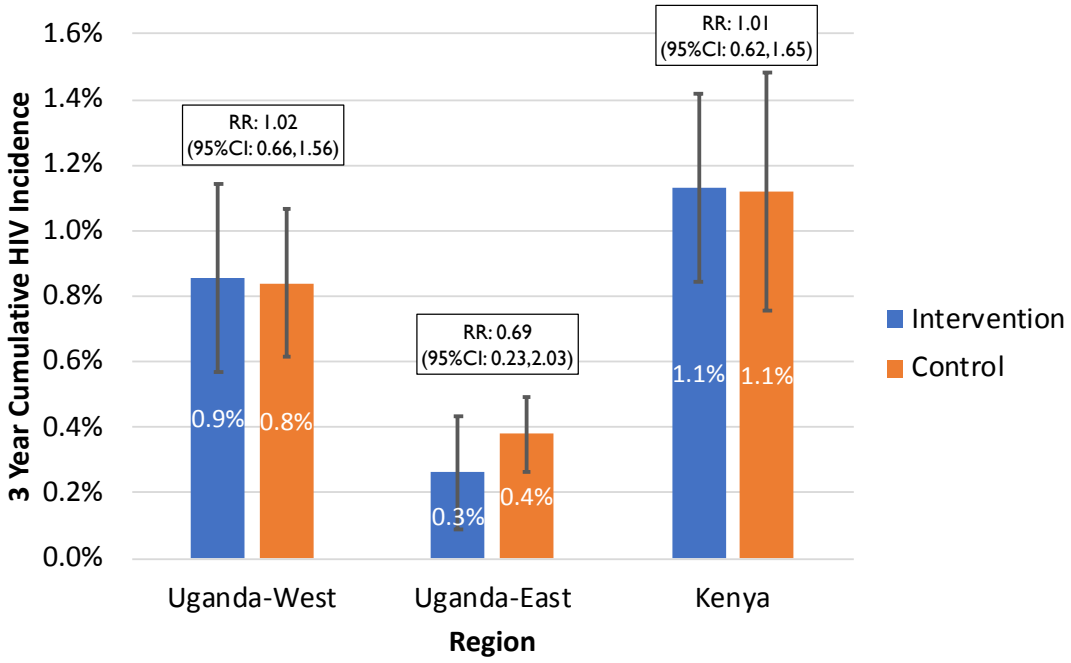


Figure S15: Annual HIV Incidence Cohorts in Intervention Arm. Number of residents of 16 intervention communities (inclusive of in-migrants and newly 15-year-olds) who were aged≥15 years and had a negative HIV test at baseline, Year 1 and Year 2, respectively; of those, number of residents (inclusive of those who had out-migrated) who had a repeat HIV test one year later.

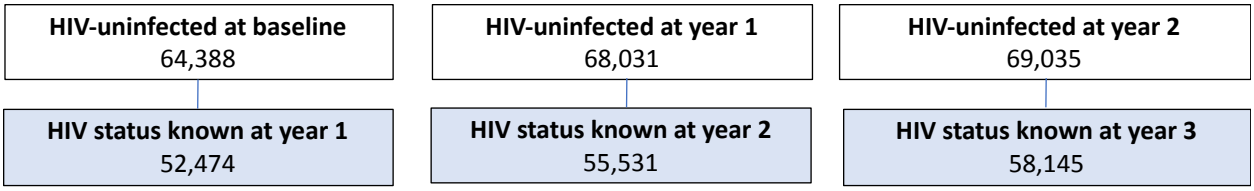
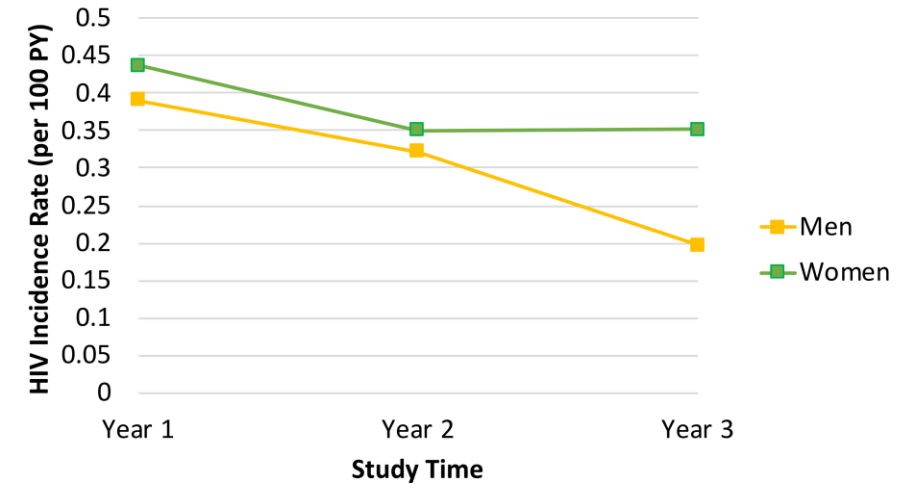


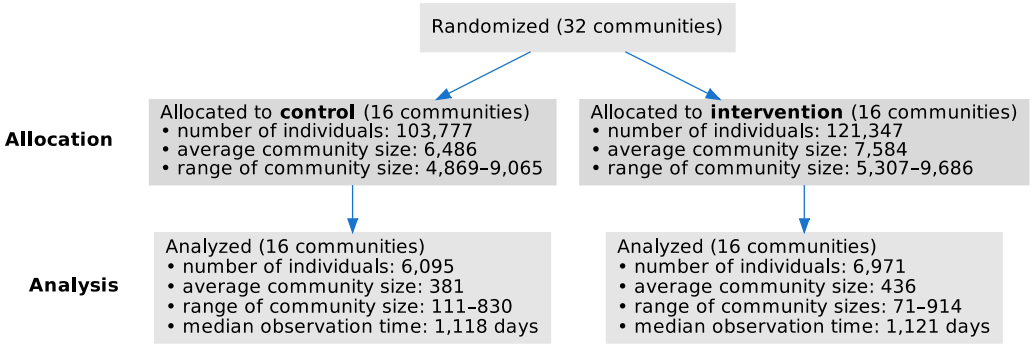
Figure S16: Change in HIV Incidence Over Time by Gender in the Intervention Arm. Incidence rate calculated in 3 annual incidence cohorts of HIV-uninfected adult residents (including in-migrants) with repeat HIV test one year later (including out-migrants) by gender. Among Men: Year 1: N= 22,803, 22,463 person-years follow-up (PY); Year 2: N=23,925, 22,938 PY; Year 3: N=25,106, 22,735 PY. Among Women: Year 1: N= 29,671, 29,512 PY; Year 2: N=31,606, 30,433 PY; Year 3: N=33,039, 29,831 PY. For incident infections, the date of infection was imputed as the midpoint of the time between repeat HIV tests. *Relative rate (Year 3 vs. Year 1) based on Poisson generalized estimating equations, adjusted for age and mobility, and using exchangeable covariance matrix.



Annual HIV Incidence (per 100 Person Years)	Study Year 1	Study Year 2	Study Year 3	Relative Rate* (95% CI)
Men	0.39	0.32	0.20	0.50 (95% CI 0.34, 0.72)
Women	0.44	0.35	0.35	0.82 (95% CI 0.63, 1.07)

Figure S17: CONSORT Diagrams for Mortality End Points. Death due to illness among:

A) Baseline stable residents who were HIV infected at baseline- excluding 200 of the 13,266 (1.5%) with missing vital status.



B) All baseline stable residents

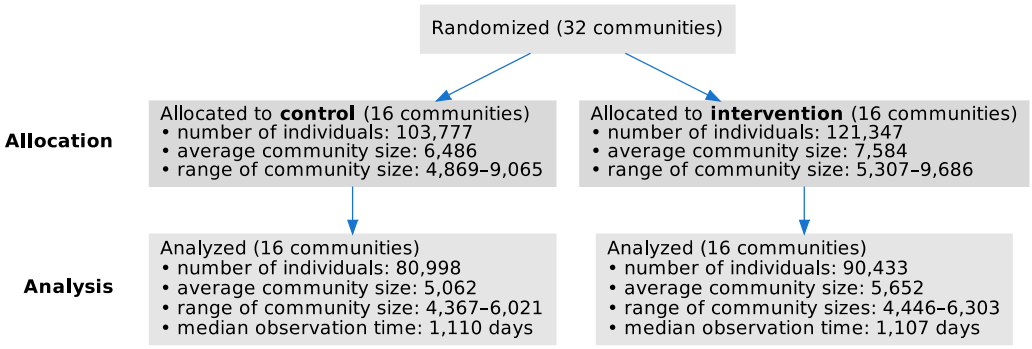


Figure S18: CONSORT Diagram for TB Endpoint. HIV-TB or death due to illness among baseline stable residents who were HIV-infected at baseline or with unknown baseline HIV status.

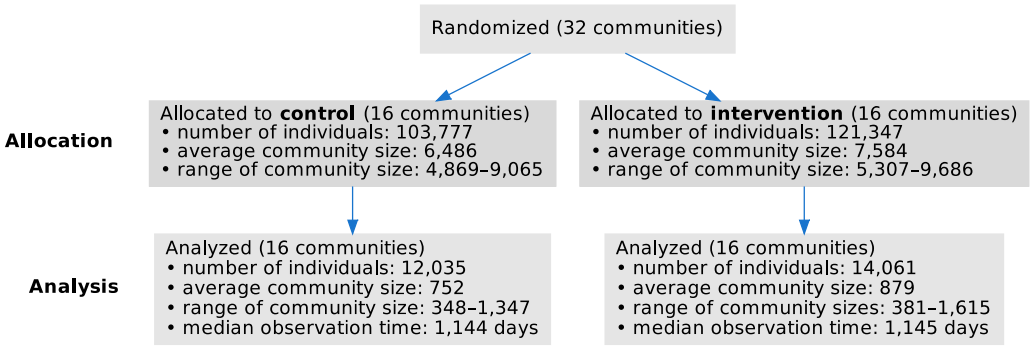
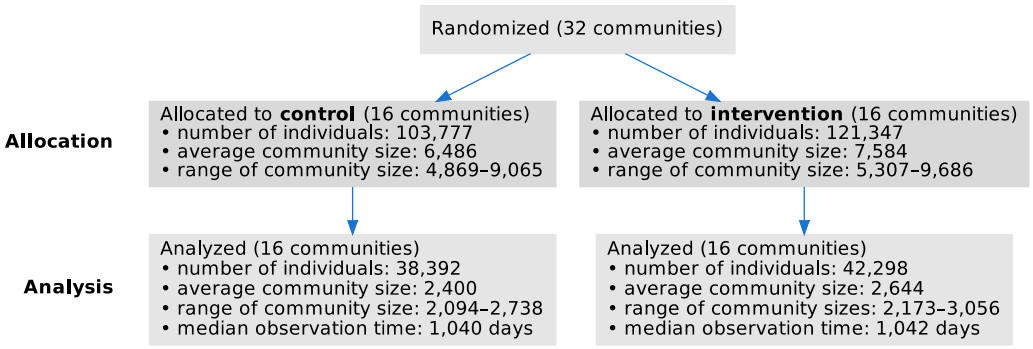


Figure S19: CONSORT Diagrams for Hypertension Endpoints. Hypertension control among:

A) Baseline stable adult residents ≥30 years with prevalent hypertension at Year 3



B) Baseline stable adult residents ≥30 years with prevalent hypertension and HIV-infection at Year 3

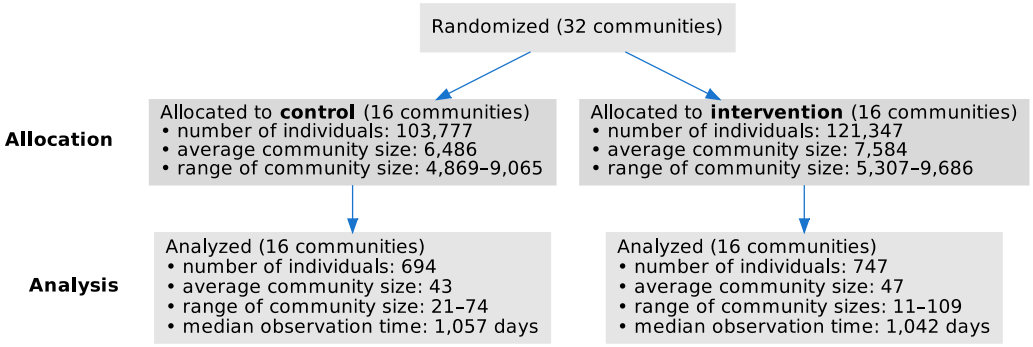


Figure S20: Control of Prevalent Hypertension (HT) and HIV in Intervention vs. Control Arm. Among baseline stable residents and aged ≥30 years with prevalent HT, all measures adjusted for incomplete measures of HT control using individual-level TMLE (adjustment variables: age, sex, marital status, education, occupation, alcohol use, wealth, mobility, BMI, and campaign attendance); *further adjusted for incomplete measures of HT prevalence; **further adjusted for incomplete measures of viral suppression. Comparison between arms based on community-level TMLE.

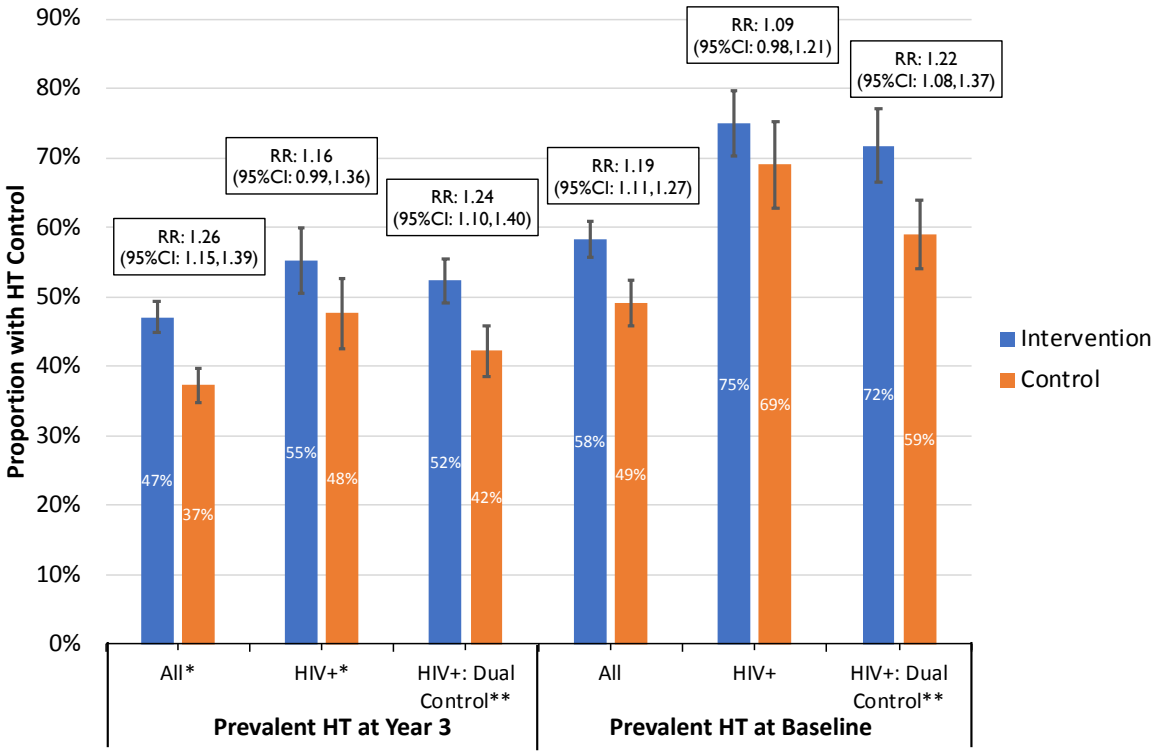


Figure S21: Control of Prevalent Hypertension or Diabetes and HIV in Intervention vs. Control Arm. Among baseline stable residents and aged ≥30 years with prevalent hypertension or diabetes (NCD), all measures adjusted for incomplete measures of NCD control using individual-level TMLE (adjustment variables: age, sex, marital status, education, occupation, alcohol use, wealth, mobility, BMI, and campaign attendance); *further adjusted for incomplete measures of NCD prevalence; **further adjusted for incomplete measures of viral suppression. Comparison between arms based on community-level TMLE.

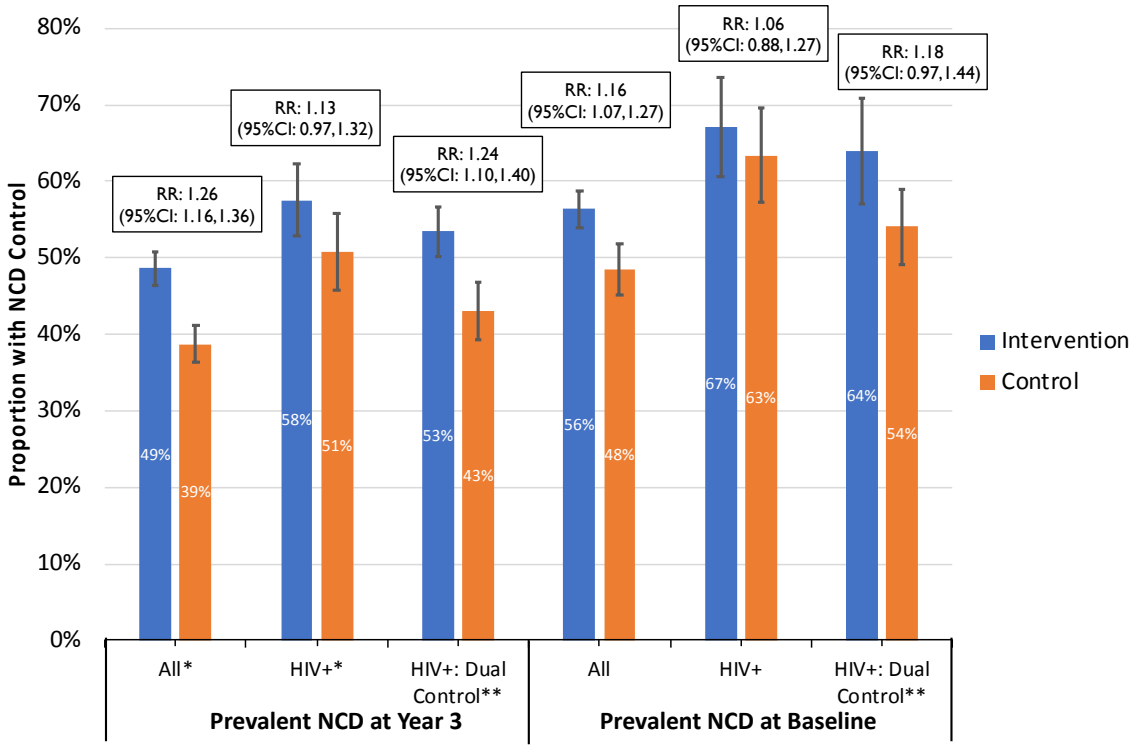


Table S1: Endpoint Measurements

Endpoint	Definition of Measurement
Cumulative HIV Incidence at 3 years	Confirmed rapid HIV antibody testing with Geenius and Western Blot confirmation at Year 3 campaigns
Annual HIV incidence	Rapid HIV antibody testing at annual health campaigns in the intervention arm
Antiretroviral therapy initiation	Ministry of Health record of antiretroviral therapy initiation
HIV RNA level	Plasma HIV RNA level during annual health campaign measured with Roche assay
Mortality	Obtained by key informant report at Year 3 and classified as due to illness, childbirth, suicide or accident
Incident tuberculosis disease • With death due to illness • With HIV infection	TB registry at dispensaries in community, mortality as above, HIV status via registry or SEARCH HIV testing
Hypertension	Hypertension: Previous or current self-report of prior diagnosis OR previous or current systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg on all 3 measurements at the health campaign or on all measures if < 3 measurements done Uncontrolled Hypertension: Systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg on all 3 measurements at the health campaign or on all measures if < 3 measurements done Controlled Hypertension: At least one measurement where systolic blood pressure is < 140 mmHg and diastolic blood pressure is < 90 mmHg
Diabetes	Diabetes: Previous or current self-report of prior diagnosis OR Finger-prick blood glucose level >11 mmol/L Uncontrolled Diabetes: Blood glucose >11 mmol/L Controlled Diabetes: Blood glucose ≤ 11 mmol/L

Table S2: Baseline Characteristics by Randomization Arm

	Number of Residents (%)		
	Intervention (n=79,818)	**Control** (n=70,577)	**Total** (n=150,395)
Male sex	36,048 / 79,818 (45.2)	31,933 / 70,577 (45.2)	67,981 / 150,395 (45.2)
Age category			
15-20 yr	20,053 / 79,818 (25.1)	16,602 / 70,577 (23.5)	36,655 / 150,395 (24.4)
21-49 yr	44,047 / 79,818 (55.2)	39,975 / 70,577 (56.6)	84,022 / 150,395 (55.9)
≥50 yr	15,718 / 79,818 (19.7)	14,000 / 70,577 (19.8)	29,718 / 150,395 (19.8)
Marital status			
Single	23,692 / 79,604 (29.8)	19,392 / 70,436 (27.5)	43,084 / 150,040 (28.7)
Married	46,684 / 79,604 (58.6)	42,502 / 70,436 (60.3)	89,186 / 150,040 (59.4)
Widowed, divorced or separated	9,228 / 79,604 (11.6)	8,542 / 70,436 (12.1)	17,770 / 150,040 (11.8)
Polygamous marriage	9,575 / 79,595 (12.0)	9,210 / 70,429 (13.1)	18,785 / 150,024 (12.5)
Education			
Below primary school	50,912 / 79,656 (63.9)	45,691 / 70,404 (64.9)	96,603 / 150,060 (64.4)
Completed primary school	11,478 / 79,656 (14.4)	10,305 / 70,404 (14.6)	21,783 / 150,060 (14.5)
Any secondary school or higher	17,266 / 79,656 (21.7)	14,408 / 70,404 (20.5)	31,674 / 150,060 (21.1)
Occupation[a]			
Formal sector	19,753 / 79,597 (24.8)	15,733 / 70,434 (22.3)	35,486 / 150,031 (23.7)
High-risk informal sector	3,235 / 79,597 (4.1)	4,944 / 70,434 (7.0)	8,179 / 150,031 (5.5)
Low-risk informal sector	48,753 / 79,597 (61.2)	42,341 / 70,434 (60.1)	91,094 / 150,031 (60.7)
Other	3,595 / 79,597 (4.5)	3,201 / 70,434 (4.5)	6,796 / 150,031 (4.5)
No job or disabled	4,261 / 79,597 (5.4)	4,215 / 70,434 (6.0)	8,476 / 150,031 (5.6)
Household wealth index quintile[b]			
First, indicating least wealth	12,078 / 79,619 (15.2)	11,876 / 70,280 (16.9)	23,954 / 149,899 (16.0)
Second	13,474 / 79,619 (16.9)	12,652 / 70,280 (18.0)	26,126 / 149,899 (17.4)
Third	15,448 / 79,619 (19.4)	14,371 / 70,280 (20.4)	29,819 / 149,899 (19.9)
Fourth	17,384 / 79,619 (21.8)	15,703 / 70,280 (22.3)	33,087 / 149,899 (22.1)
Fifth, indicating most wealth	21,235 / 79,619 (26.7)	15,678 / 70,280 (22.3)	36,913 / 149,899 (24.6)
Stable residents[c]	76,111 / 79,816 (95.4)	67,759 / 70,577 (96.0)	143,870 / 150,393 (95.7)
Residents living with HIV	7,212 / 71,605 (10.1)	6,317 / 63,879 (9.9)	13,529 / 135,484 (10.0)
Residents with prevalent hypertension[d]	5,953 / 28,877 (20.6)	5,911 / 26,884 (22.0)	11,864 / 55,761 (21.3)

Abbreviations: HIV, human immunodeficiency virus

[a] A formal sector occupation was defined as a teacher, student, government worker, military worker, health worker, or factory worker. A high-risk informal sector occupation was defined as a fishmonger, fisher, bar owner, bar worker, transportation worker, or tourism worker. A low-risk informal sector occupation was defined as a farmer, shopkeeper, market vendor, hotel worker, homemaker, household worker, construction worker, or miner.

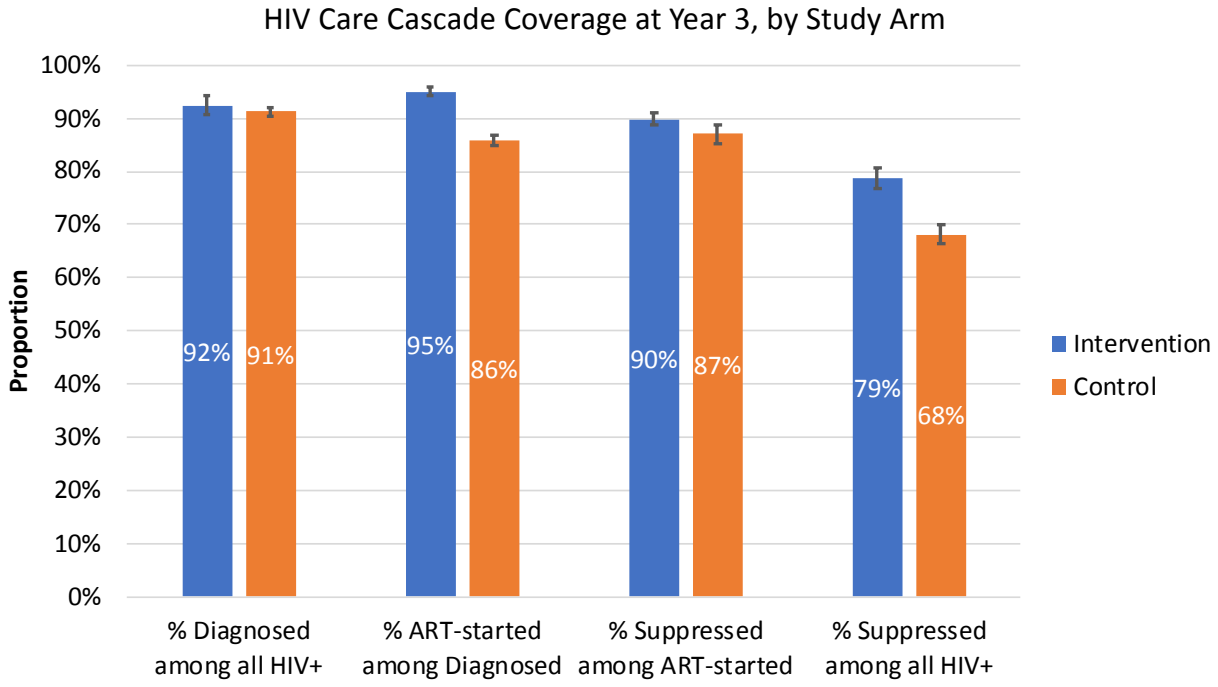
[b] Quintiles were based on a principle components analysis of the household wealth survey and were calculated at the level of the household.

[c] Stable residents were defined as residents who had spent at least 6 months of the previous year in the trial community.

[d] Adults 30 years of age or older were included in the analysis.

Table S3: HIV Care Cascade Coverage at Year 3, by Study Arm[a]

	Study Arm	Unadjusted proportion[b]	Adjusted estimate[c] (95% CI)
Proportion of HIV+ who were previously diagnosed	Intervention	96% (6702/6991)	92% (91%,94%)
	Control	94% (5871/6239)	91% (90%,92%)
Proportion of HIV+ previously diagnosed who had been treated with ART	Intervention	98% (6549/6702)	95% (94%,96%)
	Control	92% (5388/5871)	86% (85%,87%)
Proportion of HIV+ treated with ART who were virally suppressed	Intervention	90% (5737/6376)	90% (89%,91%)
	Control	87% (4586/5262)	87% (85%,89%)
Proportion of all HIV+ who were virally suppressed	Intervention	85% (5737/6738[d])	79% (77%,81%)
	Control	76% (4586/6042[e])	68% (67%,70%)



[a] Among all residents of SEARCH study communities aged ≥15 years at Year 3, including individuals who migrated into the study community by Year 3, excluding residents who died or migrated out of the community by Year 3.
[b] Unadjusted proportions calculated among persons contacted at Year 3 population-based testing; i) for the proportion of HIV+ who were previously diagnosed: number of HIV+ with prior HIV diagnosis / number of HIV+ at Year 3; ii) for the proportion of HIV+ previously diagnosed who had been treated with ART: number of HIV+ with prior documented ART use or with Year 3 HIV RNA<500 copies/ml / number of HIV+ with prior HIV diagnosis; iii) for the proportion of HIV+ treated with ART who were virally suppressed: number of HIV+ with Year 3 HIV RNA< 500 copies/ml / number of HIV+ with Year 3 HIV RNA measured and either prior documented ART or with Year 3 HIV RNA<500 copies/ml; and, iv) for the proportion of HIV+ who were virally suppressed: number of persons with Year 3 HIV RNA<500 copies/ml/ number of HIV+ with Year 3 HIV RNA measured.
[c] Adjusted proportions estimated among all residents of SEARCH study communities aged ≥15 years at Year 3, irrespective of known HIV status or contact at Year 3, adjusted for unknown HIV status at Year 3, and for missing HIV RNA level among HIV+ at Year 3. Adjustment used individual-level TMLE, with candidate adjustment set including sex, age group, marital status, education, occupation, alcohol use, household wealth, mobility, prior HIV testing, and care status.
[d] Excluding individuals known to be HIV+ but with missing HIV RNA; 253/6,991 (4%) of HIV+ contacted at Year 3; 1,248/8,048 (16%) of all known HIV+ at Year 3
[e] Excluding individuals known to be HIV+ but with missing HIV RNA; 197/6,239 (3%) of those contacted at Year 3; 1,024/7,075 (14%) of all known HIV+ at Year 3