Update | April 2014

Antiretroviral Treatment for Prevention of HIV and Tuberculosis

2013 update on current and planned research efforts

In asking for very strong evidence I would, however, repeat emphatically that this does not imply crossing every 't', and swords with every critic, before we act.

All scientific work is incomplete – whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time.

Austin Bradford Hill, "The Environment and Disease: Association or Causation?," Proceedings of the Royal Society of Medicine, 58 (1965), 295-300.

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Executive Summary

There is considerable scientific evidence supporting the use of antiretroviral therapy (ART) for prevention of HIV and tuberculosis (TB) related morbidity, mortality and transmission. Despite historic gains in expanding treatment services to 9.7 million people living with HIV, only 34% of the 28.3 million people eligible for ART were receiving it in 2012. In 2013, the UNAIDS *Treatment 2015* initiative was launched to expedite progress in scaling up treatment through innovation and the rapid translation of science into practice. The evidence base for HIV treatment is rapidly evolving and will answers open questions regarding the role of ART and 'when' and 'how' to provide early ART to maximize health benefits. This study summarizes the ongoing and planned treatment as prevention (TasP) research activities that evaluate the impact of ART plus other interventions on HIV- and/or TB-related morbidity, mortality, risk behaviour, viral suppression, HIV incidence and transmission.

Using an Internet-based search and *snowball* opportunistic survey of experts and researchers, 61 projects were identified, representing 6 regions and 59 countries. While the principle of ART for prevention of HIV and TB illness, death and transmission applies to most settings, there is considerable heterogeneity between studies in terms of the design, prioritization, interventions (e.g. early ART, expanded coverage, seek-test-treat-retain strategies), funding and geographical location.

There are 28 randomized controlled clinical trials with at least 19 large randomized individual or community cluster trials in resource-constrained settings. Five randomized controlled trials are assessing the potential benefits and risks associated with use of ART at higher CD4 counts (≥ 350 cells/mm^3) in diverse settings with varying HIV prevalence and economic resources. Also, planned/ongoing implementation research in this area will address the technical, operational, programmatic and ethical challenges faced by policy-makers while expanding the ART eligibility criteria.

After availability of strong evidence from observational studies and HIV Prevention Trials Network (HPTN) 052 trial, countries are piloting programmes to scale-up immediate ART for serodiscordant couples. It is plausible that ART will have similar preventive benefits for people who inject drugs (PWIDs), men who have sex with men (MSM), transgender people and sex workers. However, the evidence base is less solid than for the prevention benefit during heterosexual sex and a few observational studies (in Thailand, Viet Nam and Canada) will evaluate the feasibility of the "universal test and treat" strategy among these hard-to-reach and vulnerable populations.

Presently there are more than 24 ongoing/planned studies, with global distribution, evaluating various test, treat, link and/or retain strategies to improve treatment outcomes and achieve viral suppression among people living with HIV. Most importantly, community-based approaches to HIV counselling and testing (multi-disease prevention campaign) are gaining increasing attention as innovative strategies for generating demand for treatment.

The total funding for the 61 currently ongoing/planned TasP research projects is over US$307 million. The majority of this investment has been made in studies in Africa (33%) and North America (51%). Public-sector agencies from the US have provided a significant portion of

funding, with an estimated US$160 million (53%) from the National Institutes of Health and US President's Emergency Plan for AIDS Relief (PEPFAR) being invested globally. The Government of British Columbia, Canada has invested nearly US$68 million in the Stop HIV/AIDS campaign in British Columbia.

The large number and wide variety of research projects on ART for prevention emphasize the importance of this research issue. These studies will answer key questions, including the potential impact of ART on HIV and TB; ART for key populations; effective provision of HIV services, especially in Sub-Saharan Africa; and feasibility, acceptability and cost of TasP. UNAIDS will continue to work with key stakeholders to map outstanding research issues, encourage collaboration among researchers and the community, and translate new evidence into policy and practice.

Introduction

Globally an estimated 35.3 million people are living with the human immunodeficiency virus (HIV), around 61% of them in sub-Saharan Africa (1). Without antiretroviral therapy (ART), the vast majority of these individuals will develop progressive immunosuppression, leading to HIV-related illnesses and premature death. ART not only reduces morbidity and mortality related to HIV, but also has substantial potential as a prevention intervention, as it reduces viral load in people living with HIV (2-7). The prevention benefits of expanded access to early ART was first demonstrated in observational, mathematical and ecological studies from Taiwan, South Africa, British Columbia and San Francisco (4-7). Evidence also supports the use of ART for prevention of tuberculosis (TB) (8-12). Building on these basic science, observational and ecological studies, the HIV Prevention Trials Network (HPTN) 052 trial demonstrated the efficacy of early ART in preventing HIV transmission among serodiscordant couples and has provided compelling evidence on *Treatment as Prevention* (TasP) of HIV and TB illness and transmission (3).

The term TasP describes the use of ART to decrease illness, death and HIV transmission independent of CD4 cell count, with priority to HIV-positive persons who are severely immune-compromised and/or have a CD4 cell count ≤ 350 cells/mm^3 and key populations (13). ART is only one component of TasP, which consists of a combination of complementary interventions along the HIV care cascade. Higher coverage of HIV testing, effective linkage and retention in care, access to ART and adherence support are also required to realize the potential impact of TasP.

At the end of 2012, 9.7 million people were on ART in low- and middle-income countries, a 40-fold increase in access to treatment since 2002 (1). This rapid treatment scale-up has led to significant declines in AIDS-related deaths and lower rates of new HIV infections. Still there were 2.3 million new HIV infections and 1.6 million AIDS deaths in 2012 (1). Recently released 2013 World Health Organization (WHO) treatment guidelines recommend ART at CD4 count <500 cells/mm^3 for asymptomatic people living with HIV and irrespective of CD4 count for pregnant women, serodiscordant couples, children below age of five and HIV-positive people with TB or hepatitis B (14). In 2012, ART coverage in low- and middle- income countries was 34% of the 28.3 million people eligible for ART according to these guidelines (1). Treatment coverage for key populations is even lower as they face substantial barriers to essential health services. Getting to zero new HIV infections and zero AIDS-related deaths would require stronger commitment, innovation and community-centered strategies to achieve universal access to HIV testing and treatment.

The *Treatment 2015* provides a result-driven framework to expedite progress in scaling up HIV treatment (15). *Treatment 2015* emphasizes *speed* in scaling up, enhanced strategic *focus* to intensify scale-up in key geographic areas and populations, and *innovation* in programme planning and service delivery. Evidence base for HIV testing and HIV treatment is rapidly evolving, providing new opportunities to translate trial data into effective programmes. As part of *Treatment 2015,* this document summarizes the ongoing and planned ART in prevention research activities that will answer open questions regarding role of ART and 'when' and 'how' to provide early ART to achieve maximum impact on individual health and alter the trajectory of the HIV and TB epidemics.

Methodology

We searched for ongoing and planned studies evaluating the impact of ART plus other interventions on HIV- and/or TB-related morbidity and mortality, risk behavior, HIV incidence and transmission. We searched the websites of National Institute of Health (NIH), HPTN, Clinical Trials Network (CTN), and other organizations involved in TasP research activities. The search strategy included the keywords "antiretroviral or HIV treatment or ART" along with "early or universal or immediate or prevention or campaign or tuberculosis or TB."

The strategy for validation of study information included a snowball opportunistic survey of experts and researchers. The Internet and existing researcher contact list of principal investigators (PIs), funding agencies, and scientific experts in this research area was included in the initial survey. Everyone on the list was contacted (with repeated follow-ups) to supplement the existing information regarding ongoing and planned projects. They are asked to (a) review the list of TasP research projects to determine whether the information was correct and all projects were relevant to the topic; (b) provide detailed information on relevant projects not on the list and/or study protocols; and (c) add to the existing list of researchers and experts in this area. All the new projects were reviewed to ensure that they fulfilled the inclusion criteria. Any issues or questions were followed-up with the information provider.

The focus was on ongoing and planned TasP research evaluating the (a) impact of early/expanded ART (at any CD4 count), ART initiation strategies (e.g. Seek, Test, Treat and Retain) or ART adherence strategies on HIV incidence, HIV transmission risk, HIV risk behavior and/or community viral load; and (b) impact of ART at CD4 count ≥ 350 cells/mm^3 on HIV- and/or TB-related morbidity and mortality or HIV transmission. The target populations included the general population, pregnant women, serodiscordant couples, people who inject drugs (PWIDs), men who have sex with men (MSM), sex workers, and prisoners, parolees and probationers. The search was restricted to community-based studies, randomized controlled trials and cohort studies; purely modeling studies were excluded. The following studies were also excluded (a) studies that focus on other aspects of expanding ART treatment or improving ART outcomes/adherence (e.g. best regimens, medication-assisted therapy, adherence monitoring alone without looking at HIV transmission, drug resistance); and (b) completed studies with published results including abstracts (**Figure 1**). Studies that met the inclusion criteria were included without evaluating the ethics of the study design.

From the selected projects, the following details were extracted and summarized: focus of the study, study design, target populations, principal interventions in the different arms, primary outcomes assessed, ART eligibility criteria in controlled arm, region, time period (along with current status), agency and funders, and funding received. Funding levels are approximate as some projects and donors preferred to keep funding confidential.

Results

The search methodology identified 61 ongoing and planned projects examining ART as prevention, representing 6 regions and more than 59 countries (**Table 1**). Of the 61 studies, 27 were from Africa, 19 from North America, two from South America, eight from Asia, one each

from Europe and Australia, and three were multi-site international studies.

Summary of Studies

Region: Africa

The *Botswana Combination Prevention Project (BCPP)* is a village-randomized controlled trial in Botswana (16). It is a partnership between Harvard School of Public Health, the Botswana Ministry of Health, the Centers for Disease Control and Prevention (CDC) and the Botswana Harvard AIDS Institute Partnership. The estimated total cost is US $70 million, divided between CDC and Harvard. The trial will evaluate the impact and cost effectiveness of combination HIV prevention interventions on cumulative HIV incidence in approximately 104,000 (16-64 year old) residents. The combination prevention package will consist of enhanced and accelerated scale-up of HIV testing; active linkage to HIV care and treatment; expanded ART for those with high viral load (≥10,000 copies/mL); enhanced support for retention in care and ART adherence; and enhanced active linkage to expanded male circumcision and prevention of mother-to-child transmission (PMTCT) services. Efficacy based on cumulative incidence will include viral phylogenetic analysis to estimate village origin of incident infections. The trial is being funded since 2011 and will last for four years (2013-2017) following initiation of field activities.

French National Agency for Research on AIDS and Viral Hepatitis (ANRS) is conducting the study *Early Antiretroviral Treatment and/or Early Isoniazid Prophylaxis* against Tuberculosis in HIV-infected Adults (ANRS 12136, TEMPRANO) study is collaboration with Université Bordeaux Segalen, France, and Treichville University hospital, Abidjan, Côte d'Ivoire (17). This randomized trial will compare the benefits and risks of initiating ART according to the most recently updated WHO ART guidelines to the benefits and risks of initiating ART immediately among HIV-positive adults with CD4 counts ≤800 cells/mm^3. In this study, half the patients will also receive six-month isoniazid prophylaxis. This study, conducted in Côte d'Ivoire from 2008-2014, is funded by ANRS at US $6.5 million.

The *Test and Linkage to Care* for injecting drug users *(TLC-IDU)* Kenya study (2011-2016) will provide data regarding implementation of seek, test, treat and retain paradigm for IDUs in sub-Saharan Africa (18). New York University along with the Kenyan National AIDS & STI Control Programme (NASCOP) are conducting this stepped wedge trial of TLC-IDU study-specific elements utilizing rapid HIV and point of care CD4 testing and referral to peer ART case managers for people living with HIV with CD4 count ≤350 cells/mm^3, while also evaluating Kenya's national needle and syringe exchange programme. The primary outcomes will include community viral load and HIV incidence. A total of 1785 eligible PWID enrolled at baseline, of whom 87% were male, 90% of whom injected the day before, and 39% of whom had sex without a condom in the last year. There were 348 HIV-positive PWID, of whom 104 (30%) were newly diagnosed. The study has received funding of US $2.4 million from the National Institute of Drug Abuse (NIDA).

The Academic Model Providing Access to Healthcare (AMPATH) consortium, a partnership between Moi University, Moi Teaching and Referral Hospital, and a consortium of North American universities headquartered in Eldoret, Kenya, will continue an observational

evaluation of its testing, linkage, care and treatment programmes on HIV incidence in its catchments. This study will evaluate the impact of its on-going door-to-door home-based HIV testing programme initiated in 2007, re-testing every 3 years, linkage to comprehensive HIV care clinics, HIV treatment, long-term retention in care and peer-based outreach on HIV incidence. ART will be provided at CD4 count ≤500 cells/mm^3 and irrespective of CD4 count for serodiscordant couples, pregnant women and children. The aim is to demonstrate for Kenya and other African countries that PMTCT can be reduced to less than 3% in a population-based setting, and the incidence of new HIV infections can decrease by more than 50%. The Bill and Melinda Gates Foundation, Abbott and the Abbott Fund have helped to finance this evaluation. Exact funding amounts were not available.

Enhance Prevention in Couples (EPIC) is a study being conducted by the International Center for AIDS Care and Treatment Programmes (ICAP) at Columbia University in collaboration with the Ministry of Health in Lesotho aimed at addressing HIV transmission among discordant couples (19). National Institutes of Health (NIH) has financed this four-year study at US $4.2 million, from 2010-2013, to conduct several feasibility, acceptability and modelling studies aimed towards a randomized clinical trial that will evaluate the effect of an enhanced prevention package versus the current standard of care (SOC) on risk of HIV acquisition in HIV-negative partners within HIV-discordant couples enrolled from antenatal clinics (ANCs). The enhanced prevention package will include the following interventions: ART for the HIV infected partners at threshold of CD4 cell count ≤500cells/mm^3; couple-focused counseling for decreasing sexual risk behavior and enhancing adherence with ART; and circumcision for HIV negative male partners.

The *Malawi Epidemiology and Intervention Research Unit (MEIRU)* is a partnership between the Malawi College of Medicine and the London School of Hygiene and Tropical Medicine (LSHTM) (20). The research programme started in Karonga District in 1979 and has been predominantly funded by the Wellcome Trust since 1996. A major new focus for the programme (since 2011) is research on the individual and population level impact of ART. Key elements of the work include understanding the impact of HIV treatment on HIV incidence, morbidity and mortality impacts of ART for adults and children, uptake of HIV testing, sexual behavior and transmission of other infectious diseases in the community. This 4-year initiative has received US $8.5 million from the Wellcome Trust.

Assessment of ART scale up, male circumcision and other HIV prevention strategies in Rwanda and its effects to HIV transmission (2003-2014) is a multi-state time series analysis being conducted by National University of Rwanda, Rwanda Biomedical Centre and Stanford University across the 30 districts in Rwanda capturing data on 460 health catchment areas. Using data from a national information and technology registration system (TRACnet) and census data, the study will model trends, over time, in new HIV infections using (a) ART coverage; (b) male circumcision; and (c) PMTCT coverage. The study is funded by Bill and Melinda Gates Foundation. Initial results will be available in April 2014.

*Impact of Immediate Versus South African Recommendations Guided ART Initiation on HIV Incidence (*ANRS 12249 *Treatment-as-prevention - TasP)*, in rural KwaZulu-Natal, South Africa is a cluster randomized controlled trial started by the Africa Centre for Health and Population

Studies at the University of KwaZulu-Natal (Africa Centre) and the Bordeaux School of Public Health (ISPED) of Bordeaux University (21, 22). This trial, from 2011 onwards, aims to show the effectiveness of ART for all HIV-infected adults irrespective of CD4 count in reducing the incidence of HIV at the population-level. The phase 1 of the trial (to be completed in early 2014) is funded by ANRS for US $3 million with additional funding by GIZ to evaluate the feasibility and acceptability of the intervention. Co-funding by ANRS and the Bill & Melinda Gates Foundation / 3iE will allow the conduct of phase 2 to assess effectiveness, starting in 2014. The primary outcome of the trial is longitudinally measured HIV incidence; secondary outcomes will cover the clinical, behavioral and socio-economical dimensions of the universal test and treat intervention.

The Africa Centre for Health and Population Studies, University of KwaZulu-Natal, initiated a household surveillance *Impact of HIV and ART at population level* starting in 2000, twice annually (thrice annually from 2012 onwards). A household key informant provides information on socio-demographic characteristics of all household members, from approximately 12,000 households with approximately 100,000 members. Since 2003, an annual HIV and Health surveillance collects information from approximately 11,000 adults with a finger-prick sample for HIV testing. Since late 2004, the Centre has partnered with the local Department of Health in the HIV treatment and care programme. Clinical and laboratory data relating to the more than 26,000 people on ART (by the end of April 2013) and the over 35,000 who are not yet eligible for ART are hosted at the Africa Centre. The Centre produces evidence of the impact of ART on overall and cause-specific morbidity and mortality; HIV incidence; HIV prevalence; PMTCT rates; long-term safety of and adherence to ART and drug resistance.

Médecins Sans Frontières (MSF), in collaboration with the Department of Health, piloted a community-based *Treatment as Prevention* project in KwaZulu-Natal, South Africa beginning in 2011. The programme aims to reduce HIV and TB incidence along with HIV- and TB-related morbidity and mortality and demonstrate the feasibility and acceptability of different approaches to enhanced testing, linkage to care, ART, retention in care and virologic suppression. The project will offer ART to all HIV-positive people at CD4 count <500 cells/mm^3, and irrespective of CD4 count to pregnant women, serodiscordant couples and those with active TB. Combination prevention, including medical male circumcision, will be offered and substantial efforts will be made to reduce leakages across the test, link, treat and retain cascade by utilizing, among others, community-based services. HIV impact (including ART coverage, incidence, prevalence and viral load) will be measured by repeated cross-sectional population-based surveys. The annual budget for the study is US $3.25 million.

Combination Prevention For Vulnerable Women In South Africa (2011-2016) is a geographically clustered randomized trial designed by Research Triangle Institute with funding of US $2.3 million from NIDA (23). A biomedical intervention - test, treat and retain (TTR) strategy using voluntary counselling and testing (VCT) will be combined with an evidence-based behavioral intervention (i.e., the Women's Health CoOp) for more at-risk, vulnerable, alcohol and other drug using women. The study will measure the effectiveness of this combined prevention strategy on ART initiation, adherence, retention, risk behavior and HIV incidence in South Africa.

Rapid Initiation of Antiretroviral Therapy to Promote Early HIV/AIDS Treatment in South Africa (RapIT) study (2012-2015) is designed as an un-blinded randomized strategy trial comparing the current standard of care to a rapid ART initiation strategy for outpatient adults and pregnant women who come to a South African clinic for an HIV test and are eligible for ART (24). Those who are offered rapid ART initiation will receive their first dose on the same day, while those in standard care will follow the clinic's usual procedures for starting ART. The study aims to evaluate whether offering rapid ART initiation is an effective and cost-effective strategy for increasing the proportion of ART-eligible patients with undetectable viral load within 9 months of HIV testing. Boston University Medical Campus in US is conducting this study and has received US $0.4 million for 2013 from National Institute of Allergy and Infectious Diseases (NIAID).

Multi-component, targeted HIV Prevention for Sub-Saharan Africa: PreventionRx (2009-2013) is a study by University of Washington and is receiving US $4.3 million in funding from NIH (25). Based on epidemiologic analyses and mathematical modelling of determinants of heterosexual HIV transmission in Uganda and South Africa and potential impact of targeted preventive interventions, this study will design an evidence-based behavioral and biomedical intervention package to be delivered through home-based VCT to highest-risk individuals. A community-randomized effectiveness trial of this prevention package (which will include interventions like ART and male circumcision) will be implemented to determine the effects of the interventions on population-level HIV transmission.

Interventions to Decrease HIV Infectiousness in South Africa and Uganda study (2010-2013) is a University of Washington project being funded by the NIAID at US $5 million (26). It will build on the home-based counselling and testing platform (HBCT-plus) in high HIV prevalence areas of South Africa and Uganda. The aim is to increase the proportion who are tested for HIV and are aware of their HIV-positive status, bring behavioral change with prevention-for-positives risk-reduction counseling and discordant couples counseling, and reduce HIV infectiousness through effective linkages to ART and treatment of co-infections. The performance of the HBCT-plus programme will be measured by impact on community viral load and transmission potential.

Swaziland HIV Incidence Measurement Survey (SHIMS) is designed to be a four-year, population-level HIV incidence study assessing the impact of expanded HIV prevention, care and treatment activities in Swaziland (27). The assessment, taking place from 2011-2014, entails a household-based survey to compare HIV incidence rates before and after a community-based testing programme, national male circumcision campaign, ART scale-up and other prevention activities. Primary outcomes include HIV incidence rates in men and women, HIV incidence rates in circumcised and uncircumcised men and sexual risk behaviors in high-risk age groups of men and women. The SHIMS study is a joint endeavour of the Swaziland Ministry of Health, the US President's Emergency Plan for AIDS Relief (PEPFAR) programme in Swaziland, CDC, ICAP at Columbia University and the University of Washington. Information on funding for this research was not available.

MSF is studying the feasibility and acceptability of the "Universal Treatment" model in the Nhlangano health zone in the Shiselweni region, Swaziland whereby all HIV-positive people will be provided with treatment regardless of their CD4 count and WHO clinical staging through a

phased introduction; first for all HIV-positive pregnant women and lactating mothers, afterwards for all HIV-positive individuals (28). The pilot project began in 2012 with the introduction, in all three health zones, of routine viral load monitoring and community based testing; community provision of ART is still under development. Early in 2013, PMTCT Option B+ was introduced in the Nhlangano health zone. Early access to ART regardless of CD4 and WHO clinical staging will be expanded to eventually all HIV-positive individuals in the same health zone in early 2014. The study from 2012-2016 has received funding of nearly US $1.5 million.

LINK4HEALTH: A Combination Strategy for Linkage and Retention study (2012-2015) is designed by Columbia University Health Sciences and received approximately US $0.96 million in funding from NIH (29). It will take place in Swaziland and examine the impact of a combination intervention strategy (CIS) versus SOC on linkage to HIV testing, retention in care, time to ART initiation, HIV disease progression and new HIV infections. The CIS will include point of care CD4+ count assays; accelerated ART initiation; short message service (SMS) reminders for clinic appointments and active tracking of patients who miss visits; and financial incentives for linkage and retention in care. This study will help identify an effective pragmatic multicomponent strategy to improve linkage and retention of HIV-positive patients in care.

STOP AIDS NOW! and Clinton Health Access Initiative (CHAI) have been granted US $10 million by Dutch Postcode Lottery to implement the *Max*ART project, *Maximizing ART for Better Health and Zero New Infections* in Swaziland (30). The initial phase of the project (2011-2014) supports the National Swaziland ART Programme to achieve universal access to treatment according to national guidelines (CD4 count ≤350 cells/mm^3) by strengthening the continuum of care, implementing social science research to better understand realties on the ground, and monitoring human rights whilst accelerating treatment access. The *Max*ART programme is led by the Ministry of Health and partner organizations within the Consortium include the Swaziland National Network of People Living with HIV, the Global Network of People Living with HIV, the South African Centre for Epidemiological Modeling and Analyses, the University of Amsterdam, and the Southern African AIDS Information Dissemination Service.

The Sustainable East Africa Research for Community Health or SEARCH collaboration (National Clinical Trials or NCT 018646603) is an ongoing HIV "universal test and treat" study in Uganda and Kenya (31). The study is evaluating immediate, cumulative and downstream effects of offering treatment to all HIV-positive persons on health (HIV, TB, malaria and maternal mortality), economic (costing and productivity) and education outcomes. Intervention communities receive annual HIV testing during a community health campaign; streamlined ART for all children and adults living with HIV through community care delivery systems; and diagnosis and linkage to care of multiple communicable and non- communicable disease (hypertension, diabetes). HIV incidence is measured directly during repeated community health campaigns and follow-up home testing of those not attending. HIV RNA is measured annually and incorporated into monitoring for the intervention community. Retention in the care cascade for HIV and other chronic diseases is measured throughout the study. Qualitative studies include social networks, provider and patient attitudes and behavior. The study is conducted by the University of California, San Francisco, the International Development Research Centre (IDRC) and the Kenya Medical Research Institute (KEMRI) from 2013-2017. Information on funding for this research was not available.

Kakyerere Community Health Campaign took place in Kakyerere parish, a rural area in southwestern Uganda in May 2011 and 2012 (32). This is an ongoing evaluation of community health campaigns designed to understand participation, outcomes and cost of a multi-disease approach to disease identification and linkage to care. It serves to inform the SEARCH study. Study outcomes include incidence of HIV, community HIV RNA metrics and the prevalence of TB malaria, diabetes and hypertension.

Early HIV Therapy in Patients With High CD4 Cell Counts (EARLI) is an observational pilot study on early ART initiation conducted by the SEARCH collaboration in Uganda (33). It is evaluating the treatment outcomes, virological suppression and costs associated with delivering ART at CD4 counts between 250-350 cells/mm^3 and ≥ 350 cells/mm^3 under a "streamlined" model of care in rural western Uganda from 2011-2015. Information on funding for this research was not available.

Assessing the Impact of Antiretroviral Therapy on Population Level Incidence of HIV/AIDS study (2011-2015) is designed by investigators at the British Columbia Centre for Excellence in HIV/AIDS in British Columbia, Canada along with the Joint Clinical Research Centre in Uganda (34). This study uses a randomized step-wedge design to examine the impact of home-based testing and increased access to ART in Ugandan regions on HIV incidence and HIV-related morbidity and mortality. This study has received funding of US $250,000 per annum from the Canadian Institutes of Health Research (CIHR).

The HPTN-071 *Population Effects of Antiretroviral Therapy (PopART) trial* (2012-2017) is a community randomized trial being conducted in 21 communities (total population of approximately 1.2 million) in Zambia and South Africa (35). The purpose of the trial, which commenced in November 2013, is to evaluate the impact of a "universal testing and treatment" intervention on population-level HIV incidence compared to enhanced standard of care in sub-Saharan Africa. As part of a comprehensive combination prevention package (including door-to-door home based testing, referral for care, voluntary medical male circumcision, prevention of mother-to-child transmission, STI and TB services, and condom promotion), immediate treatment is being offered to all those who test positive for HIV irrespective of CD4 cell count in the main intervention arm (Arm A). In a second intervention arm (Arm B) all of the HIV prevention strategies in the PopART combination prevention programme above are being provided, while HIV treatment is only offered to those who are eligible according to national guidelines. The trial will compare Arms A and B, and will also compare each of these with Arm C, which will continue to provide current standard of care. A *Population Cohort* of 2,500 individuals from each community is being randomly selected (total sample of 52,500) to measure the reduction of HIV incidence over 3 years of the intervention. Nested research within the trial includes three case-control studies which will examine the factors associated with uptake and non-uptake of key interventions and social science research which will provide important contextual data and more in-depth exploration of community response to the PopART intervention. In addition, mathematical modelling work which has informed the design of the trial will continue and be refined as trial data emerge, in order to project longer term impact of the trial interventions; and economic evaluation will assess the incremental health benefits of the PopART intervention in relation to its incremental costs. The main door-to-door home-based testing intervention is being delivered by PopART Community HIV-care Provider

(CHiPs) staff, but treatment and care related services are being provided by existing health systems in-country, with support from PopART. The study is being conducted by the NIH-funded HPTN. The study is led by investigators at the LSHTM in collaboration with Imperial College London, the Zambia AIDS Related Tuberculosis Project (ZAMBART) and the Desmond Tutu TB Centre at Stellenbosch University, South Africa. The study is sponsored by NIAID, with funding from PEPFAR. Additional funding is provided by the International Initiative for Impact Evaluation with support from the Bill & Melinda Gates Foundation, NIAID, NIDA and the National Institute of Mental Health (NIMH). This study has received US $23 million as of December 2013.

The *Max*ART project in Swaziland will also include a *Treatment as Prevention implementation study on immediate access to treatment for all* within a government-managed health system (30). The planned study is designed to answer practical questions concerning specific elements of implementation of earlier treatment for people (irrespective of CD4 count) who are feeling healthier. These questions include whether or not people will seek health services, accept and start treatment and stay in care – evaluating retention and viral suppression as primary endpoints. The study will compare differences in health outcomes as well as gather evidence around feasibility, acceptability, affordability and scalability of implementing earlier treatment in the context of a government-managed health system. The evidence generated will inform national policy on future of HIV treatment programming and contribute to answering the global community's questions around how to implement an immediate access to ART strategy in a resource-limited country with a high prevalence of HIV. A pre-study assessment that studied the readiness of communities, people living with HIV, and health workers for ART initiation irrespective of CD4 cell count was finalized mid-2013. The implementation study is expected to start in 2014. Financing for the study currently comes from the Dutch Postcode Lottery (US $1.3 million), all ARVs are being supported by Mylan Laboratories, resistance monitoring is being supported by the British Columbia Center for Excellence in HIV/AIDS, and the team plans to collaborate with MSF in-country on viral load monitoring. Resource mobilization efforts are ongoing to bridge the funding gap of US $2.3 million.

Geographically Concentrated Multi-Level HIV Prevention in Bukoba Urban District: Outcome Evaluation of a Combination Prevention Programme (2013-2017) in Tanzania is a planned study by ICAP at Columbia University, with CDC Tanzania and CDC Atlanta. The programme's aim is to evaluate the impact of increased uptake of evidence-based behavioral and biomedical interventions on HIV transmission and acquisition. The combination prevention programme will include the following six components: community mobilization; expanding access to HIV testing and counselling (HTC); male circumcision; strengthened linkage services; expanding access to ART for all persons with CD4 counts ≤ 350 cells/mm^3, for all HIV-positive pregnant or lactating women regardless of CD4 count (Option B+) and for HIV-positive members of serodiscordant couples up to CD4 count ≤ 550 cells/mm^3; and increased retention in care. The project has received funding of US $2.5 million from PEPFAR.

The Rakai Health Sciences Programme (RHSP) in Uganda is planning a study titled *Impact Evaluation of Combination HIV Prevention (CHP) to Reduce Population-Level HIV Incidence in Rakai, Uganda* from 2013-2017 (36). CHP components and targets are: ART (target 70% HIV-positive persons with CD4 <500 cells/mm^3), ART for HIV-positive partners in discordant

relationships irrespective of CD4 count, PMTCT using Option B+, medical male circumcision (MMC, target coverage >70% non-Muslim men) and demand creation/behavioral modification. Scale-up will be in collaboration with the Ministry of Health and non-governmental organizations (NGOs). CHP will be evaluated via the Rakai Community Cohort Study (RCCS), an open cohort established in 1994, which currently has ~15,800 persons, aged 15-49 in 50 rural communities with an HIV prevalence of around 12.5% and an incidence ~1.0 per 100 person years. Additionally, surveillance has been extended to HIV hotspots in four fishing communities with an HIV prevalence of 35-43% and an incidence of 3.9 per 100 years and two transport hubs with HIV prevalence of 15-25%. This proposal tests the hypotheses that CHP scale-up targets can be achieved in 2-3 years and will reduce HIV incidence by changing transmission dynamics within and between the general and hotspot populations. The study is attempting to secure funding from multiple organizations of US $4.1 million.

ICAP at Columbia University along with the Centre for Infectious Disease Research in Zambia (CIDRZ), CDC Zambia, CDC Atlanta and other partners have planned a study titled *Evaluation of an Integrated Community-Based and Clinical HIV/AIDS Programme in Sinazongwe District, Zambia* (2013-2017). The study will compare population-level HIV incidence before and after the community-based HIV prevention project Total Control of the Epidemic (TCE) and district-wide service scale-up using laboratory-based methods. The study also seeks to examine related factors including HIV knowledge, attitudes and behaviors. Data from this evaluation will be used to inform district-level programming and enhance HIV prevention, treatment and support programmes targeting whole communities. Information on funding for this research was not available.

Region: Asia

"Active Treatment" pilot project in China: A before/after intervention study was implemented in Guangxi province from 2012 onwards. Sponsored by the National Center for AIDS/STD Control and Prevention and China CDC, the study will determine whether implementation of one-stop shop for HIV screening, white-blood (WB), and CD4 test and linkage to HIV treatment will increase the proportion of HIV-positive who are linked to ART and reduce mortality. The Abbott Fund and Chinese Ministry of Health have funded this study. Exact funding amounts were not available.

Multi-component HIV Intervention Packages for Chinese MSM (2011-2015) is an observational study that will evaluate the impact of a multi-component test-and-linkage-to-care (TLC) intervention package on HIV incidence among MSM in Beijing, China (37). The study will pilot test the feasibility, acceptability and efficacy of expanded HIV testing with prompt initiation of risk reduction intervention and optimal ART among an HIV high-risk population. SMS-I intervention by cell phones, web advertisement, community outreach, and peer referral strategies will be used to recruit MSM for receiving HIV testing. This project is a collaboration between Vanderbilt University Medical Center, China CDC and the local MSM community-based organizations and has received funding of nearly US $2 million from NIMH, NIAID and the National Institute on Alcohol Abuse and Alcoholism (NIAAA). This study will also help refine the

HIV prevention package for a multi-site randomized clinical trial in 12 Chinese cities to evaluate its impact on new HIV infections.

Integrated Care Clinics for Injecting Drug Users (IDUs) in India: A cluster-randomized trial is a 5-year (2011-2016) study by John Hopkins University financed by NIDA for US $3.7 million (38). This study will evaluate the effectiveness of IDU-oriented integrated care clinics (ICCs) for improving outcomes along the "seek, test, treat and retain" (STTR) continuum. The study will measure effects of providing ART and WHO-recommended IDU services on HIV prevention and treatment outcomes in this vulnerable population along with community viral load.

Study to evaluate the feasibility of universal HIV testing and ART regardless of CD4 count using the test and treat strategy among MSM and transgender women in Thailand is a collaborative project between the Thai Red Cross AIDS Research Centre and the Department of Disease Control at the Thai Ministry of Public Health (39). The observational study aims to study the feasibility of the "universal test and treat" strategy among Thai MSM and transgender (TG) individuals in Bangkok, Ubonratchathani and Lampang. In addition to evaluating the acceptance of regular HIV testing and immediate ART, this project also collects data on HIV RNA levels in blood and ano-genital compartments to support the biologic plausibility of ART use to reduce HIV transmission among MSM and TG. A questionnaire and rates of symptomatic and asymptomatic STI will be used to assess changes in risk behaviors over time. The National Research Council, National Health Security Office, Government Pharmaceutical Organization, Department of Disease Control at the Ministry of Public Health, TREAT Asia, WHO and AIDS Fonds are financing this study for US $0.6 million.

Seek, Test, Treat Strategies for Vietnamese Drug Users: A Randomized Controlled Trial (2010-2015) is a project being undertaken by Johns Hopkins University, with US $2.5 million in grants from NIDA (40). This project will intervene with PWIDs who are released from drug treatment centers by implementing a new approach to expanding HIV testing, promptly referring HIV-positive people to care and retaining those individuals on ART in treatment. In addition, behavioral risk reduction interventions will be provided. Using a randomized controlled trial, effects of this seek, test and treat strategy on ART uptake, ART adherence and treatment outcomes will be evaluated.

Antiretroviral therapy for prevention and treatment in HIV serodiscordant couples in Viet Nam study (2013-2014) aims to assess operational feasibility of offering couple HIV testing and counseling (CHTC) and providing ART for prevention and treatment in 150 serodiscordant couples (both heterosexual and homosexual relationships) in Can Tho and Dien Bien provinces. The couples will also be counseled to use other prevention methods consistently, including condoms and clean needles (in case of PWIDs). The study will document HIV transmission within serodiscordant couples when the seropositive partner is receiving ART irrespective of CD4 count. The cascade of interventions will also be monitored from HIV diagnosis, couple HTC, linkage to care, and retention, clinical status (viral load, CD4 count, ART adherence, active TB), viral suppression of HIV positive partner, HIV sero-status of HIV negative partner and risk behaviors of both partners. Potential adverse effects associated with antiretroviral drugs will be recorded. This study by Viet Nam Authority for HIV/AIDS Control, Ministry of Health; Hanoi School of Public Health; WHO; CDC Atlanta; and Family Health International (FHI) 360 has received funding of US $100,000 from the MAC AIDS Foundation, WHO, PEPFAR, CDC and the

Global Fund.

Testing and Linkage to HIV Care in China: A Cluster Randomized Trial is a planned study (from 2013 onwards) by China CDC and will determine whether implementation of two structural interventions will increase the proportion of HIV-positive people who are linked to ART and who achieve viral load suppression, thereby reducing mortality. This study in Guangxi, China will assess the effectiveness of two interventions: a new testing algorithm, consisting of rapid point-of-care HIV and CD4 testing, with viral load testing; and an innovative provider and patient incentives programme designed to enhance linkage and retention in HIV care. Funding information for this study was not available.

Periodic HIV testing and counseling and immediate ART for treatment and prevention in people who inject drugs in Viet Nam (2013-2015) is a planned operations research study in Thai Nguyen and Thanh Hoa provinces that will explore the feasibility of expanded HIV testing and counseling and provision of immediate ART among PWID. Other interventions will include community outreach (needle-syringe programme, treatment literacy training, link to HIV testing and counseling, referral to methadone maintenance), screening for hepatitis B and C, and for active TB, treatment for the identified co-morbidities, promotion of condom use, HTC for partners, CD4 and viral load testing and ART adherence support through health-care workers and people living with HIV peer educators through support group activities and home visits. The study will assess the retention in care, adherence and retention on ART, incidence of clinical events (mortality and morbidity related to TB), behavioral changes (on-time drug pick up, condom use and needle-sharing behaviors) and viral suppression among HIV-positive PWID who initiate ART regardless of CD4 count. United Nations in Viet Nam, MAC AIDS Foundation, WHO and the Global Fund have financed this study by Viet Nam Authority for HIV/AIDS Control, Ministry of Health and WHO for US $150,000.

Region: North America

British Columbia Centre for Excellence in HIV/AIDS (BCCfE) at St. Paul's Hospital, Vancouver, Canada has concentrated efforts on mitigating the HIV epidemic in the community. It focuses on hard-to-reach populations including aboriginal peoples, PWIDs, women and MSM. BCCfE's AIDS Research Programme has focused work on treatment as prevention in Canada, US, China and sub-Saharan Africa. Key projects look at the impact of expanded highly active antiretroviral therapy (HAART) access on HIV/AIDS-related morbidity, mortality and HIV incidence, and the cost and cost-effectiveness of such strategies. British Columbia Ministry of Health has provided major support for the BCCfE's efforts to decrease HIV incidence in the community. The following are BCCfE supported studies:

HAART Optimism, Drug Use and Risky Sexual Behavior among MSM in British Columbia (2011-2016) is a prospective study in collaboration with Simon Fraser University and is financed by NIH for US $1.2 million (41). This study examines the effect of expanded universal access to free-of-cost ART as an HIV prevention measure on HIV risk behavior among MSM.

Effect of HAART Expansion on Community Levels of HIV Viral Load and HIV Risk Behaviors Among Men Who Have Sex with Men in British Columbia (2010-2013) is being funded by

CIHR for US $0.4 million (42). It will examine the impact of expansion of access to ART on HIV risk behavior among the MSM population in Greater Vancouver and on community HIV viral load as a marker of community infectivity.

In 2009, BCCfE launched an internationally innovative research programme *Seek and Treat for Optimal Prevention of HIV/AIDS (STOP HIV/AIDS)* (43). STOP HIV/AIDS pilot project (2010-2013) expanded HIV testing, HAART access and support services among hard-to-reach and vulnerable populations in Vancouver's Downtown East Side and Prince George. The pilot phase received funds worth US $48 million from British Columbia (BC) Provincial government and US $2.5 million grant from NIDA. This strategy has led to a marked decrease in morbidity, mortality and new HIV cases. From April 2013, STOP HIV/AIDS Research Programme has been scaled-up province-wide in BC. The study will continue to monitor and evaluate the decline in HIV incidence in BC. Following its success as a pilot, the government of BC has committed US$19.9 million in annual funding to roll out the initiative across the province and NIDA's support of US $2.5 million for 5 years will further advance the research.

Impacts of Universal Access to HIV/AIDS Care among HIV-positive Injection Drug Users is part of an ongoing study of HIV-positive PWIDs that proposes to assess the effect of expanded access to HIV treatment on patterns of ARV drug resistance and patterns of HIV transmission in Vancouver, Canada (44). This prospective cohort study will also answer questions regarding the impact of province-wide "Seek, Test and Treat" campaign on HIV incidence. The University of British Columbia has received renewed funding of US $4.2 million from NIDA for the period 2006-2013 for this long-running study on PWIDs.

Seek and Treat for Optimal Outcomes and Prevention in HIV & AIDS in IDU (2008-2013) is a population-based observational study in collaboration with the University of California, San Diego (45). This study will test the effect of expanded HAART coverage on number of new HIV infections and adverse HIV/AIDS health outcomes among PWIDs. NIH has funded this study for an amount of US $3.9 million.

Same-Day HIV Testing and Treatment Initiation to Improve Retention in Care (2013-2015) is a randomized trial in Port-au-Prince, Haiti that proposes to establish the effectiveness of same-day ART initiation for patients who present for HIV testing and qualify for ART at CD4 cell count ≤350 cells/mm^3 (46). All patients in the intervention group will receive rapid HIV testing, CD4 cell testing, screening for opportunistic infections, WHO staging, comprehensive counseling and social support, and ART initiation on the day of presentation. The standard group will receive three sequential visits for ART readiness counselling and testing for opportunistic infections prior to ART initiation. The proportion of patients in the standard and intervention groups that are alive and in-care with an undetectable HIV viral load at 12 months after HIV testing will be compared. The study by Brigham and Women's Hospital, Boston, US has received funding of US $0.66 million for 2013 from NIAID.

HPTN 065: A Study to Evaluate the Feasibility of an Enhanced Test, Link to Care, Plus Treat Approach for HIV Prevention in the United States (TLC-Plus) is being conducted by the HPTN from 2010-2014 (47). There are two intervention communities (Washington, District of

Columbia [DC] and the Bronx, New York) and four non-intervention communities (Chicago, Illinois; Houston, Texas; Miami, Florida; and Philadelphia, Pennsylvania). The purpose of the study is to evaluate the feasibility of an enhanced community-level "test, link to care, plus treat" strategy in the US. The study includes the following interrelated components: expanded HIV Testing component which involves social mobilization, with targeted messaging to promote testing, and implementation of the universal offer of HIV testing in emergency departments and hospital inpatient admissions; linkage-to-care and viral suppression components which involves site randomization to test the effectiveness of a financial incentive (FI) intervention compared with the SOC; prevention for positives component that uses individual randomization to compare the SOC plus a computer-delivered intervention with the SOC and; patient and provider survey component administered at specific time points during the study to assess knowledge, attitudes and practices regarding early initiation of ART and the FI interventions. This study has received US $32 million from NIH and CDC and is being implemented in collaboration with Columbia University and local health departments.

The *Peer-driven Intervention to Seek, Test & Treat Heterosexuals at High Risk for HIV (HHR) study* (2011-2016) will use National HIV Behavioral Surveillance System methodologies to target HHR and overcome individual attitudinal, social and structural barriers to HIV testing and treatment (48). The primary goal of the proposed study is to evaluate the efficacy of peer-driven intervention (PDI) to 'seek, test, treat and retain' HHR to improve HIV health and treatment outcomes and viral load suppression among HHR in New York City. The enhanced PDI is tailored specifically for HHR and includes computerized, navigation and peer-delivered components to enhance future sustainability. In addition, the project will compare rates of newly diagnosed HIV infection produced by the PDI to a venue-based sampling "seek and test" intervention in the same geographical location, and examine the cost-effectiveness of each. This NIDA funded study has received US $5 million and is being conducted by New York University.

A Randomized Controlled Trial and Cohort Study of HIV Testing and Linkage to Care (2010-2015), undertaken by Friends Research Institute and The Miriam Hospital-Lifespan is being conducted in community-based corrections facilities at two sites—Providence, Rhode Island and Baltimore, Maryland in the US (49). First, a randomized controlled trial of HIV testing will study the efficacy of on-site rapid testing at a probation or parole office versus off-site referral at a community health center or HIV testing clinic. For the cohort study, all individuals identified with HIV at community corrections will be offered enrollment in a one-year intervention study using Project Bridge[1] to help improve linkage into HIV care. The study will evaluate whether improvement in access to testing and treatment for at-risk populations can stem the tide of HIV infection in the United States (US). This project has received a funding of US $2.8 million from NIH.

Effectiveness of Peer Navigation to Link Released HIV+ Jail Inmates to HIV Care (2010-2015) study is being conducted by University of California, Los Angeles among HIV-positive male ex-inmates who are being released from Los Angeles County Jail system (50). The aim of this five-

[1] **Project Bridge**, started in 1997, is an ongoing project to provide intensive medical care through social stabilization to HIV-positive ex-offenders being released from the Rhode Island state prison to the community. The treatment plan includes mental illness triage and referral, substance abuse assessment and treatment, HIV and other medical conditions, and referral for assistance to community programmes that address basic survival needs.

year NIH funded study, which received US $3.6 million, is to examine the individual and structural barriers to HIV care after release from jail and to utilize a randomized design to evaluate the impact of adapted peer-based health system navigation intervention compared to a usual care condition on linkage with and retention in HIV care, self- reported ART adherence and HIV RNA viral load suppression.

Randomized Control Trial of an Augmented Test, Treat, Link, and Retain Model for North Carolina and Texas Prisoners (2010-2015) is an ongoing trial that compares standard prison practice with a comprehensive multi-component package that spans incarceration and release (51). It includes interventions that address the vulnerabilities identified in the HIV testing and treatment paradigm for prisoners: client engagement and participation in HIV care; systematic screening for ancillary needs and rapid personalized linkage to outside HIV care; and supportive services (e.g., mental health and substance abuse). The study is conducted in North Carolina and Texas (which combined incarcerate 15% of all those in prison in the US). Participants are about-to-be-released inmates with suppressed plasma HIV RNA levels. The primary aim is to determine the effect of the intervention on maintaining suppression of viraemia post-release via adherence to ART and engagement in ongoing HIV care. Secondary outcomes include risk behavior following release. University of North Carolina, Chapel Hill has received an NIH grant of US $6.1 million for this study.

Seek, Test, Treat: An Integrated Jail-Prison-Community Model for Illinois (2010-2015) is being developed by University of Illinois in the US (52). The project received funds amounting to US $5.2 million from NIH. It constructs and evaluates a 'seek, test, treat (STT) model' that begins at entrance to jail, continues through prison and extends into the community after release. STT has five components: opt-out HIV testing in jail and prison; transition case management for HIV-positive persons leaving jail and prison; university-based telemedicine for all state prisoners living with HIV and HIV specialty care from jail based staff; incentives to visit community-based organizations following release from jail; and social network HIV testing and partner notification. The study will assess each component of the STT model and its overall impact on community-level HIV viral load.

CARE Corrections: Technology for Jail HIV/HCV Testing, Linkage, and Care Study (2010-2015) is a research project being conducted by Miriam Hospital/Brown University, New York University, and George Washington University and is being supported by funding of US $4 million from NIH (53). The study uses a communication technology-based tools, CARE+ and SMS texting, for use among recently released jail detainees in Washington, DC. The tools address hepatitis C infection and substance use behaviors, maintain HIV treatment with linkage to community care following jail release and automate text messaging to support linkage to community HIV. Using a randomized controlled trial design, this project evaluates the cost and effectiveness of CARE+ Corrections to facilitate linkage to community HIV care, maintain HIV viral suppression and decrease HIV transmission behaviors.

Finding, Testing and Treating High-risk Probationers and Parolees with HIV (2010-2015) is a study by Research Triangle Institute to be conducted in Oakland, California (54). It received grants of US $2.6 million from NIH. This project seeks to design and implement a community-based strategy of HIV testing and counselling for drug users on probation or parole, and assess the efficacy of Project Bridge compared with a usual care for HIV-positive patients using a

randomized controlled trial. Outcomes of interest will be the proportion of eligible individuals who are identified and recruited, accept HIV testing, have not been HIV tested in the previous six months and report recent HIV risk behavior. HIV viral load, HIV care and HAART among participants in Project Bridge will be compared to those that get standard referral to HIV care.

START Together: HIV Testing and Treatment in and after Jail (2010-2015) is an NIH-funded project focused on HIV prevention, testing and treatment for individuals in jails (55). It is undertaken by National Development and Research Institutes at the Rikers Island correctional facilities in New York City. START Together has three components: Project START (an HIV reentry programme), CARE to promote adherence and Peer Health Navigators. The randomized controlled study seeks to test whether START Together increases the proportion of inmates receiving HIV testing and the proportion of individuals with undetectable HIV viral load post-release. The total funding for this project is US $1.2 million.

Project HOPE - Hospital Visit as Opportunity for Prevention and Engagement for HIV-infected Drug Users (CTN 0049) is a randomized controlled trial from 2012-2014 that will determine the most effective strategy in achieving HIV virologic suppression among HIV-infected substance users recruited from the hospital setting (56). This NIH-funded study is currently recruiting patients at ten sites in urban centers across the US that are heavily affected by HIV. Participants will be randomized to one of three groups: an active patient navigator component: a strengths-based case management approach that includes motivation, physical escort to treatment and face-to-face booster sessions; and a passive incentives and contingency management component to further motivate and reinforce completion of target behaviors; or treatment as usual. The study will also determine linkage and retention in HIV primary care, medication adherence, all-cause mortality and reduction in numbers of hospitalizations.

Behavioral Intervention to Enhance HIV Test/Treat (2012-2017) is a randomized controlled trial that will test a theory-based behavioral intervention to simultaneously improve ART adherence and reduce HIV transmission risk in people living with HIV/AIDS who use alcohol and other drugs in Atlanta and surrounding impoverished areas (57). The intervention will be delivered in a single office-based counseling session followed by four cell phone delivered counseling sessions and effects on HIV transmission risk behaviors, HIV treatment adherence, viral load and STI prevention. This University of Connecticut study is funded by NIDA for US $1.3 million.

APTcare is a multi-component intervention with the primary aim of increasing the number of HIV patients who achieve and sustain an undetectable viral load. The study *Implementation and Evaluation of a Comprehensive Prevention with Positives Intervention at HIV Clinics* will be conducted from 2011-2016 at six HIV clinics in the US. In a group (clinic) randomized design, three clinics will initiate the intervention for a 12-16 month period while the other three will delay initiation and serve as concurrent controls during that time period. The CBI and health coach counseling is focused primarily on patients who have a detectable viral load; the other intervention components (screening and messaging) are given to all patients. The intervention components are delivered by trained project staff as well as existing clinic staff. Sources of data include clinics' archived data on patients' viral load labs and clinic attendance and patients' self-reports of ART adherence and sexual risk behavior. The intervention will be initiated in January of 2014. This collaborative effort between CDC and the NIMH is scheduled to receive total funding of approximately US $9 million.

HOME: A Comprehensive HIV Testing and Linkage Package For Young MSM of Color (2012-2017) is a planned clinical trial in Oakland and San Francisco that will evaluate the desirability of a package of home-based HIV testing, in-person support and linkage to care including ART (58). The study will test whether the package of HIV services will break the cycle of HIV infection between young African American and Latino MSM. This study is being conducted by Public Health Foundation Enterprises and is being financed by NIH for US $1.1 million.

Region: South America

HIV Testing And Treatment To Prevent Onward HIV Transmission Among High-Risk MSM and transgender women (2011-2016) is a study in Lima, Peru by Fred Hutchinson Cancer Research Center that received financing worth US $4.2 million from NIDA (59). The study aims to assess the impact on community-wide HIV transmission of intervening with ART and evidence-based treatments for alcohol use disorders for MSM and transgender women, especially those with substance use disorders (including alcohol and cocaine). Individuals will be provided with community mobilization and partner services to improve testing, linkage to care and timely ART: While one group will be randomized to start ART immediately (just at the time of the enrollment visit), the other group will wait until week 24 of the study to start ART. The study will evaluate the frequency of drug and alcohol use among this population, successful linkages to care and treatment, effect of ART on HIV viral load, retention in care and medication adherence.

Enhanced Access to HIV Care for Drug Users in San Juan, Puerto Rico (2013-2018) is a study by Columbia University that will evaluate a community-level, structured approach to enhance HIV care access and retention for drug users (60). The proposed intervention will be to: identify drug users living with HIV who either do not know their HIV status and/or are not engaged in HIV care; provide direct HIV care services through a mobile health van; and support identified HIV-infected drug users with patient navigators to enhance their ability to engage in HIV care, to initiate ART and to maintain adherence to their treatment regimens. Using a randomized design, virologic suppression, HIV care visits, uptake of ART and adherence to HIV treatment regimens will be assessed. The study has received US $1.8 million from NIH and NIDA.

Region: Europe

Partners of People on ART: a New Evaluation of the Risks (PARTNER) study (2010-2014) is a collaborative effort between University College London and Copenhagen HIV Programme (CHIP) and has received US $1.5 million funding from the National Institute for Health Research (NIHR), UK (61). This study aims to assess HIV serodiscordant partnerships that report having unprotected sex, to determine the risk of HIV transmission when the HIV-positive partner on ART has plasma viral load <50 copies/mL. Also, factors responsible for non-usage of condoms and for adoption of consistent condom use will be examined. A total of 75 clinics in 14 EU-countries are currently taking part in PARTNER. By May 2013, 1,000 couples have been enrolled and 362 of the couples are MSM. The first stage of the PARTNER study (2010-2014) will be able to provide an overall estimate of transmission risk for penetrative sex without condoms. Financial support is being sought for the second phase of PARTNER which will allow the study to continue to enroll and follow-up with MSM couples and to provide a precise estimate of the transmission rate for anal sex.

Region: Australia

The *Opposites Attract Study* (2011-2015) examines HIV treatment outcomes, viral load and HIV transmission in gay male serodiscordant couples (62). Coordinated by the Kirby Institute at the University of New South Wales in Australia, with funding of US $1.2 million from National Health and Medical Research Council, it will be conducted in up to 18 high HIV caseload clinics in Sydney, Melbourne, Brisbane, Cairns and Canberra. It aims to determine the HIV incidence in the initially HIV-negative partners in partnerships where the HIV-positive partner is (a) on HIV treatment, and (b) on HIV treatment with undetectable viral load; compared with the HIV incidence in partnerships where the HIV-positive partner is not on HIV treatment. It also aims to explore the extent to which viral load is used in negotiating unprotected anal intercourse within the partnerships. Couples in the study will be followed two to four times per year for blood testing, STI testing and to complete short questionnaires.

Region: Global

The Strategic Timing of Antiretroviral Treatment (START) (2009-2016) is an international randomized trial being conducted by the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT) (63, 64). START is being carried out in 35 countries to determine if the chance of dying or developing a serious non-AIDS event or AIDS is less if patients start taking HIV medicines at a time when their CD4 cell count is above 500 cells/mm^3 rather than waiting for it to drop to 350 cells/mm^3. The study plans to enroll 4,628 participants by December 23, 2013 and follow them through 2016. The study is primarily funded by NIAID but also includes funding from several other NIH Institutes and international organizations. Data are collected on a number of important secondary outcomes, including sub-studies on pulmonary complications, arterial elasticity, liver disease, bone disease, neurocognitive impairment and genomics. Information is also being collected on resistance to HIV medicines, quality of life, health care utilization and the cost of medical care. The total cost of this trial over the seven years of the trial is uncertain because it is an event-driven trial but has been estimated to be at least US $80 million.

The HIV Prevention Trials Network (HPTN) 052 Randomized Trial to Evaluate the Effectiveness of Antiretroviral Therapy Plus HIV Primary Care Versus HIV Primary Care Alone to Prevent the Sexual Transmission of HIV-1 in Serodiscordant Couples is an ongoing study by University of North Carolina in nine countries (3). Assessing the effect of early ART initiation on HIV incidence reduction in discordant couples, the study results were announced early when the data and safety monitoring board (DSMB) found a 96% reduction in HIV transmission in the arm that received ART immediately between 350-550 CD4 cells/mm^3 versus deferral of ART to CD4 count < 250 cells/mm^3. On DSMB recommendation, as of May 10, 2011, all HIV-infected participants in the controlled arm who had not already initiated ART were offered ART as soon as possible and the trial was continued as an open label study looking at durability of prevention among other outcomes.

Test & Treat to End AIDS (TTEA) is a partnership of international NGOs, scientists, doctors, people living with HIV/AIDS and evaluation experts formed in 2010 to advocate for "universal test & treat" as the lead strategy to end HIV transmissions globally (65). TTEA has been working with the United States Congress to provide information on how Test & Treat can significantly

reduce and/or eliminate HIV transmissions at the population level, significantly reduce long-term pandemic costs, generate additional tax revenues for national governments, save lives and begin rebuilding communities devastated by the pandemic. With funds worth US $30 million, TTEA has developed and begun implementing a 5-year 12 country professional lobbying plan designed to convince key stakeholders that Test & Treat should be adopted as national policy; fully funded in national budgets; and evaluated for impacts at both the individual and populations levels.

Research questions

There are various research questions that the ongoing/planned studies will answer in the near future. We classified the studies according to their primary research question (most studies answer multiple questions).

- What is the impact of earlier initiation of ART on morbidity and mortality?
- What is the impact of early ART on TB incidence and mortality?
- What is the impact of earlier initiation of ART on behavioral outcomes?
- What are the prevention benefits of expanded access to ART?
- What are the prevention benefits of starting ART earlier?
- How can the research data be translated into effective programmes?
- What is the appropriate mix of HIV prevention interventions for the greatest impact on HIV incidence?
- What is the efficacy of ART for prevention of HIV transmission in key populations, particularly among MSM and PWIDs?
- What are the best (most effective and efficient) ways to deliver ART and how can optimal retention in treatment be achieved?

Earlier Initiation of ART

There are nine studies, including five randomized controlled trials, assessing the potential benefits and risks associated with use of ART at higher CD4 counts (≥ 350 cells/mm^3) and how to implement/scale-up TasP (**Figure 2**). The *'START trial'* (63) and ANRS-funded *'TEMPRANO trial'* (17) are large randomized trials examining the optimal timing for initiating ART, with results expected in 2014-2015 (**Figure 3**). While the former is comparing the benefits and risks of initiating ART with CD4 cell counts ≥ 500 cells/mm^3 to ART according to 2010 WHO guidelines largely in developed countries, the *'TEMPRANO trial'* looks at ART initiation criteria of CD4 count ≤800 cells/mm^3 in a generalized epidemic setting (Cote d'Ivoire). Other randomized trials such as *'ANRS 12249 TasP'* in South Africa (22), *'HPTN 071 (PopART)'* in South Africa and Zambia (66), and the *'SEARCH study'* in Uganda and Kenya (31) are additionally looking at population-level impact of earlier ART (**Table 2**).

Observational studies in Uganda, South Africa and Swaziland are in the planning phase. They include the *'MaxART implementation study'* (30) and *'MSF Treatment as Prevention approach'* in Swaziland (28), where universal ART will be provided irrespective of CD4 count within the existing health system.

TasP for Serodiscordant Couples

After availability of strong evidence from HPTN 052 randomized trial (3), Viet Nam is planning an implementation study on use of ART in serodiscordant couples (in both heterosexual and homosexual relationships). This study will evaluate the effectiveness of providing TasP for serodiscordant couples under a national programme and determine the factors affecting it (e.g., access to ART, adherence). The '*PARTNER study*' in Europe will address the gaps in evidence about impact of behavioral factors (non-usage of condom) on risk of HIV transmission when the HIV-positive partner is on treatment (61).

TasP for Key Populations

The search methodology identified 16 studies among MSM, transgender women and PWIDs that are looking at early ART, expanded treatment coverage and STTR strategies in geographically diverse settings (**Figure 4 and 5**). While an observational study in Thailand will evaluate the feasibility of the "universal test and treat" strategy among MSM and transgender women (39), the Stop HIV/AIDS project in British Columbia will measure the impact of "universal test and treat" among hard-to-reach and vulnerable populations (43). The other studies are measuring the prevention benefits of ART initiated according to the national guidelines. The *'Opposites Attract'* study in Australia is the first study that will evaluate the impact of ART (according to national guidelines) on HIV transmission in gay male serodiscordant couples (62). Viet Nam is undertaking implementation research to assess the feasibility and acceptability of ART irrespective of CD4 count among HIV-positive people who inject drugs. Three other studies in British Columbia and Puerto Rico will evaluate the impact of expanded access to ART among PWIDs on individual and community viral load (44, 45, 60).

Combination Approach to HIV Prevention

Along with '*MSF Treatment as Prevention (TasP) study in South Africa*' and '*HPTN 071 (PopART)'*, there are seven other studies from sub-Saharan African countries that look at combination HIV prevention strategies among general population, serodiscordant couples and high-risk women (**Figure 2 and 6**). The most common prevention interventions include male circumcision, HIV testing and ART (**Table 3**). While early ART (CD4 count ≥ 350 cells/mm^3) is provided in '*MSF Treatment as Prevention (TasP) study in South Africa*' and '*HPTN 071 (PopART)',* ART is provided at CD4 count of ≤ 350 cells/mm^3 or according to national guidelines for asymptomatic people living with HIV in the other seven studies. Between 2013 and 2017, results from these studies will provide the combined effectiveness of different HIV prevention packages.

Knowledge of HIV Status and Expanded Access to ART

Community-based approaches to HIV counselling and testing are gaining increasing attention as an innovative strategy for improving access to treatment. For example, the *Kakyerere Community Health Campaign* in Uganda is an ongoing multi-disease prevention campaign providing easy access to HIV testing and counselling and early linkages to care and treatment (32).

Large population-based studies in Uganda, Swaziland and South Africa are focusing on demonstrating the effectiveness and impact of expanded access to testing and treatment (according to national guidelines) on HIV transmission rates among adult population (27, 30, 34). Results from these studies will have important epidemiological implications for HIV and TB

incidence and will help in projecting future resource needs. Some of these studies will also examine the negative outcomes of expanded treatment, including their potential impact on risk behaviors among people living with HIV.

Service Delivery: Seek, Test, Treat and Retention in Care

Presently there are more than 24 ongoing/planned studies evaluating various test, treat, link and/or retain strategies to improve treatment outcomes and achieve viral suppression among people living with HIV. The studies are globally distributed in low and high-income countries and also target hard to reach populations such as MSM, IDU and prisoners.

Funding

Over the past eight years, the reported funding for currently ongoing/planned TasP research projects has reached over US$307 million. The majority of this investment has been made in studies in Africa (33%) and North America (51%) as shown in **Figure 7**. Nearly 70% of the total funds have been invested in five countries – Canada, US, Swaziland, South Africa and Uganda. Public-sector agencies from the US have provided a significant portion of funding, with an estimated US$160 million (53%) from the NIH and PEPFAR being invested globally (**Table 4**). The Government of British Columbia, Canada has invested nearly US$68 million in the Stop HIV/AIDS campaign. The majority of philanthropic and private non-profit funding has come from the Dream Fund of the Dutch Postcode Lottery (for *Max*ART study in Swaziland) and MSF.

Discussion

There is considerable evidence supporting the use of ART in prevention of HIV and TB (2-12) and a growing number of ongoing and planned research activities that focus on adding to this growing body of evidence. Our search methodology found 61 projects with 28 randomized controlled clinical trials, including 19 randomized individual or community cluster trials in resource-constrained settings, which are in the planning and early implementation stages. While the principle of ART for prevention of HIV and TB applies to most settings, there is considerable heterogeneity between studies in terms of the design, prioritization, interventions (e.g. early ART, expanded coverage, STTR strategies), funding and geographical location.

The debate on 'when to start ART' has been accentuated by strong evidence demonstrating the prevention benefits of providing ART. The five planned/ongoing randomized controlled trials will provide definite data on both the clinical and prevention benefits of early ART in diverse settings with varying HIV prevalence and economic resources (17, 22, 31, 63, 66). Implementation research in this area will not only add to the evidence base but will also address the technical, operational, programmatic and ethical challenges faced by policy-makers while expanding the eligibility criteria for ART (28, 30).

Many national and international guidelines recommend ART irrespective of CD4 count for serodiscordant couples and are piloting programmes for expansion of immediate ART for this target population (67). It is plausible that ART will have a similar preventive benefit for people

who inject drugs, MSM, transgender people and sex workers. However, the evidence base is less solid than for the prevention benefit during heterosexual sex and we found that there are only a few ongoing observational studies looking at immediate ART for MSM and IDUs especially in low-income countries (39). Although data from observational studies is of considerable value and forms the basis for many WHO recommendations, reliance on evidence from randomized trials for policy development around when to start ART provides a cautionary tale regarding further delays in recommending earlier treatment for these high-risk and vulnerable populations.

For ART to have substantial clinical and prevention benefits, effective approaches to HIV testing, linkage and retention in care, and adherence support are needed. We found that TasP research is increasingly focusing on innovative seek, test, treat and retain strategies (e.g., community-based multi-disease prevention campaigns and SMS reminders) that will address certain critical issues affecting availability and accessibility of services especially for hard to reach populations.

The study has a number of limitations. While a standardized methodology was used and we reviewed studies collected from various sources, some planned or ongoing studies might have been missed. This is particularly true for studies in the planning phase, as these sorts of efforts are often not widely publicized. The search was done in English and key projects in other languages were excluded. Any ongoing or planned modelling research was not included as the focus was on empiric studies. Additionally, data on funding for TasP studies were collected through survey responses and public sources of information. For 12 studies out of the 61 studies, funding information was not available. We also did not review the studies for ethical considerations, however, are cognizant that it is becoming increasingly difficult to study the "when to start ART question" given WHO recommends starting ART at CD4 cell count ≤500 cells/mm^3 and for many other categories (e.g., TB, Hepatitis B, serodiscordant couples, pregnant women, and children under 5) and other national guidelines (e.g., US, the Netherlands, Brazil, France, B.C. Canada) recommend starting treatment after diagnosis irrespective of CD4 cell count.

There is considerable urgency to find effective solutions to prevent the estimated 6,500 new HIV infections that occur each day. ART is both life-saving and plays a key role in HIV prevention. Together with other biomedical and behavioral prevention interventions, it can have greater impact on HIV prevention than a single intervention. The key questions that are actively being researched include the potential individual and public health impact of ART on HIV and TB, ART for key populations, feasibility of effective provision of HIV services, and the acceptability and cost of TasP. A blend of research methodologies that answer these key questions will not only add to the evidence base but also determine the effectiveness of TasP in real-world settings. Determining minimum programme standards necessary to ensure optimal impact should result in improved services for people living with HIV and their community. Findings should also inform our current allocation of resources towards blends of interventions and services that have maximal impact. Of course, gathering data and understanding is a moving target and we will never know as much as we would like to know—in this sort of setting we will need to continue to keep the millions of people living with HIV right now in mind and make the hard policy choices that will benefit them using the data we have in hand. As we move from an era of "does it work?" to "how can we best expand access?" UNAIDS will continue to work with key stakeholders to map outstanding research issues, encourage collaboration

among researchers and the community, and support the rapid translation of new evidence into policy and services for people living with HIV.

Figure 1: Flowchart of literature review process

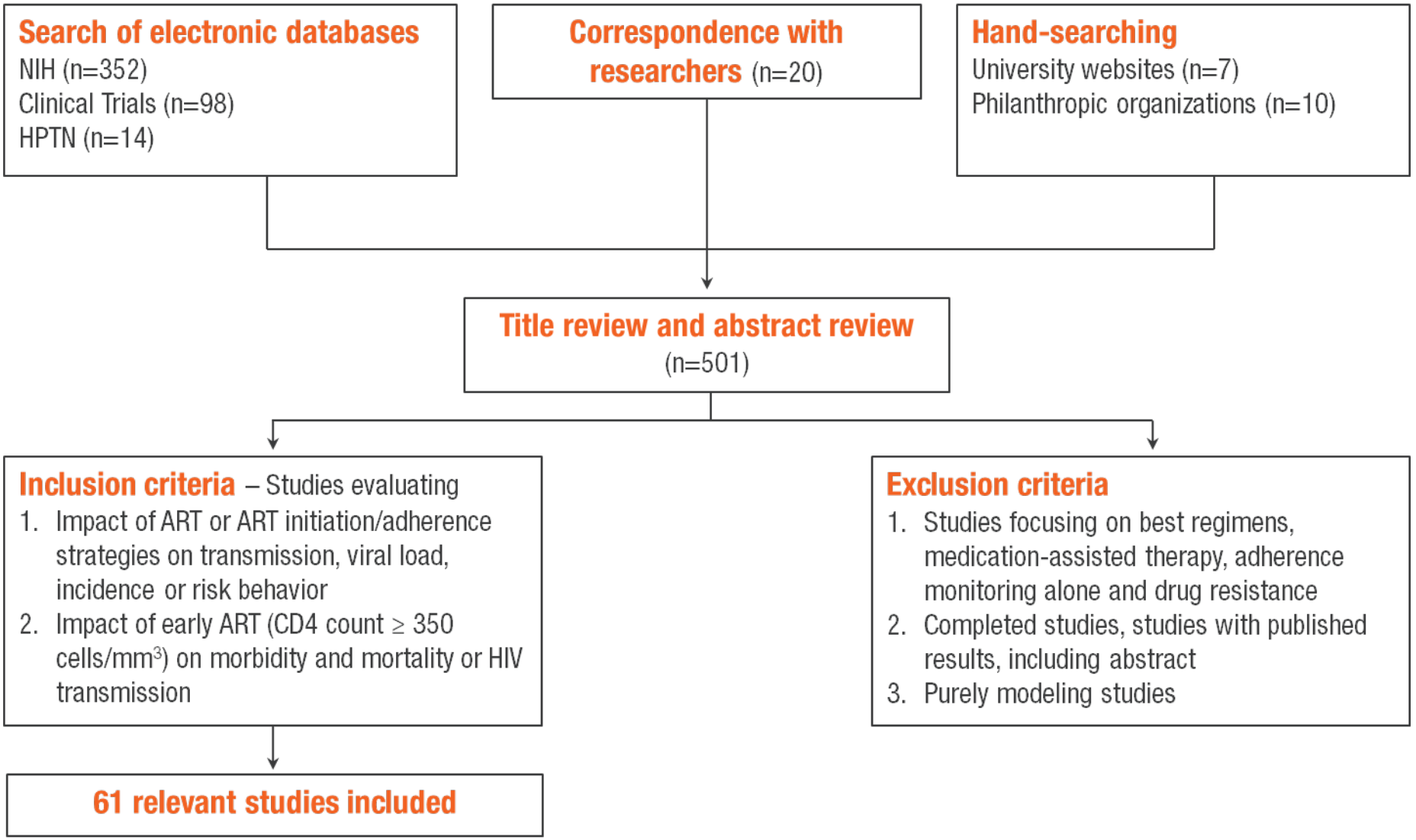


Table 1: List of Ongoing/ Planned Research Projects on Antiretroviral Therapy (ART) in Prevention of HIV and Tuberculosis (TB)

Project	Study Design	Focus	Principal Interventions	Outcomes	Region	Time Period
Africa						
Impact Evaluation of Combination HIV Prevention Interventions in Botswana -The Botswana Combination Prevention Project (BCPP)	Family randomized controlled trial	Impact of combination HIV prevention interventions on population-level HIV incidence	TREATMENT group: Community mobilization and education; enhanced HTC; household testing; linkage to care and immediate viral load testing; point-of-care CD4 testing; enhanced monitoring; male circumcision, PMTCT, option B+, ART at 1. CD4 count ≤350 cells 2. HIV-1 RNA≥10,000 copies/ml (3 drug combination) CONTROL: Standard of care (ART at CD4 count ≤350 cells and standard prevention services)	HIV incidence, population-level coverage of enhanced treatment and prevention services	Botswana	2011-2017
Early Antiretroviral Treatment and/or Early Isoniazid Prophylaxis against TB in HIV-infected Adults **(**ANRS 12136 TEMPRANO)	Randomized controlled trial	Benefits and risks of early ART and/or Isoniazid Prophylaxis	TREATMENT group: 1. Immediate ART (CD4 <800 cells/mm^3) 2. Immediate ART (CD4 <800 cells/mm^3) + IPT for 6 months CONTROL: 1. Standard of care (WHO guidelines) 2. Standard of care (WHO guidelines) + IPT for 6 months	Death (all-cause), AIDS-defining disease, non-AIDS-defining malignancy or invasive bacterial disease	Abidjan, Cote d'Ivoire	2008-2014
Test and Linkage to Care (TLC-IDU) Kenya	Stepped wedge cluster randomized trial	Efficacy of seek, test, treat and retain strategy for IDUs	TREATMENT group: Rapid HIV testing, point of care CD4, link to ART and support of ART adherence via peer case manager and conditional cash transfers; referrals CONTROL: Standard of care (HIV testing, referrals)	Community viral load (individual VLs collected by dried blood spot); Linkage to care; Time to ART initiation	Nairobi and coastal Mombasa, Kenya	2011-2016

Project	Study Design	Focus	Principal Interventions	Outcomes	Region	Time Period
Academic Model Providing Access to Healthcare (AMPATH) Find-Link- Treat- Retain programme	Observational implementation research	Impact on testing, linkage, care and treatment programmes on population-based HIV incidence in AMPATH catchments	Door-to-door, village-by-village home-based HIV counselling and testing, re-testing all HIV-negative persons every 3 years; linking HIV-positive persons into AMPATH or other Ministry of Health HIV comprehensive care clinics; ART; retain all persons enrolled in care and ensure a high degree of adherence to care and treatment using peer-based outreach	HIV incidence	Kenya	2007 onwards
Enhance Prevention in Couples (EPIC)	Feasibility and acceptability studies for planned randomized controlled trial	Effects of combination HIV prevention interventions for serodiscordant couples	TREATMENT group: Enhanced Prevention Package (EPP): Early ART, couples counselling for decreasing sexual risk behavior and enhancing adherence to HIV treatment and care, male circumcision to HIV-negative male partner CONTROL: Standard of care	HIV transmission in HIV-negative partner; feasibility and acceptability of early ART, couples counselling and male circumcision	Lesotho	2009-2013
Malawi Epidemiology and Intervention Research Unit (MEIRU) [Karonga Prevention Study]		Individual and population level impact of ART	ART	HIV incidence, morbidity and mortality, uptake of HIV testing, sexual behavior, TB transmission	Karonga, Malawi	
Assessment of ART scale up, male circumcision and other HIV prevention strategies in Rwanda and its effects to HIV transmission	Multi-state time series analysis	Measuring population level effects of HIV prevention strategies on HIV transmission	ART, male circumcision, prevention of mother-to-child transmission	New HIV infections	460 health catchment areas in Rwanda	2003-2014

Project	Study Design	Focus	Principal Interventions	Outcomes	Region	Time Period
Impact of Immediate Versus South African Recommendations Guided ART Initiation on HIV Incidence (ANRS 12249 TasP)	Cluster-randomized controlled trial	Effectiveness of TasP in reducing HIV incidence at population-level	TREATMENT group: ART irrespective of CD4 count CONTROL: ART at CD4 count < 350 cells or drug resistant TB or WHO clinical stage 3 or 4 irrespective of CD4 count	Acceptability of repeat HIV counseling and testing, treatment acceptance and linkage to care, sexual partnerships and quality of life; mortality and morbidity, retention in care, adherence to ART, virologic failure; HIV drug resistance; cost effectiveness of immediate ART initiation; population-level HIV incidence	Hlabisa sub-district, KwaZulu-Natal, South Africa	2011 onwards
Africa Centre for Health and Population Studies Impact of HIV and ART at population level	Longitudinal household surveillance	Impact of ART coverage on HIV incidence; on mortality; on economic and social environment	Free ART provided in any of the primary health care clinics to all HIV infected adults with a CD4 count of < 350 cells and those with drug resistant TB; option B for pregnant and breastfeeding HIV infected women	At population level: Overall and cause-specific mortality; HIV incidence; ART coverage; HIV prevalence; prevalence of primary resistance; prevalence of acquired resistance; PMTCT; rates of morbidity and mortality by HIV and ART status; burden of disease at hospital level At individual level: mortality before and after ART initiation; long-term safety of and adherence to ART, drug resistance	Rural Hlabisa sub-district; KwaZulu-Natal, South Africa	2000-ongoing
MSF Treatment as Prevention (TasP)	Prospective cohort study	Feasibility and acceptability of early ART and other preventive interventions	POST IMPLEMENTATION: Early ART; male circumcision; and test, link, treat and retain strategy PRE IMPLEMENTATION: Standard of care	HIV and TB incidence, HIV- and TB-related morbidity and mortality, ART coverage, incidence, prevalence and viral load	KwaZulu-Natal, South Africa	2011 onwards

Project	Study Design	Focus	Principal Interventions	Outcomes	Region	Time Period
Combination Prevention For Vulnerable Women In South Africa	Cluster randomized controlled trial	Impact of an integrated set of biomedical and behavioral prevention interventions on HIV incidence for at risk women	TREATMENT group: Test, treat, and retain (TTR) strategy using voluntary counselling and testing (VCT); Women's Health CoOp: HIV prevention strategy that addresses drug use, sex risk behaviors, gender-based violence, empowerment, skills training, and personalized action plans CONTROL: Standard of care (VCT)	ART initiation, adherence, retention, risk behavior, and HIV incidence	South Africa	2011-2016
Rapid Initiation of Antiretroviral Therapy to Promote Early HIV/AIDS Treatment in South Africa (RapIT)	Randomized trial	Evaluation of the feasibility, effectiveness, and cost-effectiveness of rapid ART initiation	TREATMENT group: Rapid ART initiation, if possible on the same day as testing positive for HIV CONTROL: Standard of care	Viral suppression at the routine six-month monitoring visit within 9 months of a positive HIV test; adherence to ARV among pregnant women till delivery	South Africa	2012-2015
Multi-component, Targeted HIV Prevention for Sub-Saharan Africa: PreventionRx	Randomized controlled trial	Effects of evidence-based behavioral and biomedical preventive interventions on HIV incidence	TREATMENT group: ART, male circumcision, behavioral interventions [delivered through a household-based VCT (HBCT) platform] CONTROL: Standard of care	Population-level HIV transmission	South Africa and Uganda	2009-2013
Interventions to Decrease HIV Infectiousness in South Africa and Uganda	Community randomized trial	Impact of efficient delivery of proven HIV prevention and treatment services on HIV infectiousness	TREATMENT group: HBCT-plus: Point-of-care (POC) CD4 testing, enhanced HIV testing, prevention-for-positives risk-reduction counseling and discordant couples counseling, effective linkages to ART and treatment of co-infections	Community viral load and HIV transmission potential before and after HBCT- plus; feasibility of HBCT-plus; uptake of HIV testing by people and their partners, condom use, sexual frequency, disclosure to partners and family, number of	High prevalence areas in KwaZulu-Natal, South Africa and southwestern Uganda	2010-2013

Project	Study Design	Focus	Principal Interventions	Outcomes	Region	Time Period
			CONTROL: Standard of care	partners before and after prevention counseling		
Swaziland HIV Incidence Measurement Survey (SHIMS)	Observational cohort study	Impact of expanded HIV prevention, care and treatment activities on HIV incidence	POST IMPLEMENTATION: Accelerated expansion of HIV prevention, care, and treatment activities - rapid HIV test, pre- and post-counseling, referral to care PRE IMPLEMENTATION: Standard of care	HIV incidence, sexual risk behaviors	Swaziland	2011-2014
Treatment as Prevention approaches in Shiselweni, Swaziland	Prospective cohort studies with nested qualitative studies and costing analysis	Implementation of universal ART	INTERVENTIONS: Early Access to ART: • Phase 1: ART for all HIV+ pregnant and breast-feeding women irrespective of CD4 count and clinical stage; • Phase 2: ART for all HIV+ individuals irrespective of CD4 count and clinical stage HIV Cascade optimization (community based testing, community provision of ART and routine viral load monitoring for guiding adherence support and treatment decisions) STANDARD OF CARE: WHO 2010 Treatment Guidelines + HIV Cascade Optimization	Uptake of ART, retention in care, virological suppression; MTCT and birth outcomes; cost per patient treated; patient perception & operational experiences with implementation	Shiselweni Region, Swaziland	2012-2016
LINK4HEALTH: A Combination Strategy for Linkage and Retention, Swaziland	Cluster site randomized trial	Impact of test, treat and retain on prevention of HIV transmission	TREATMENT group: Combination intervention strategy (CIS): point of care CD4+count assays; accelerated ART initiation; provision of a basic care and prevention package; short message service (SMS) reminders for clinic appointments and active tracking of patients who miss visits; and financial incentives for linkage and retention CONTROL: Standard of care	Linkage to HIV; retention in care; time to ART initiation; HIV disease progression; patient acceptability; and infections averted	Swaziland	2012-2015
*Max*ART (Maximizing ART for Better Health and Zero New Infections)	Implementation science	Universal access to treatment within a government-managed health system	POST IMPLEMENTATION: By 2014, increase testing to 250,000 people (adults and children) annually, increase people on ART to 90% of eligible individuals (101,734 people – adults and children), and reduce loss-to-follow-up at 12	People tested each year (adults and children), people on treatment (adults and children) and proportion of patients on treatment lost to follow-up	Swaziland	2011-2014

Project	Study Design	Focus	Principal Interventions	Outcomes	Region	Time Period
			months for people on ART to 10% PRE IMPLEMENTATION: 157,632 people (adults and children) tested each year, 67,871 people (adults and children) on treatment and 22% loss-to-follow-up rate of those on treatment	(adults and children)		
Sustainable East Africa Research for Community Health (SEARCH)	Community cluster-randomized trial	Health, economic and education outcomes of community based health interventions	TREATMENT group: Annual HIV testing, ART for all, diagnosis and enhanced linkage to care of multiple diseases, improving and building community health delivery for ART and other diseases using new, efficient and sustainable care models CONTROL: Annual HIV testing, Standard of care	TB, AIDS, maternal, HIV and all-cause mortality; viral suppression; HIV incidence; education and economic outcomes	Uganda and Kenya	2013-2017
Kakyerere Community Health Campaign	Campaign population-based observational study	Campaign-based approach to testing and referral to care	POST IMPLEMENTATION: Universal HIV voluntary testing and counseling, early linkage to HIV clinical services, multi-disease care PRE IMPLEMENTATION: Standard of care	Uptake and re-uptake of interventions, HIV incidence, population level HIV RNA metrics, and prevalence of TB, hypertension, diabetes	Uganda	2011, 2012 (ongoing)
Early HIV Therapy in Patients With High CD4 Cell Counts (EARLI)	Observational study	Treatment outcomes in HIV-positive people initiating early ART with streamlined delivery system	TREATMENT group: ART at 1. CD4 cell counts between 250-350 (standard ART) 2. CD4 count ≥ 350 cells (study-provided ART) CONTROL: No ART	Virological suppression, adherence and retention in care, adverse events, cost of streamlined ART model	Uganda	2011-2015
Assessing the Impact of Antiretroviral Therapy on Population Level Incidence of HIV/AIDS	Step-wedge community level randomized trial	Impact of expanded access to ART on HIV incidence	TREATMENT group: Increased access to ART CONTROL: ART at current level of coverage	HIV-related morbidity and mortality, population-level incidence of HIV in high-risk populations	Uganda	2011-2015

Project	Study Design	Focus	Principal Interventions	Outcomes	Region	Time Period
HPTN 071 (Population Effects of Antiretroviral Therapy to Reduce HIV Transmission or PopART)	Cluster-Randomized controlled trial	Impact of community-level combination prevention packages on HIV incidence	TREATMENT group: Door-door home-based HIV testing; active linkage to care; referral for male circumcision and PMTCT (with Option B+) services as well as TB and STI services; provision of condoms; ART irrespective of CD4 count (Arm A) and according to national guidelines (Arm B) CONTROL: Standard of care for testing, referral and ART at current national guidelines (Arm C)	HIV incidence; community viral load, ART adherence and viral suppression, ART drug resistance, HIV disease progression, retention in care, death and ART toxicity, sexual risk behavior, HIV-related stigma, case reporting and recording of TB and TB mortality, and process measures on the implementation and delivery of interventions	Zambia and South Africa (Western Cape)	2012-2017
*Max*ART – Treatment as Prevention Implementation Study: Immediate Access to ART for All	Implementation study	Immediate access to ART for all irrespective of CD4 count within a government-managed health system	ART for all HIV-positive individuals irrespective of CD4 count	Retention, viral suppression, ART initiation, adherence, drug resistance, TB, sociocultural factors, cost-effectiveness and return on investment, and estimated new HIV infections	Swaziland	2014-2016 (Planned)
Geographically Concentrated Multi-Level HIV Prevention in Bukoba Urban District: Outcome Evaluation of a Combination Prevention Programme	Interventional study	Prevention of new HIV transmission and acquisition among residents of Bukoba	Individual and couples HIV testing and counseling, voluntary medical male circumcision, ART, Option B+, structural and other behavioral interventions including community mobilization, programme expansion, strengthened linkage, retention, and ART-adherence services	Rate of individual and couple HIV testing; new HIV cases detected; prevalence and incidence of male circumcision; viral suppression; proportion of HIV-positive individuals who enter HIV care and initiate ART/ARV prophylaxis	Tanzania	2013-2017 (Planned)

Project	Study Design	Focus	Principal Interventions	Outcomes	Region	Time Period
Impact Evaluation of Combination Prevention to Reduce Population-Level HIV Incidence in Rakai, Uganda	Observational Cohort (Rakai Community Cohort Study), Interrupted Time Series Analysis	Impact of combination HIV prevention, including TasP, on HIV incidence	ART (CD4<350 cells/uL, WHO Stage 4, Option B+, HIV+ member of discordant couples at any CD4 levels), medical male circumcision (MMC), HIV counseling and testing, behavioral interventions, PMTCT, demand creation	HIV incidence and service coverage	Rakai, Uganda	2013-2017 (Planned)
Evaluation of an Integrated Community-Based and Clinical HIV/AIDS Programme in Sinazongwe District, Zambia	Interventional study	Evaluation of changes in HIV incidence following implementation of the integrated HIV programme	Confidential home-based HIV counseling and testing; support groups and networks; support and referral services between the community and health facilities through trained community members and groups; HIV prevention intervention; couples counseling and testing, male circumcision, ART and PMTCT	HIV incidence rates in men and women	Zambia	2013-2017 (Planned)
Asia						
Active treatment pilot project in China	Observational study	Impact of early linkage to ART on mortality	One-stop shop for HIV antibody, CD4 and WB test and linkage to HIV care	Mortality of newly diagnosed of HIV/AIDS cases	Guangxi, China	2012 onwards
Multi-component HIV Intervention Packages for Chinese MSM	Observational study for planned clinical trial	Impact of Test and Link-to-Care (TLC) on HIV sero-incidence for MSM	TREATMENT group: Multi-component TLC intervention package: Expanded HIV testing with prompt initiation of risk reduction intervention and optimal ART CONTROL: Standard of care	HIV incidence	Beijing, China	2011-2015
Integrated Care Clinics for IDUs in India: A cluster randomized trial	Randomized controlled trial	Effectiveness of IDU-oriented integrated care clinics (ICCs) for improving outcomes along seek, test, treat, and retain continuum	TREATMENT group: Single-site, integrated provision of IDU/HIV services including HIV VCT; ART; risk-reduction counseling; needle exchange; opioid substitution therapy; condom distribution; treatment of sexually transmitted infections, TB and viral hepatitis screening CONTROL: Existing (fragmented) IDU/HIV services	Access to VCT; HIV transmission risk behaviors; use of ART; community viral load	India	2011-2016
Study to evaluate	Observational	Acceptance of	All participants receive HIV testing and ART	Repeated HIV testing rate and	Bangkok,	2012-

Project	Study Design	Focus	Principal Interventions	Outcomes	Region	Time Period
the feasibility of universal HIV testing and ART regardless of CD4 count using the Test and Treat strategy among MSM and transgender women in Thailand	study (randomizatio n of retention strategies)	regular HIV testing among HIV-negative MSM/TG and of immediate ART regardless of CD4 count among newly diagnosed HIV-positive MSM/TG	counseling (if tested HIV-positive, regardless of CD4 count) Participants are randomized 4:1 to receive intensive retention strategy (regular communication via social networking tools) or standard retention strategy (telephone call reminder)	immediate ART acceptance rate; Retention rate in the intensive and standard retention arms; Adherence to ART and HIV RNA suppression in blood and ano-genital compartments; Changes in risk behaviors and rates of STI	Ubonratchatha ni and Lampang, Thailand	2015
Seek, Test, Treat Strategies for Vietnamese Drug Users: A Randomized Controlled Trial	Randomized controlled trial	Effectiveness of seek, test, treat model for IDUs	TREATMENT group: Text messaging and methadone access to support adherence and retention of people on ART in treatment CONTROL: Standard of care	ART uptake, ART adherence, treatment outcomes	Hanoi, Viet Nam	2010-2015
Antiretroviral therapy for prevention and treatment in serodiscordant couples in Viet Nam	Implementatio n research – One arm intervention study	Feasibility of providing couples HIV testing and counseling, and early ART in serodiscordant couples	Couples HIV testing and counseling; ART regardless of CD4 count for the HIV-positive partner	CD4 count at diagnosis; Couples HTC uptake; Linkage to care; ART retention; viral suppression; self-reported risk behavior; ARV adverse events	Viet Nam	2013-2014
Testing and Linkage to HIV Care in China: A Cluster Randomized Trial	Cluster randomized controlled trial	Effectiveness of test-and-linkage-to-care innovations	TREATMENT group: A new testing algorithm, consisting of rapid point-of-care HIV and CD4 testing, with viral load testing in parallel; provider and patient incentives programme designed to enhance linkage and retention in HIV care CONTROL: Standard of care	Proportion of HIV-positive patients linked to ART, proportion who achieve viral load suppression, mortality	Guangxi, China	2013 onwards (Planned)
Periodic HIV testing and counselling and immediate ART among people who	Implementatio n research – Two-arm quasi-	Feasibility and acceptability of universal voluntary HTC, and	TREATMENT group: Immediate ART regardless of CD4 count CONTROL: ART initiation at CD4 count < 350 cells	CD4 count at diagnosis; HTC uptake; Linkage to care; retention in care and on ART; viral suppression; self-reported	Viet Nam	2013-2015 (Planned)

Project	Study Design	Focus	Principal Interventions	Outcomes	Region	Time Period
inject drugs in Viet Nam	experimental intervention study	early ART among PWID		risk behavior; ARV adverse events; (incidence in needle-sharing partner)		
North America						
HAART Optimism, Drug Use and Risky Sexual Behavior among men who have sex with men (MSM) in British Columbia	Population-based observational study	Effects of universal and free-of-cost ART as a preventive measure for high-risk population	Universal and free ART access, linkage to care, rapid HIV testing	HIV risk behavior among MSM, HAART optimism, treatment adherence and continuation	British Columbia, Canada	2011-2016
Effect of HAART Expansion on Community Levels of HIV Viral Load and HIV Risk Behaviors among MSM in British Columbia	Population-based observational study	Effects of expanded access to ART on HIV risk behavior and viral load	Universal access to ART	HIV risk behavior among MSM, HIV viral load	British Columbia, Canada	2010-2013
Seek and Treat for Optimal Prevention of HIV/AIDS	Province-level interventional study	Effects of seek and treat for high-risk population	Expanded HIV testing, HAART access and support services	HIV/AIDS-related morbidity and mortality and number of new infections (HIV incidence)	Vancouver, British Columbia, Canada	2009 onwards
Impacts of Universal Access to HIV/AIDS Care among HIV-positive Injection Drug Users	Prospective cohort study	Effects of universal ART as a preventive measure for high-risk population	Seek, test and treat campaign; HAART free of charge	Community-level viral loads, HAART resistance, HIV incidence	Vancouver, British Columbia, Canada	2006-2013
Seek And Treat For Optimal Outcomes And Prevention In HIV & AIDS in IDU	Population-based observational study	Effects of seek and treat for high-risk population	Expanded HAART coverage	Health outcomes, new HIV infections	British Columbia, Canada	2008-2013
Same-Day HIV Testing and Treatment Initiation	Randomized trial	Impact of same-day HIV testing and ART initiation	TREATMENT group: Counseling and social support, and ART initiation on the day of presentation for HIV testing	Proportion of patients who are alive and in-care with a plasma HIV-1 RNA level <50 copies at	GHESKIO Center, Port-au-Prince, Haiti	2013-2015

Project	Study Design	Focus	Principal Interventions	Outcomes	Region	Time Period
to Improve Retention in Care		on retention in care	CONTROL: 3 sequential visits for ART readiness counseling and testing for OIs prior to ART initiation	12 months after HIV testing		
TLC+ (HPTN 065): A Study to Evaluate the Feasibility of an Enhanced Test, Link to Care, Plus Treat Approach for HIV Prevention in the United States	Community-based study	Feasibility of test, link-to-care and treat strategy	INTERVENTION group: Expanded HIV testing, linkage to HIV care and viral suppression (financial incentives), a computer-delivered prevention for positives intervention, and surveys of patients and clinicians NON-INTERVENTION group: Standard of care	Feasibility and/or effectiveness of components of TLC; new cases of HIV infection	Washington DC, the Bronx, New York; 4 non-intervention communities (Chicago, Houston, Miami, Philadelphia) in US	2010-2014
Peer-driven Intervention to Seek, Test and Treat Heterosexuals at High Risk for HIV	Community-based study	Efficacy of a peer-driven intervention (PDI) and a venue-based sampling intervention to seek, test, treat and retain HHR	INTERVENTION group: Peer-driven seek strategy with peer education, HIV counseling and testing, and patient navigation if HIV-infected NON-INTERVENTION group: Peer referral seek strategy, HIV counseling and testing, standard of care if HIV-infected	Rates of newly diagnosed HIV infection, time to HIV care and HAART initiation, CD4, viral load suppression, and retention; HIV health/treatment outcomes	New York City, US	2011-2016
A Randomized Controlled Trial and Cohort Study of HIV Testing and Linkage to Care	Randomized controlled trial and cohort study	Efficacy of test and link-to-care strategy at community correction	1. On-site rapid HIV testing with Project Bridge to improve linkage to care 2. Referral for rapid HIV Testing at a community health center or HIV testing clinic with Project Bridge to improve linkage to care	HIV testing, retention in care, ART initiation, HIV viral load suppression	Providence, Rhode Island and Baltimore, Maryland, US	2010-2015
Effectiveness of Peer Navigation to Link Released HIV+ Jail Inmates to HIV Care	Randomized controlled trial	Peer-based navigation versus usual care to improve linkage and retention in care	TREATMENT group: Individually delivered peer-based learning approach to address barriers to and facilitators of linkage and retention in HIV care CONTROL: Standard of care	Barriers to HIV care, linkage and retention in care, ART adherence, viral load suppression	Los Angeles, US	2010-2015

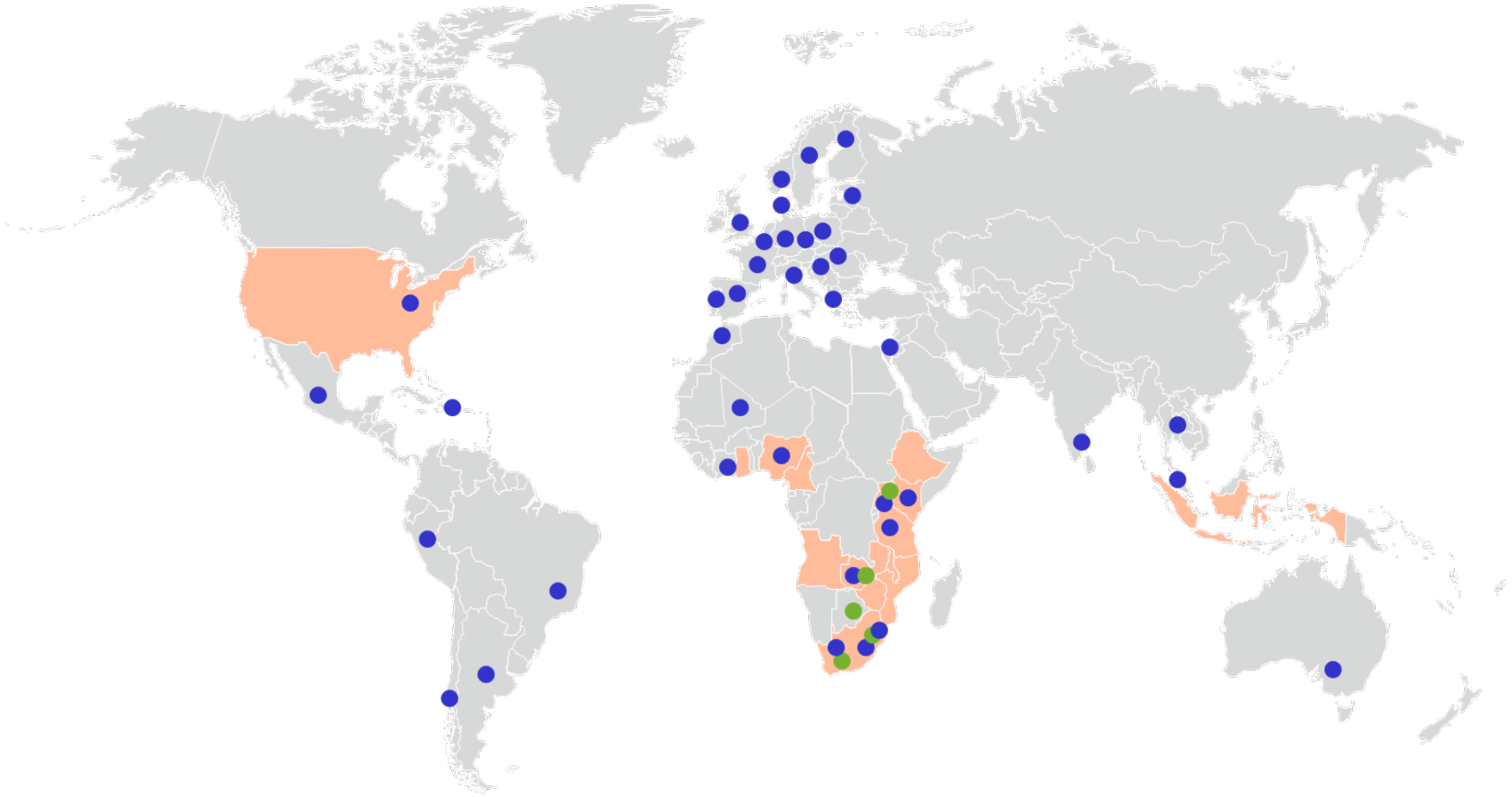
Project	Study Design	Focus	Principal Interventions	Outcomes	Region	Time Period
Randomized Controlled Trial of an Augmented Test, Treat, Link, & Retain Model for North Carolina and Texas Prisoners	Randomized controlled trial	Multi-component intervention programme for prisoners pre- and post-release	TREATMENT group: Client engagement and participation in HIV care, personalized linkage to care and support services, supportive services (e.g., mental health and substance abuse) CONTROL: Mandatory or opt-out HIV testing, universal ART access	Plasma HIV RNA post-release, HIV transmission risk behaviors, incident STIs, ART adherence and utilization of care, predicted HIV transmission events	North Carolina and Texas, US	2010-2015
Seek, Test, Treat: An Integrated Jail-Prison-Community Model for Illinois	Community-based observational study	Effectiveness of seek, test, treat model (STT) integrating jails, prisons, community-based organizations	Opt-out HIV testing in jails, transition case management, university-based telemedicine, incentives for retention in care and social network HIV testing and partner notification	Effectiveness of component of the STT model, community-level HIV viral load, new HIV infection, HIV treatment outcomes	Illinois, US	2010-2015
CARE Corrections: Technology for Jail HIV/HCV Testing, Linkage, and Care (TLC)	Randomized controlled trial	Use of information and communication tools (ICT) for jail detainees	TREATMENT group: CARE+ corrections counseling session, and SMS texting to enhance linkage to and retention in community care CONTROL: Behavioral reporting only on computer, and standard jail discharge planning services with respect to linkage to care	HIV viral suppression, HIV transmission behaviors and cost-effectiveness compared to traditional services	Rhode Island and Washington DC, US	2010-2015
Finding, Testing and Treating High-risk Probationers and Parolees with HIV	Comparison design	Linkage and retention in HIV care in the community for people involved in criminal justice system	"Project Bridge" case management focused on meeting multiple needs and maintaining continuity of care between criminal justice and community setting	HIV viral load, HIV care and HAART uptake	Oakland, California, US	2010-2015
START Together: HIV Testing and Treatment in and after Jail	Randomized controlled trial	Efficacy of START Together in criminal justice system	TREATMENT group: HIV reentry programme for incarcerated populations, computer assessment and risk-reduction education, peer health navigators CONTROL: Standard of care	Proportion of inmates receiving HIV testing and proportion of individuals with undetectable HIV viral load post-release	New York City, US	2010-2015

Project	Study Design	Focus	Principal Interventions	Outcomes	Region	Time Period
Project HOPE - Hospital Visit as Opportunity for Prevention and Engagement for HIV-infected Drug Users	Randomized controlled trial	Effective strategies for achieving HIV virologic suppression among hospitalized substance-using HIV patients	TREATMENT group: Active patient navigator (PN) component; PN with contingency management component CONTROL: Treatment as usual	Viral suppression, drug use, all-cause mortality, linkage to and retention in HIV care and in drug abuse treatment, medication adherence, hospitalization rate	Multi-site, US	2012-2014
Behavioral Intervention To Enhance HIV Test/Treat	Randomized controlled trial	Effectiveness of behavioral interventions to improve ART adherence	TREATMENT group: Integrated HIV treatment adherence - risk reduction intervention - Single office-based counseling session followed by 4 cell phone delivered counseling sessions CONTROL: Time-matched non-contaminating attention control condition	HIV transmission risk behaviors, HIV treatment adherence, viral load and STI prevention	Atlanta, US	2012-2017
Implementation and Evaluation of a Comprehensive Prevention with Positives Intervention at HIV Clinics *(APTcare)*	Group-randomized design with 6 HIV clinics	Evaluate effectiveness of a multi-component intervention to improve HIV patients' health and reduce transmission risk	TREATMENT group: Behavioral screening of all patients, provider messaging, clinic metrics to providers, brief computer-based intervention (CBI) for patients with detectable viral load, and counseling from health coach for VL detectable patients who didn't benefit from CBI CONTROL: Standard of care	Viral load status of patients, ART adherence, retention in care, sexual behavior risks	US	2011-2016
HOME: A Comprehensive HIV Testing And Linkage Package For Young MSM Of Color	Population-based observational study	Efficacy of home-based HIV testing in reducing HIV transmission	POST IMPLEMENTATION: Home HIV tests; online videos, social networking, SMS texting, and telemedicine (live video) linkage from patient to clinician); support network for young men to test and get linked into care PRE IMPLEMENTATION: Standard of care	HIV new infections; HIV testing rates and access to care; reduction in health disparities	Oakland and San Francisco, US	2012-2017 (Planned)
South America						
HIV Testing And Treatment To Prevent Onward HIV Transmission Among High-Risk MSM and	Randomized controlled trial	Effect of rapid ART after HIV infection on HIV viral load	TREATMENT group: Evidence-based treatments for alcohol use disorders; community mobilization and partner services to increase the number of at-risk MSM tested; expansion of testing algorithms to detect and establish infection; linkage to care; linkage to care and ART at enrollment visit; and	HIV viral load in the blood, semen and rectal secretions	Lima, Peru	2011-2016

Project	Study Design	Focus	Principal Interventions	Outcomes	Region	Time Period
transgender women			promotion of continued HIV care and treatment CONTROL: Standard of care			
Enhanced Access to HIV Care for Drug Users in San Juan, Puerto Rico	Randomized controlled trial	Seek, Test, Treat, and Retain paradigm for drug users	TREATMENT group: HIV care services and ART through a mobile health van and patient navigators CONTROL: Standard of care	Virologic suppression, HIV care visits, uptake of ART, and adherence to ART	San Juan, Puerto Rico	2013-2018
Europe						
Partners of People on ART: a New Evaluation of the Risks (PARTNER Study)	Observational study	Risk of HIV transmission in serodiscordant couples on ART who do not use condoms always	3-6 monthly reporting of transmission risk behavior, HIV testing for the HIV negative partner	HIV transmission risk to partners, reasons for non-usage of condoms, rate of infection in partners per person year of unprotected sex	14 European countries	2010 onwards
Australia						
Opposites Attract Study	Observational cohort study	Impact of ART on HIV transmission in gay male serodiscordant couples	3-6 monthly reporting of ART & viral load in HIV-positive partner; HIV antibody tests and transmission risk behavior in HIV-negative partner	HIV transmission risk to HIV-negative partners	Sydney, Melbourne, Brisbane, Cairns and Canberra, Australia	2011-2015
Global						
START - Strategic Timing of Antiretroviral Treatment	Randomized controlled trial	Effects of early ART initiation on morbidity and mortality	TREATMENT group: Immediate ART initiation following randomization CONTROL: ART initiation at CD4 count <350 cells or when AIDS develops	Serious non-AIDS (major cardiovascular, liver, and renal disease and non-AIDS defining cancers), AIDS, or all –cause mortality	235 sites in 35 countries	2009-2016

Project	Study Design	Focus	Principal Interventions	Outcomes	Region	Time Period
HPTN 052 A Randomized Trial to Evaluate the Effectiveness of Antiretroviral Therapy Plus HIV Primary Care versus HIV Primary Care Alone to Prevent Sexual Transmission of HIV-1 in Serodiscordant couples	Randomized controlled trial	Early ART for prevention for prevention of sexual transmission of HIV in serodiscordant couples	TREATMENT group: ART upon enrollment (at 350-550 cells/mm^3) and HIV primary care, couples HIV counseling CONTROL: ART at CD4 count below 250 cells/mm^3 or AIDS-defining illness	Rates of HIV infection among partners of HIV-infected participants, long-term safety of and adherence to ART, drug resistance, rates of AIDS-defining illnesses, sexually transmitted diseases, opportunistic infections, and immune reconstitution syndromes	21 sites in 9 countries (Botswana, Brazil, India, Kenya, Malawi, South Africa, Thailand, US, Zimbabwe)	2005-2015
Test and Treat to End AIDS (TTEA)	5-year 12 country Global Lobbying Plan	12 countries disproportionally impacted by HIV/AIDS	Professional lobbying and the use of advance technology communication tools	Have national governments adopt test & treat as national policy, fully fund test & treat in national budgets (at 90% coverage) and evaluate test & treat for impacts at both individual and population levels for transmission reduction, costs/economic benefits, tax generation, mortality, stigma, discrimination	Multi-site (12 countries)	2014-2019 (Planned)

Figure 2: Map representing countries with studies on early ART for general population and combination HIV prevention programmes



Note: Orange represents countries with more than 10,000 new HIV infections (age 15+) in 2011; the blue dots represent countries conducting research on early ART for general population and the green dots represent countries with combination HIV prevention strategies.

Figure 3: Timeline on projects with early antiretroviral therapy (CD4 count ≥ 500 cells/mm^3) for general population

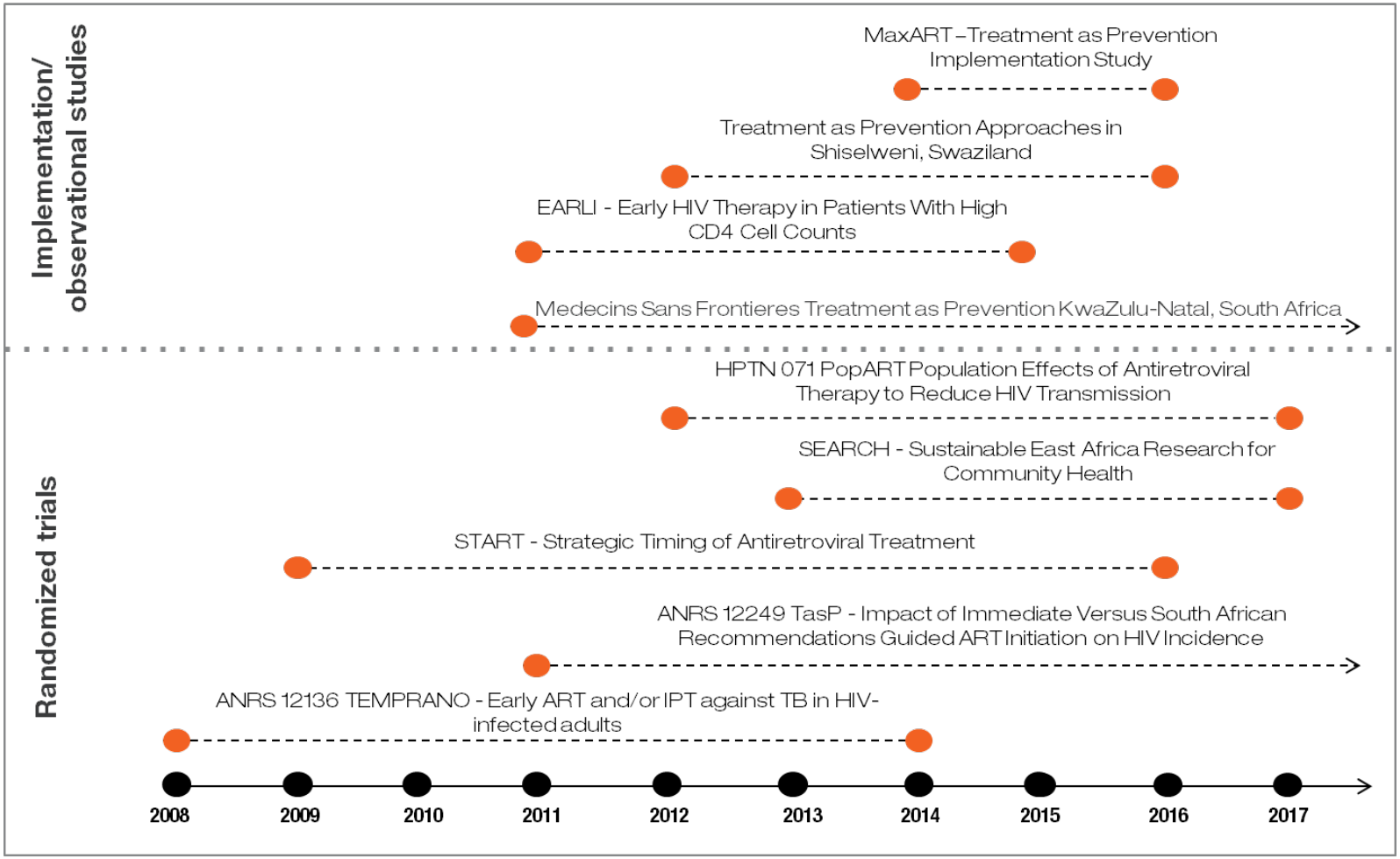
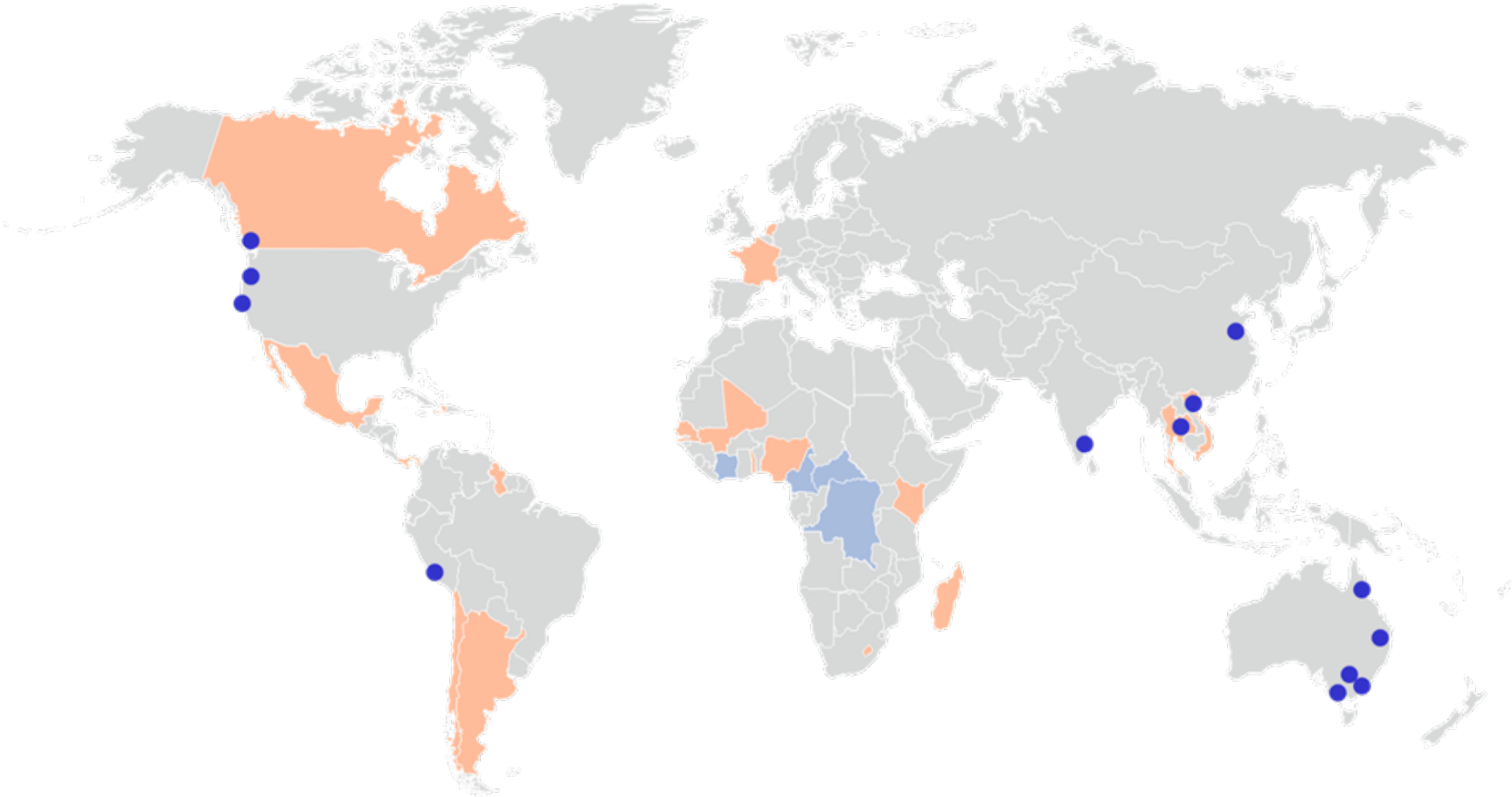


Table 2: Outcomes of earlier initiation of ART on morbidity, mortality and transmission being evaluated by TasP randomized trials

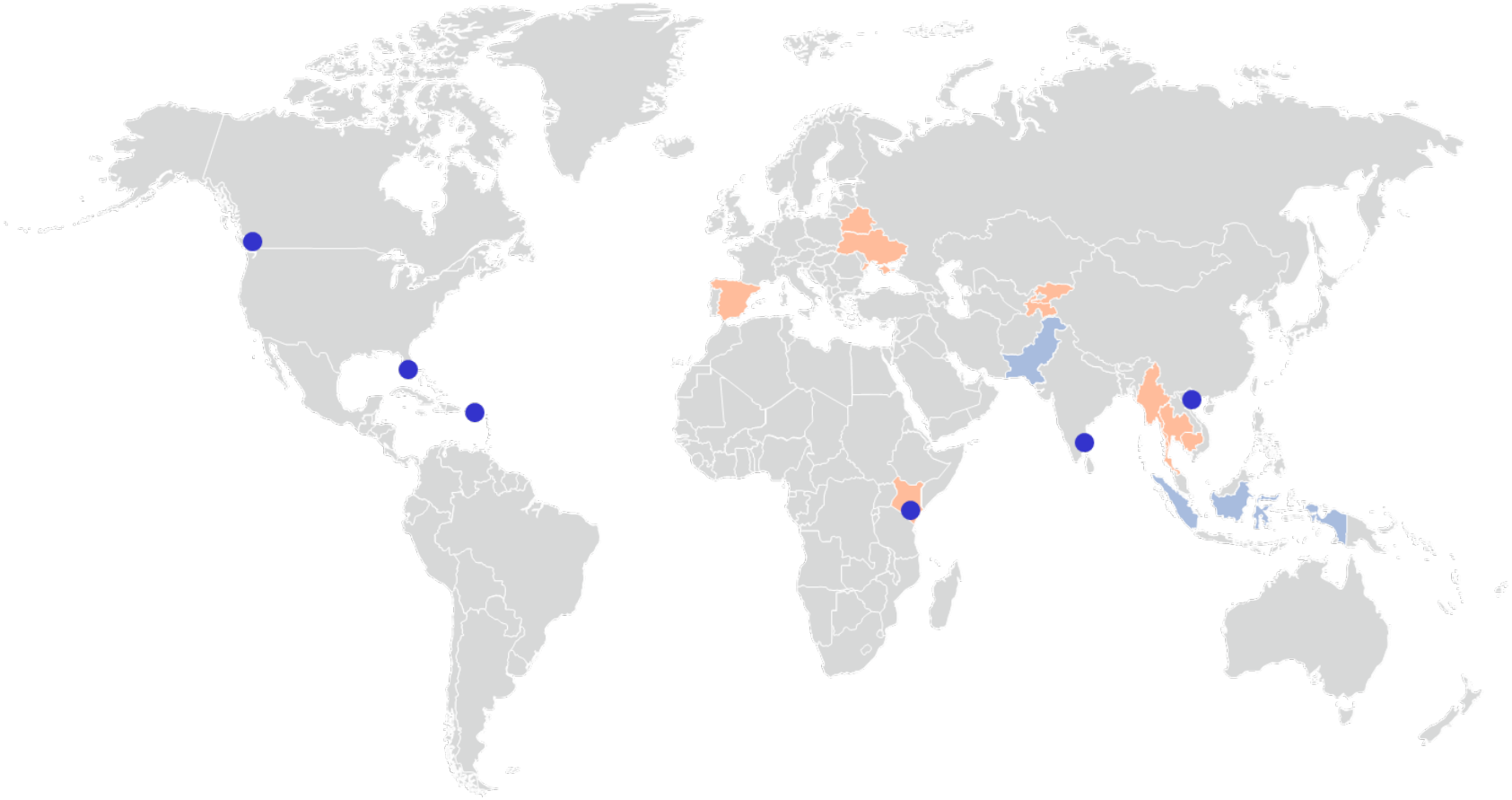
Randomized Controlled Trials	ART Eligibility Criteria	Clinical Outcomes	Socio-Behavioral Outcomes	Population-Level Outcomes	TB Outcomes
Early ART and/or Early IPT against TB in HIV-infected Adults (ANRS 12136 TEMPRANO)	CD4 count < 800 cells/mm^3	Death (all-cause), AIDS-defining disease, non-AIDS-defining cancer or bacterial disease			TB incidence and TB mortality
START - Strategic Timing of Antiretroviral Treatment	CD4 count > 500 cells/mm^3	Non-AIDS (major cardiovascular, liver, and renal disease and non-AIDS defining cancers), AIDS and all–cause mortality			
Impact of Immediate Versus South African Recommendations Guided ART Initiation on HIV Incidence (ANRS 12249 TasP)	ART irrespective of CD4 count	Mortality and morbidity, retention into care, adherence to ART, virologic failure and acquired HIV drug resistance	Acceptability of repeat HIV counseling and testing, treatment acceptance, sexual partnerships and quality of life	HIV incidence; cost-effectiveness	
Sustainable East Africa Research for Community Health (SEARCH)	ART irrespective of CD4 count	TB, malaria, maternal, HIV and all-cause mortality; viral suppression		HIV incidence; education and economic outcomes	TB mortality
HPTN 071 Population Effects of Antiretroviral Therapy to Reduce HIV Transmission (PopART)	ART irrespective of CD4 count	ART adherence, viral suppression, ART drug resistance, HIV disease progression, retention in care, death and ART toxicity	Sexual risk behavior, HIV-related stigma, factors associated with uptake and non-uptake of the testing and treatment intervention; community response to the PopART intervention	HIV incidence, community viral load, cost-effectiveness, mathematical modelling of longer term impact	TB incidence and TB mortality

Figure 4: Map representing countries with studies on TasP for men who have sex with men (MSM)



Note: Orange represents countries where 15-25% of MSM are living with HIV (2011); light blue represents countries where >25% of MSM are living with HIV (2011) and the blue dots represent countries conducting research.

Figure 5: Map representing countries with studies on TasP for injecting drug users (IDUs)



Note: Orange represents countries where 15-25% of IDUs are living with HIV (2011); dark blue represents countries where >25% of IDUs are living with HIV (2011) and the blue dots represent countries conducting research.

Figure 6: Timeline on studies evaluating the effectiveness of combination HIV prevention interventions (with ART at CD4 count ≤ 350 cells/mm^3 or according to national guidelines)

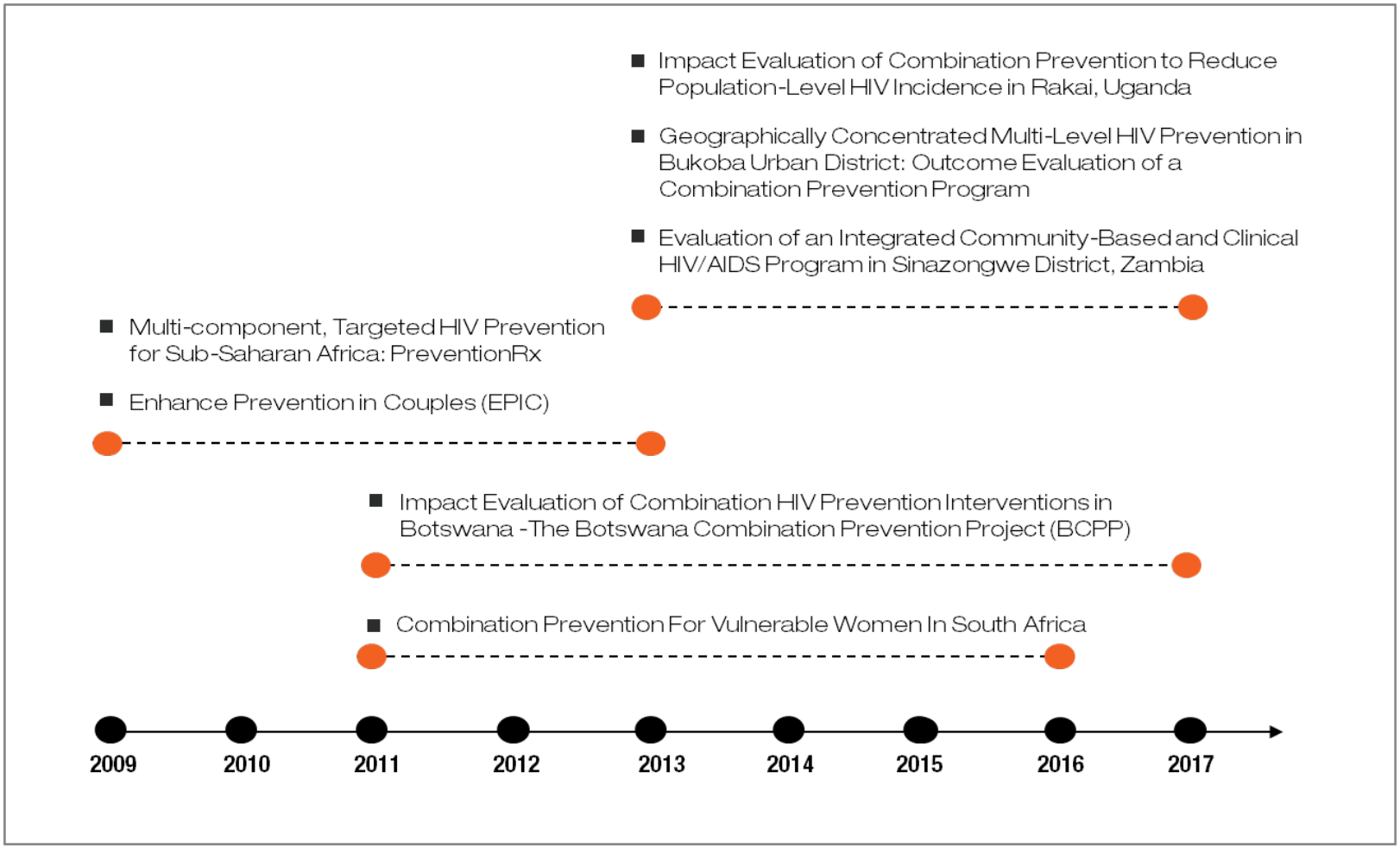


Table 3: The combination of behavioral, biomedical and structural HIV prevention interventions included in multi-component HIV prevention studies

Study	Behavioral strategies	Biomedical strategies	Structural strategies
Combination Prevention For Vulnerable Women In South Africa		Voluntary counselling and testing, ART	Women's Health CoOp to address drug use, risk behaviors, gender-based violence, empowerment, skills training
Multi-component, Targeted HIV Prevention for Sub-Saharan Africa: PreventionRx	Household-based education	ART, male circumcision	
Impact Evaluation of Combination HIV Prevention Interventions in Botswana -The Botswana Combination Prevention Project (BCPP)	Community mobilization and education	Partner testing, ART, male circumcision, PMTCT	Mobile night clinics; linkage with community organizations
Impact Evaluation of Combination Prevention to Reduce Population-Level HIV Incidence in Rakai, Uganda	Behavioral interventions	HIV counseling and testing, ART, male circumcision, PMTCT	
Geographically Concentrated Multi-Level HIV Prevention in Bukoba Urban District: Outcome Evaluation of a Combination Prevention Programme in Tanzania	Community mobilization and education	Individual and couples HIV testing and counseling, ART, male circumcision, PMTCT	Strengthened linkage, retention and ART-adherence services
Evaluation of an Integrated Community-Based and Clinical HIV/AIDS Programme in Sinazongwe District, Zambia		Home-based and couples HIV counseling and testing; ART, male circumcision, PMTCT	Support groups; support and referral services between the community and health facilities through trained personnel
Enhance Prevention in Couples (EPIC) in Lesotho	Couples counselling	Early ART, male circumcision	
HPTN 071 Population Effects of Antiretroviral Therapy to Reduce HIV Transmission (PopART)		Male circumcision, PMTCT (with Option B+), ART irrespective of CD4 count	
MSF Treatment as Prevention (TasP) in South Africa		Early ART, male circumcision	

Figure 7: Total investment in ongoing/planned TasP research in each region (2007 onwards)

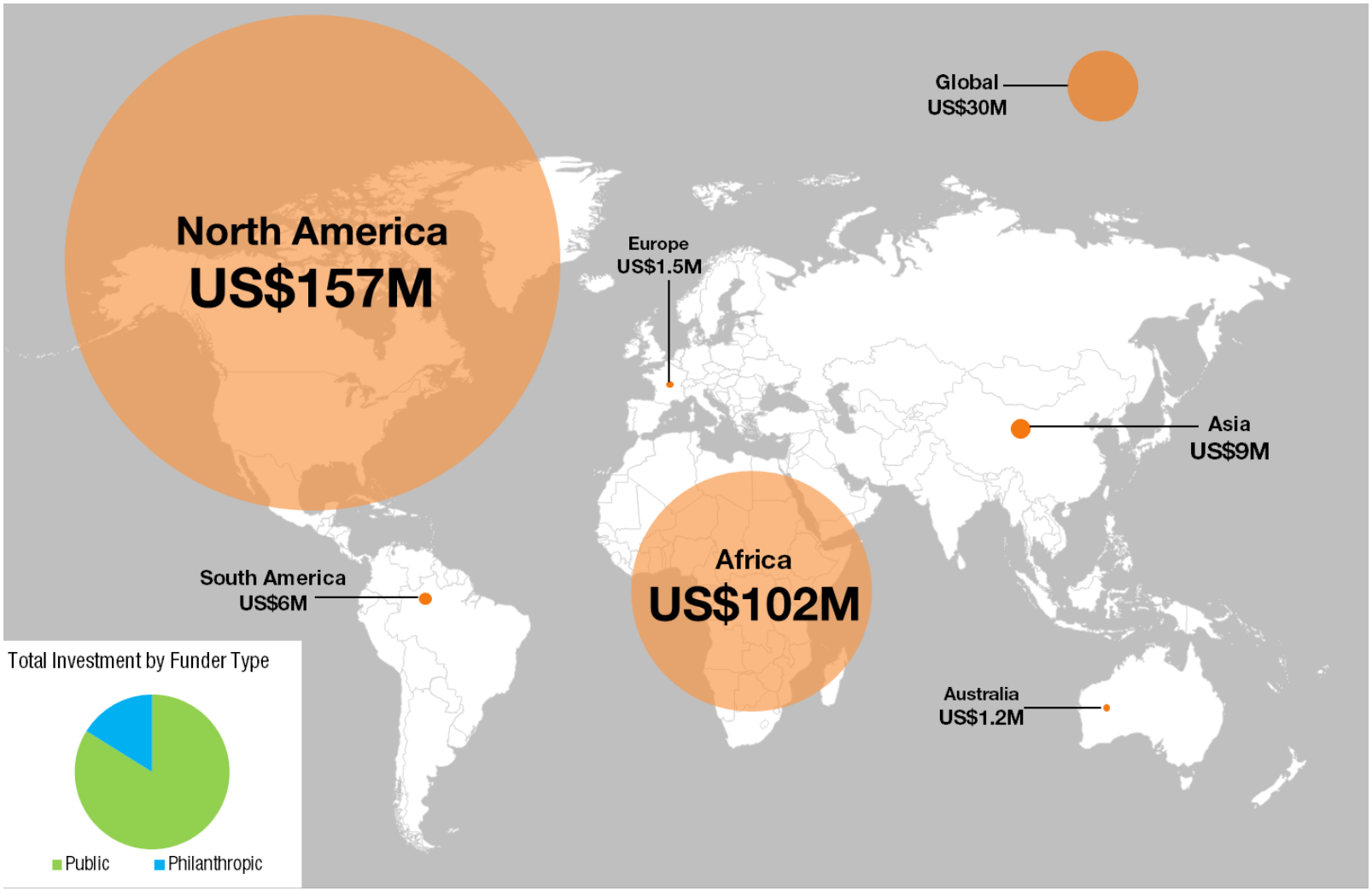


Table 4: Public sector and philanthropic-sector investments in Treatment as Prevention since 2007

Funders	Africa	Asia	North America	South America	Europe	Australia	Global	Total
Public sector								
NIH	$21,096,661	$8,126,545	$79,831,184	$6,056,650				$115,111,040
Multiple funders (including NIH, CDC, PEPFAR)	$39,350,000	$250,000	$9,216,342					$48,816,342
BC government			$67,900,000					$67,900,000
ANRS	$9,486,926							$9,486,926
Others	$1,250,000	$627,132	$432,672		$1,500,000	$1,243,775		$5,053,579
Philanthropic sector								
Dutch Postcode Lottery	$11,310,000							$11,310,000
MSF	$11,226,000							$11,226,000
Others	$8,448,335						$30,000,000	$38,448,335
TOTAL	**$102,167,921**	**$9,003,677**	**$157,380,198**	**$6,056,650**	**$1,500,000**	**$1,243,775**	**$30,000,000**	**$307,352,221**

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