TREATMENT TO PREVENT HIV TRANSMISSION IN SERODISCORDANT COUPLES IN HENAN, CHINA

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ABSTRACT

M. Kumi Smith: Treatment to Prevent HIV Transmission in Serodiscordant Couples in Henan, China
(Under the direction of William C. Miller)

Suppressive antiretroviral therapy (ART) can prevent sexual HIV transmission by reducing viral concentration in the blood and genital tract of infected partners. Whether or not this effect can be achieved in the non-trial settings is a matter of debate. Aim 1 assessed the effect of ART on HIV transmission risk between partners in an open cohort of serodiscordant Chinese couples, past analyses of which have resulted in contradictory findings. Public health data collected for disease control purposes was used to analyze seven years of follow-up data for an open cohort of 4916 previously untreated HIV serodiscordant couples. Using marginal structural Cox proportional hazard models to weight for time varying confounding by treatment and censoring, we found that ART reduced the risk of HIV transmission by 55% (95% CI, 0.23-0.88). However graphical plots of weighted survival curves and stratified analyses by time period indicated a lack of effect before 2009 (HR, 1.27, 95% CI, 0.39-4.11) followed by a much greater effect from 2009 onward (HR, 0.36, 95% CI, 0.19-0.68). This periodicity coincides with a phase of massive scale up and introduction of second line antiretrovirals in China's free ART program, though the protective effect did not appear to vary by specific type of ART regimen. In Aim 2 we used a data from the subset of the same couples who ever received ART in the course of follow-up (N=3939) to assess the impact of distance to the HIV care center and patient load per clinician on HIV transmission risk. Higher patient load (over 100 patients per clinician) was

significantly associated with higher risk of HIV transmission (HR=1.24, 95% CI, 1.27-4.03), particularly among those assigned to village HIV care centers (HR=2.26, 95% CI, 1.27-4.03). Adjusted Cox proportional hazards models found that living farther (>10 kilometers, km) from the clinic was associated with HIV transmission risk (HR=1.18, 95% CI, 0.44-3.1). We hypothesize that motivation for care seeking and minimum thresholds for distances willing to be traveled may differ by the tier of designated HIV care centers.

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AIDS	Acquired Immune Deficiency Syndrome
CI	Confidence Interval
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
IDU	Injection Drug user
MSM	Marginal structural model
STI	Sexually Transmitted Infection

CHAPTER 1: SPECIFIC AIMS

Antiretroviral therapy (ART) administered in clinical trial settings can effectively reduce heterosexual HIV transmission risk by suppressing the amount of virus in the blood and genital tract of the infected partner.[1] Whether or not this effect can be achieved in the real world is a matter of debate. Critics argue that the requirements of durable and reliable viral suppression—optimal drug regimens, routine lab monitoring, timely treatment of other infections, etc.— make this strategy unrealistic for immediate use in resource constrained settings.[2–4] Supporters maintain that the preventive benefit of ART in the real world is already reflected in patterns of transmission at the population level[5] and in the experiences of several cohorts of heterosexual couples where only one partner is HIV infected (known as "serodiscordant couples").[Muessig, in press] Though most such studies confirm the promise of ART as a prevention tool, these reports of serodiscordant couples from China and Uganda found no statistically significant difference in transmission rates between treated and untreated couples followed from 2006 to 2008, weakening the central tenet of the treatment as prevention strategy.[6] Follow-up of the Chinese cohort has been ongoing, and an analysis of data from 2008 and 2011 found that ART was instead protective against transmission,[7] raising further questions about the relationship between ART exposure and HIV transmission in non-trial settings.

Unlike most of the other studies reporting protective effects of ART, the Chinese patients were not managed under special conditions but were rather recipients of routine medical care. Decentralization of HIV treatment to community health centers has been crucial to China's rapid roll out of its national free ART program,[8] but may have bred inconsistencies in treatment

outcomes across local care settings. Receiving primary care at village level clinics (as opposed to at a town or county healthcare centers) was recently found to be predictive of virological failure in a random sample of rural HIV patients in China, as was exposure to ART regimens containing the antiviral agent didonosine.[9] Additionally, members of the original Chinese couples cohort participating in recent qualitative interviews reported widely different experiences regarding availability and accessibility and quality of HIV care. A successful treatment as prevention program will require that ART delivered under real-world conditions like rural China provides adequate viral suppression for its use as a prevention tool. The Chinese leadership has already demonstrated initiative in using treatment to prevent HIV, underscoring the importance of understanding why ART failed to provide consistent protection against HIV transmission in this cohort.

We hypothesized that ART can reduce risk of HIV transmission, and that its efficacy may vary across key factors such as choice of antiviral agents or characteristics of the HIV care delivery model. To test this hypothesis, we investigated how these factors may have shaped the efficacy of ART on HIV transmission risk in the Chinese cohort by 1) refining our exposure variable to incorporate information on the specific agents and patterns of antiviral use and 2) developing new variables to measure characteristics of patients' designated HIV care centers. By accounting for systems-level features and by using the entire observation period (2006-2012), this analysis provides a more comprehensive picture of ART efficacy on HIV prevention in rural China. Specifically we proposed to:

Aim 1. Assess the efficacy of ART on HIV transmission in serodiscordant couples in Zhumadian between 2006 and 2012. We combined data from the initial (2006-2008)[6] and subsequent phases (2008-2011)[7] of follow-up of serodiscordant couples in the study prefecture.

to build a comprehensive database from which to estimate the effect of ART on HIV transmission over the entire observation period. We validated outcomes in the national epidemiology database and exposures in the national HIV treatment database.

Aim 2. Determine the impact of a) distance to index partners' designated HIV care center, and of b) the patient volume at each HIV care center, on the preventive effect of ART on HIV transmission. We used geospatial methods to measure the travel distance between patients' homes and their designated HIV care center, and assessed patient load per clinician to examine their impact on the protectiveness of ART against sexual HIV transmission.

This dissertation improves upon the existing understanding of the efficacy of ART for HIV prevention outside of trial settings, and features of healthcare systems in resource constrained settings that may enhance or hinder the long term efficacy of this potential HIV prevention intervention.

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CHAPTER 2: BACKGROUND

Significance

The concept of using ART to reduce infectiousness of HIV infected individuals is based on over two decades of clinical and epidemiological research.[1] Early intuition about the importance of viral suppression to prevent HIV transmission[2] and results of early randomized control trials (RCT) showing that ART could stop mother-to-child transmission[3] provided a theoretical foundation for the use of ART for HIV prevention. Risk of sexual HIV transmission has been most closely linked with HIV RNA concentrations in the blood,[4–6] which is a relatively reliable proxy for viral concentrations in the genital tract.[7,8] ART for prevention of sexual HIV transmission hinges on the ability of antiretroviral agents to penetrate the male and female genital tracts[9,10] and reduce viral shedding in these compartments. Treatment with ART can reduce (though not always eliminate[11]) HIV shedding in cervicovaginal secretions[12,13] and semen,[14,15] but factors such as co-occurring STIs,[16] drug resistant viral variants in the genital tract,[17,18] or choice of antiretroviral agent[19] have all been associated with higher viral quantities in the genital tract of ART treated individuals.

This body of research provides convincing evidence of the plausibility of using ART to control the amount of virus shed in the genital tract of treated individuals. Understanding the true implications of suppressive ART for prevention of sexual transmission, however, requires epidemiological data from the real world. To date the two major lines of investigation have involved analyses of HIV transmission in population level data (ecological studies, mathematical

modeling studies) and in HIV serodiscordant couples.

Ecological studies

Analysis of changes in regional HIV epidemics in the presence of ART have been used to assess whether a treatment as prevention policy—generally described as frequent universal testing coupled with ART initiation immediately following diagnosis, and high degrees of viral suppressions for treated individuals[20]—could be expected to slow population level HIV transmission. These studies take advantage of "natural experiments" found in settings like San Francisco or British Columbia (Table 1), where existing HIV control strategies have already achieved testing and treatment coverage rates to which future treatment as prevention strategies aspire. By examining the association between changes in ecological measures of population level infectiousness and HIV transmission in the community, these analyses can provide some understanding of the potential of a concerted treatment as prevention strategy.

Methodological limitations of these analyses, however, demand caution in interpretation of results.[21] First, associations between ecological measures can detect relationships only at the group level and lack the person-level details necessary for testing etiological hypotheses.[22,23] Moreover statistical associations do not show causation, and observed trends could be due to factors other than population level suppression due to ART. Rising incidence in the very communities where a treatment as prevention strategy would be expected to be the most successful[24,25] suggests that other forces could limit or reverse the preventive benefits of widespread testing and ART, including changes in sexual behavior in response to widely available ART,[26] saturation of HIV in high-risk groups,[27] in-migration of individuals from high prevalence regions,[20] or the possibility that ART is less protective against transmission through

riskier modes like anal sex or needle sharing.[28–30] Though some of these trends are widely acknowledged, only one of the reports described below formally controls for it in a regression model.[31] Conversely, some of the studies attribute observed declines in HIV incidence, particularly among people who inject drugs, to widespread ART uptake, without acknowledgement of the role that other programs like safe injection sites or needle exchange may have played in the observed trends.[26] Though any of these competing theories can provide plausible explanation for the lack of effect observed in some communities, the lack of data on these factors limits our ability to assess their impact on the associations of interest.

All but two of the above studies[25,32] arrive at the same conclusion that increased population exposure to ART leads to lower HIV transmission. Although ecological studies can play an important role in the development of new HIV prevention strategies, they are methodologically limited to building justification of further formal scientific inquiry into population-level effects of the potential policies in question. They are therefore the first of many steps in the path from science to policy.

Mathematical models

Mathematical models have been used to quantify and project dynamics of HIV epidemics in the presence of ART. In the absence of empirical data, mathematical modeling can be a powerful tool to inform public health decisions by calculating intervention impact, cost-effectiveness, or resource allocation. However, these models are bounded by many assumptions.

We are aware of over 30 separate mathematical models that have been used to quantify and predict the population level impact of ART on HIV transmission, summarized in several extensive reviews on the topic.[33–36] Although many modeling studies provide provocative

evidence that rapid ART scale-up could dramatically reduce[37–45]—or even eliminate[46]—sexual HIV transmission, model plausibility can sometimes be a function of its ability to account for myriad contextual factors expected to affect program outcomes. More sophisticated models have accounted for factors such as changes in sexual behavior in response to treatment;[47–55] sexual network patterns,[52,56] sub-optimal ART efficacy from inadequate coverage, adherence, or efficacy;[57–59] drug resistant HIV strains;[40,60] differential infectiousness according to disease stage;[50,61,62] and the limitations of suppressive ART provision in resource poor settings.[56,61,63] Predictably, the results of these models have been less optimistic.

Wide variation in model results can be attributed to the heterogeneity across model complexity as well as the diversity of the underlying assumptions fed into them. An informed tradeoff between simplicity and plausibility is central to effective application of their results; exceedingly complex models have limited generalizability and interpretability, but predictions generated by overly simplistic ones may be less informative. Harmonization across model choice and inputs is a central goal of modeling teams like the HIV Modeling Consortium at the Imperial College and South Africa Center for Epidemiological Modeling and Analysis, in order to build consensus on the fundamental elements of a successful treatment as prevention program.

HIV Serodiscordant Couples Studies

HIV serodiscordant couple studies provide a critical window into the process of HIV transmission by allowing investigators to observe occurrence of viral *transmission*, beyond just the usual outcome of viral *acquisition.* They also provide the necessary person-level data to inform hypotheses on causal mechanisms driving HIV transmission. In cases where a subset of the initially infected or "index" partner is exposed to ART during follow-up, estimation of the

protective effect of ART on transmission is possible (Table 2).

However the complexity of this research design faces several barriers to valid estimation of true transmission risk. For one, investigators cannot exclude the possibility that infections observed in non-index partners are acquired outside the partnership, which past research has found to be the case in up to 30% of observed events.[64,65] Sophisticated techniques of molecular virology to verify linkage between viral sequences of both partners can validate outcomes, but may be beyond the budget or technological capacity of many research teams. Second, cohorts may over-represent less vulnerable couples that are able to sustain discordancy far longer than those couples with "high and fast transmitters"[66] that become concordant before having an opportunity to enroll in such studies. Oversampling of less infective index cases or less susceptible partners may lead to underestimation of transmission risk.[67] Finally, results of these all of these studies are only generalizable to individuals in stable heterosexual relationships, though several large scale trials among male homosexual couples[68,69] and injection drug users[70] are underway to close this information gap.

These concerns notwithstanding, evidence from these studies form compelling evidence that ART may prevent HIV transmission. First among them is the HPTN 052 trial whose findings that early ART reduces HIV transmission risk by 96% provides "gold standard" evidence of ART's protective effect.[10] Though its rigorous study design confers these results a high degree of validity, the trial environment make it difficult to assess translatability of these results to real world settings where few patients have the access to top-of-the-line antiretrovirals, intensive adherence counseling, or routine laboratory monitoring provided to HPTN 052 participants. Data from non-trial settings include results from retrospective[71–74] and prospective[75–78] studies that have followed a total of over 12,000 couples, in which all but two[79,80] confirm the protective

effect of treatment against sexual transmission. Meta-findings of these studies are summarized in two recent reports.[67,81]

The results of the both studies which reported no protective effect of ART both arise from analyses of the experiences of serodiscordant couples in resource poor areas of Uganda[79] and rural China.[80] Debate on these findings have revolved around the utility of findings from rural settings that commonly lack routine viral load testing and where reliable ART delivery is limited by fundamental resource constraints.[82,83] Though more details from the Ugandan cohort are forthcoming, ongoing follow-up of the Chinese couples cohort—hereafter the "Henan couples," for the name of the study prefecture—have found that between 2008 and 2011, ART was instead highly protective against transmission,[84] raising further questions about the relationship between ART and HIV transmission in non-trial settings. Closer examination of these seemingly conflicting results from the Zhumadian cohort is the subject of this dissertation.

Treatment as Prevention in the Real World

The value of insight gained from analyzing the treatment experiences of the Henan couples depends to a certain extent on the vision of treatment as prevention programs to which one subscribes. The main appeal of using treatment to prevent HIV lays in its dual role as both a therapeutic agent and preventive tool. But our capacity to reap these benefits hinges on the assumption that existing ART programs can confer patients with sustained viral suppression necessary for reducing their infectiousness. Treatment programs in developing country settings such as rural China face various constraints that limit their ability to achieve such outcomes.[85,86] Sustained viral suppression is difficult for patients to achieve even in the best of circumstances, as it requires daily drug adherence and regular monitoring of viral levels in the blood. That rural

Chinese patients were less able to durably suppress their viral levels and prevent transmitting to their partners may be less surprising than useful for highlighting important gaps between clinical science and the real world.

The Henan couples present a scientifically compelling opportunity to assess the efficacy of ART for prevention in such settings because of the lack of other HIV risks that might otherwise undermine outcome assessment. As a rural district in a socially conservative rural community, divorce or marital separation are uncommon, and multiple sexual partnerships are thought to be less common than in urban areas.[87] Prevalence of other risk factors driving HIV infection in the non-index partner including injection drug use, male sex with other men, or sex with commercial sex workers are also low in Henan as compared to other regions in China.[88] Government crackdowns in the late 1990's also eliminated the practice of unregulated blood collection common in the early 1990's, which was responsible for much of the primary HIV infection in this population.[89]

Features of the Henan cohort also make their experiences highly relevant for future treatment as prevention strategies. Unlike the patients from most of the other serodiscordant couple studies who were treated under special conditions, these patients received care through a government-administered program, and their HIV negative partners were routinely screened as part of local health department protocol. Such conditions are notably similar to those specified by treatment as prevention designs that call for universal annual HIV testing and immediate treatment of infected individuals.[46] It is therefore imperative that we understand why treatment initially failed to prevent HIV transmission in this cohort. The Chinese leadership has already demonstrated great interest in this policy and have taken decisive steps towards national roll-out including a province-wide pilot project and four randomized control trials to assess the effect the preventive

effect expanded testing and treatment in sex workers, homosexual men, and heterosexual serodiscordant couples.[90,91] Findings from the research proposed here can therefore play a timely and critical role in ensuring that China's future treatment as prevention programs can effectively be carried out in the real world.

Predictors of Virological Failure in Former Plasma Donors

Despite its early denial about the HIV epidemic, since 2001 the Chinese government has taken decisive steps to address its HIV problem, most notably through the launch of a national free treatment program to subsidize ART for all eligible patients.[92] The program is widely noted both for its scale – about 78.5% of the estimated population of eligible patients are currently on treatment[88] – as well as its success – mortality rates among treated patients have fallen from 39.3 to 14.2 deaths per 100 person years through 2009.[93]

With expanded ART access, however, has also come an inevitable rise in population level rise of drug resistance. The rapid pace of program scale-up, and evolving guidelines that expanded the size of China's treatment eligible population—the minimum threshold for initiation rose from 200 to 350 CD4 cells/μL in 2008[94]—has meant that program coverage outpaced the program ability to deliver high quality service across the system. Care providers in resource poor rural areas also receive very little specialized training in AIDS care,[95] and care seeking behavior is often hampered by fear of stigmatization from the community[96] or even providers themselves.[97] Laboratory resources are also few, in 2011 only 30% of treated HIV patients had received a viral load test in the last year.[93] Suboptimal regimens and few resources for adherence counseling have contributed to rising prevalence of drug resistant strains in China—some estimates for which are as high as 54.67% after one year of ART[98]—boding poorly for both

therapeutic outcomes and risk of transmission to sexual partners of these unsuppressed individuals.

Heterogeneity in treatment outcomes across demographic, geographical, and HIV risk factor subgroups suggest that treatment environment plays an important role in suppressive ART. In terms of treatment response, former plasma donors fare better than most other HIV infected sub-populations, but their risk of virological failure is nevertheless high, and has been associated with factors including lack of adherence counseling[99] tier of HIV are setting,[100] and exposure to certain antiviral agents .[95]

Innovation

A great deal of interest drives HIV research to close the gap between clinical science and effective HIV prevention in the real world. Several large scale community randomized trials for treatment as prevention are underway to provide foundations of evidence for implementation of treatment as prevention policy.[101] Such studies are costly and slow moving, however, and in the meantime thoughtful use of observational data to examine ongoing effects in the community, may help close some key gaps in our understanding. Antiretrovirals and other HIV care services provided through China's free program also provide a realistic representation of conditions in which many global populations without routine ART access may experience with program roll-out. In these ways, experiences of these couples may not only inform prevention potential of ART for couples in other parts of China, but also for those in other developing countries.

Innovations of the this study include the HIV serodiscordant couples study design, which provides a method to simultaneously assess risk factors for transmission *and* acquisition of HIV. Long follow-up (7 years) large sample size (about 5000 couples contacted annually), and

acceptable retention rates for such a low-cost study (over 78% over the entire observation period), all strengthen validity of estimates from this cohort. Rigorous surveillance of the epidemic by local health authorities has also generated a rich database of clinical outcomes in treated individuals as well as results from routine screenings of their uninfected partners.

Primary methodological innovations of this study include measurement of ART as a time-varying variable and the use of marginal structural models to control for time varying confounding with the use of treatment and censoring weights. A secondary innovation is the use of existing geospatial data to calculate distances from patients' homes to their primary HIV care centers as a proxy for healthcare access.

Finally, this study also proposes an innovative and international partnership between HIV researchers in the US and China. The international collaboration between experts at the University of North Carolina Chapel Hill and the National Center for STD/AIDS in Beijing are conducted in the spirit of efforts by both sides to collaborate on large-scale research projects on health sciences, particularly in the field of HIV and STDs.

Preliminary Studies

Four past investigations of ART efficacy against HIV transmission have been conducted in this same study population, findings from which have all shaped this dissertation.

Phylogenetic Linkage of HIV Transmission Events

The first was a pilot study of phylogenetic linkage analysis of transmission events observed in the Henan couples. HIV RNA was extracted and amplified from stored blood plasma samples for 15 couples (or 30 individuals) who had experienced a transmission event between

2006 and 2008. Amplification of any target sequence (*gag*, *pol*, or *env*) had a success rate of 67%, but success of amplification for all three sequences was only 40.%. After aligning *gag* region sequences with reference sequences from the Chinese National AIDS Reference Laboratory, using Multiple alignment program for amino acid or nucleotide sequences software (MAFFT 6.0; http://mafft.cbrc.jp/alignment/software/), distances between sequences were calculated with Molecular Evolutionary Genetics Analysis (MEGA 5.05) using the Kimura 2-parameter model, and neighbor joining phylogenetic trees with bootstrap support were inferred using neighbor-joining and consensus methods.

Results of the neighbor joining and maximum likelihood phylogenetic trees (Appendix 1) were visually inspected for partners who were grouped together on a mono-phyletic branch with a high bootstrap value (>80). According to these criteria, four out of six (4/6) of the Henan couples were linked. Given the small sample size, the fact that we could only consider only a single gene (*gag*), and the lack of information about sample collection dates, meaningful interpretation of these results was not possible. Nor was a larger scale project using stored samples from Henan considered logistically feasible logistical challenges of phylogenetic analyses. Validation of the outcome for this dissertation was therefore limited to evidence from self-reported epidemiological data.

The Henan Couples: Studies 1 and 2

Two past analyses have analyzed the efficacy of ART on HIV transmission in the same population of HIV serodiscordant couples in Henan. The first analysis, "Study 1," analyzed data from 2006 to 2008[80] and the subsequent "Study 2" analyzed data from 2008 to 2011.[84] Study 1 used Cox survival analysis and found no discernable effect of ART on HIV transmission, for which the authors hypothesized that factors such as poor medication adherence, suboptimal

regimens, and exposure misclassification as possible explanations. Using the same methods, Study 2 found instead found that ART was highly protective against HIV transmissions in these same couples.

Divergent results between the two studies may have ben due to differences in sample selection and methods of effect measure estimation. Regarding sample selection, Study 1 used only 35% of eligible couples who were available for analysis in 2008, possibly due to time constraints imposed by the one-time addition of 29 extra survey questions used to assess patient quality of life. Study 2 only analyzed data from the 2007 onwards and largely relied on data collected after the establishment of the web-based reporting system in 2008. It therefore theoretically reflects the experiences of the same couples as in Study 1; however, no formal linkage to records from Study 1 was made.

Choice of statistical model and exposure assessment may have been inadequate for controlling several sources of bias. Traditional multivariate Cox models adjusted for CD4 and viral load which appropriately adjusts for confounding at baseline but which fails to address time varying confounding. In addition, ART exposure was measured as a time fixed "ever vs. never" exposure which may severely misclassify exposure status of couples who initiated ART later in the observation period.

Methods used for this dissertation were chosen expressly chosen for the purpose of addressing these analytical shortcomings.

Qualitative Sub-study on Facilitators and Barriers to HIV Care

To better inform hypotheses about factors that might enhance or hinder the preventive effect of ART, we also conducted a qualitative sub-study consisting of in-depth interviews with

patients and providers from the study prefecture in Henan.. Interview guides were designed to identify facilitators and barriers to routine HIV care, which we theorized would affect treated index partners' ability to sustain virological suppression and therefore reduce risk of HIV transmission his or her sexual partners. Interview guides were developed based on results of a literature review in English and Chinese on barriers to ART adherence in rural or developing country settings. Key informants including experts at the national and local level CDC, as well as experts on qualitative research methods in Chinese settings (Drs Yingying Huang, Gail Henderson, and Kathryn Muessig), provided input on these materials and guidance on study design, participant sampling schemes, and provided feedback on pilot interviews. Preliminary interview guides (Appendix 2) were pre-tested with two patient volunteers and one physician at the Zhumadian City infectious disease hospital. Participants provided verbal consent to have their interviews recorded, transcribed, and reviewed by study staff to assess interview quality and to inform future methods. Pilot interview content was reviewed and discussed by the study team to edit the interview guide for improved flow, culturally appropriate phrasing, and possible probing questions for key content areas. The content of pilot interviews was not directly included in the analysis.

For the full study, HIV infected participants of the annual serodiscordant couple survey who had ever received ART were approached through primary HIV/AIDS care clinician (patients) by research staff to gauge interest in participating in in-depth, semi-structured interviews. Eligible provider participants, including physicians, nurses, pharmacists, and health officials or other staff who were involved in health care provision for HIV infected patients, were approached directly by study staff. Patient participants shared the same eligibility criteria as the overall parent study. Participants willing to provide informed consent took part in two-on-one

interviews in closed, unmarked clinic examination rooms, conducted in Mandarin Chinese and audio recorded unless otherwise specified (two participants declined audio recordings, for which notes were taken). Interviews for patients addressed participants' experiences with routine care seeking for HIV related medical needs, barriers and facilitators to ART adherence, and attitudes and opinions about preventing HIV transmission to sexual partners. Providers were asked about their own barriers or facilitators to helping their HIV patients sustain viral suppression, including their own attitudes towards HIV, personal experiences with stigma, and perceptions of institutional support for their work. In accordance with locally acceptable practices, participants were compensated with a 33ML bottle of cooking oil valued at about 70RMB (about 11USD) for their time and effort. Sampling was designed to maximize representativeness of patient and physician experiences from both high and low HIV prevalence settings. 15 patients and 4 providers were interviews in two high prevalence counties, and 9 patients and 5 providers were selected from a low prevalence county. Transcribed and translated recordings of interviews as well as interview notes were reviewed to generate a set of general impressions and preliminary coding notes. These were summarized into two major themes, described below.

The first theme was that of clinic resources available to HIV patients at their designated HIV care centers. This theme emerged through direct observation over the course of multiple site visits to HIV care centers across the study prefecture. Free ART and HIV care in rural areas of China is delivered through the existing three-tiered healthcare system made up of village clinics, township healthcare centers, and county hospitals. County-level health authorities described to us how they adapted this system to meet the needs of HIV patients by identifying subsets of healthcare sites to specialize in HIV care, a process in which sites are provided medical trainings for clinicians, in which clinic pharmacies are fitted for ART dispensation, and in which clinics

are provided electronic access to the national ART and HIV surveillance databases for direct data reporting. Antiretroviral drugs and HIV care is free to patients only at his or her designated HIV care center, with more severe cases referred up to higher tiers of care. Those who opt for HIV care outside of this referral chain must bear all medical costs themselves. According to county health officials, the decision of which specific healthcare clinics will specialize in HIV care is based on the geographic distribution of HIV patients in each county. Although all HIV care centers theoretically have the same basic capacity, we observed stark differences across tiers of care in terms of factors such as the overall level of medical training among clinic staff, and in-house laboratory testing capacity. The availability of HIV related resources and services therefore varied widely depending on whether the designated HIV care center was a village, township, or county-tier healthcare centers.

The second theme regarding travel distance to patients' designated HIV care centers, emerged through the course of in-depth interviews. Patients living in the same village as their designated HIV care center described the convenience of being able to walk to collect their prescriptions or to receive treatment and care for acute events. By contrast, those living farther from their designated HIV care centers described longer travel distances as a hindrance for accessing routine and emergency care, particularly if arrangements such as child care or transportation had to be made. Patients who received HIV care locally also described their providers as members of their own social community, whereas those receiving care at higher tier centers described feeling more anonymous to their providers.

Preliminary findings from these interviews suggest that the China's community-based model of HIV care delivery has been critical to the success of its free treatment program, but may have also bred inconsistencies across different treatment environments. These findings

became an important link between findings of our primary analysis (Aim 1) and subsequent analyses (Aim 2).

Tables & Figures

Table 2.1. Summary of ecological studies

Author (year)	Study Location	Exposure: population level infectiousness		Outcome: HIV transmission	
		Assessment	Measure	Assessment	Measure
Katz M et al. (2002)[25]	San Francisco, USA	Population in clinical care	Annual prevalence of ART use in HIV infected bi/homosexual men identified in HIV/AIDS registry	Convenience sample of bi/homosexual men	Incidence estimated from 1) HIV testing clinic and 2) STI clinic, using incidence estimation algorithm
Wood E et al. (2009)[31]	Vancouver, Canada	Convenience sample of injection drug users	Biannual median community viral load	Convenience sample of injection drug users	Annual testing in a cohort of HIV negative injection drug users
Castel AD et al. (2011)[32]	Washington D.C., USA	Population in clinical care	Annual mean and total community viral load; portion with undetectable viral load	Sentinel surveillance	Annual numbers of newly diagnosed cases
Das M et al. (2010)[102]	San Francisco, USA	Population in clinical care	Annual mean and total community viral load	Sentinel surveillance	Annual numbers of newly reported HIV diagnoses; annual incidence from surveillance data using serological testing algorithm
Fang C et al. (2004)[103]	Taiwan (national)	Time period	Time period (pre- versus post-ART period)	Sentinel surveillance	Surveillance data used to calculate average annual HIV transmission rate (new /prevalent cases)
Jin F et al. (2010)[104]	Sydney, Australia	No direct assessment	Comparisons to previously reported portions of treated homosexual men in with undetectable VL	Convenience sample of homosexual men	Per-contact probability of transmission in bi/homosexual men
Law M et al. (2011)[105]	Australia (national)	Population in clinical care	Annual portion of treated patients with undetectable VL	No direct assessment	Reference to previous publication describing HIV incidence trends during same period
Montaner J et al. (2010)[106]	British Columbia, Canada	Population in clinical care	Annual numbers of HIV patients receiving HAART; annual mean community viral load	Sentinel surveillance	New HIV positive tests per 100 population
Porco et al. (2004)[107]	San Francisco, USA	Probability sample of bi/homosexual men	Predicted per-contact infectivity based during the pre- and post-ART period	Probability sample of homosexual men	Annual testing in a cohort of HIV negative bi/homosexual men
Tanser F et al (2013)[108]	KwaZulu-Natal, S Africa	Population based cohort	Population level ART coverage rates	Population based cohort	Results of HIV-uninfected repeat testers in surveillance system

Caption: Table 2.1: A summary table of studies that assess the association between population level ART exposure and HIV transmission using at least one ecological measure. STI: sexually transmitted infection. VL: viral load.

Table 2.2. Studies of HIV serodiscordant couples

Author (Year)	No of couples	Study design & population	Trans-mission in treated couples	Trans-mission in untreated couples	Conclusions
Birungi Jel al. (2012)[79]	586	Prospective cohort of clients of an AIDS support organization and their negative partners	9/352	8/234	ART was not associated with reduced risk of HIV transmission in serodiscordant couples in a rural program in Uganda without viral load testing.
Castilla J et al. (2005)[71]	393	Retrospective study of HIV clinic patients and their seronegative partners	2/80	27/313	Combined ART according to current guidelines have a great potential for preventing HIV transmission to sexual partners.
Cohen M et al, (2011)[10]	1763	Serodiscordant couples prospectively enrolled in randomized control trial to compare early vs delayed ART	1/866	27/877[a]	Early ART was associated with 96% reduction in risk of HIV transmission as compared to regular ART.
del Romero J et al. (2010)[75]	625	Prospective study of couples recruited through HIV+ patients at an HIV/STI clinic	0/191[b]	5/341	Heterosexual infectivity of HIV-1 I individuals taking effective antiretroviral treatment is low.
Donnell et al. (2010)[109]	3381	Prospective study of HIV+ and HSV+ individuals and their HIV- partners from the Partners in Prevention HSV/HIV Transmission Study	1/349[c]	102/3032[c]	Molecular virology to established linked transmissions. Provision of ART to HIV-1 infected patients could be an effective strategy to achieve population-level reductions in HIV-1 transmission.
Jia Z et al. (2012)[72]	38862	Retrospective analysis of all HIV infected individuals identified in the national surveillance database who have negative partners	0/112	5/227	Transmission risk reduced 35% in the first year of treatment, an effect which becomes non-significant after the fourth year of treatment.
Melo M et al. (2008)[76]	93	Prospective study of HIV clinic patients and their seronegative partners	0/41	6/52	Transmitters showed significantly higher median viral loads, suggesting that heterosexual transmission of HIV is more a function of viral load than gender of index case. ART use may play a role in the prevention of HIV-1 heterosexual transmission.
Mussico et al. (1994)[73]	436	Retrospective study of HIV+ clinic and HIV surveillance center clients and their seronegative partners	6/64	6/52	ART in HIV-1 infected men reduces, but does not eliminate, heterosexual transmission of infection.
Reynolds et al. (2010)[74]	250	Retrospective study of serodiscordant couples offered free ART if eligible	0/32	42/218	HIV-1 transmission may be reduced among HIV-1 discordant couples after initiation of ART due to reductions in viral load and increased consistent condom use.

Sullivan et al. (2010)[77]	2993	Prospective cohort of serodiscordant couples initiated on ART if eligible	4/808 [b]	264/2125	ART was associated with a 94% reduction in transmission; ART initiation is a critical component of a package of biomedical and behavioral prevention services.
Wang et al. (2010)[80]	1927	Retrospective analysis of former plasma donors and their seronegative spouses	18/540	66/1303	Transition events occurred with equal frequency in couples regardless of whether the partner was provided ART.
Wang et al. (2013)[84]	4499	Prospective cohort of former plasma donors and their seronegative spouses	77/3505	23/583	Trends in declining HIV incidence over time was significantly associated with ART in the index partner.
Watera et al. (2009)[78]	138	Prospective cohort of couples identified at HIV testing center	0/45	3/93	ART seems to be associated with a particularly low risk of HIV transmission.

Caption: Table 2.2. [a] "Untreated" couples had standard of care ART; [b] Mono or dual therapy; [c] Genetically linked transmissions.

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CHAPTER 3: RESEARCH DESIGN & METHODS

The study design, study populations, and outcome assessments for the first and second aim were identical, and so are only described briefly for the second aim. Separate exposures that were used for Aim 2 are described in that section.

Study Setting and Population

Our study prefecture is located in the south of Henan, a rural province in the central plains region of China (Figure 3.1). The HIV epidemic in Henan Province is largely attributed to unsanitary blood/plasma selling practices prevalent in the mid-1990's which resulted in the largest known cohort of individuals infected through commercial blood selling in the world.[1] By the time government crackdowns effectively ended these practices in 2000, entire villages of former donors had been infected with HIV, with estimates of the total number of HIV infected in Henan in 2004 ranging from 50 to 170 thousand.[2,3] Among all prefectures with reported HIV cases, those living in our study prefecture made up 19,927 or 38.1% of all cases reported in the province at the time[2] (Figure 3.1).

In 2006 officials at the disease control center (CDC) of the study prefecture initiated follow up of an open cohort of HIV serodiscordant couples living in the prefecture, with technical guidance from investigators at the National Center for AIDS/STD Control & Prevention. The cohort included couples meeting all of the following eligibility requirements: 1) registered residents of the study prefecture, 2) over

16 years of age, 3) in a stable marriage (no separation or divorce), 4) in a HIV serodiscordant couple at the time of enrollment and 5) willing to provide informed consent. HIV status of both partners was confirmed at enrollment through enzyme-linked immunosorbent assay (ELISA; Wantai, Beijing, China) conducted by county-level CDC's, and positive test results are confirmed by Western Blot assay (Wantai, Bejing, China) carried out at the prefectural CDC laboratories.

Couples took part in an annual survey questionnaire in which partners were interviewed separately in face-to-face interviews with trained county-level CDC staff in their native dialect. Participants provided information on demographic characteristics, behaviors including extramarital sex and condom use, medical histories including sexually transmitted infection (STI) diagnoses, and history of, or plans for migration to other cities or provinces. HIV infected index partners provide additional information on HIV/AIDS related medical history including dates of ART initiation, regimen changes, or termination. Routine patient follow-up dictated regular CD4 testing for all HIV infected individuals, conducted at the county level CDC with guidance from the prefectural health authorities. According to national guidelines, viral load testing was only conducted for individuals after ART initiation, making this information unavailable for all unexposed person years. Non-index partners underwent HIV testing at each annual survey, and individuals who tested positive are referred to their county-level CDC for posttest counseling and screening for treatment eligibility. Beginning in 2008 a centralized web-based reporting system was established to facilitate data collection and to allow direct enrollment of newly identified serodiscordant couples.

In the first year of the survey 3407 couples participated; by 2012 an additional 1878 couples had been enrolled, for an overall retention rate of 78.8% over the entire survey period.

The average age of index partners in 2008 was 44.2 ± 7.69 years (range 30-69). 90.4% of them reported "farmer" as their occupation, and 83.6% reported sexual intercourse in the past 3 months.

HIV/AIDS Care Delivery in Henan

Henan was one of the earliest pilot sites for China's national ART program, which began in 2002. Early pilot sites were strategically located in regions hardest hit by the blood selling epidemic, in order to channel lifesaving drugs directly to patients in this region who had been infected longer and were therefore in most advanced stages of disease. To facilitate rapid distribution of ART and other HIV care, policy makers used a decentralize model to deliver services to even remote rural areas through the existing three-tier healthcare system of village, township, and county level healthcare centers[4] (Table 3.1). To accommodate the uneven geographic distribution of persons living with HIV, county level health officials designated specific facilities to specialize in HIV care and treatment based on the prevalence patterns of their county. Designated HIV care centers were fitted with additional capacity for dispensing ART and for filing electronic case reports and patient charts to the national health authorities. In addition clinical staff received training in HIV/AIDS care, sometimes through collaborations with international organizations. HIV patients were eligible for fully subsidized care at their designated HIV care center, with more severe cases referred up to higher tiers of care. HIV care (but not ART) sought outside of this vertical referral chain was possible if patients were willing to bear the entire cost themselves. The tier of clinic to which patients of a given county were assigned depended on the officials' reasoning of the most cost effective and convenient distribution of a combination of upper and lower tier clinics to provide care.

The diversity of AIDS delivery models is best captured through a description of its extremes. In the highest prevalence settings, a larger number of healthcare facilities are designated as AIDS care centers, and, as the most prevalent type of healthcare facility, village clinics can be expected to make up the majority of such facilities, and, higher-level AIDS facilities will almost exclusively handle only the most critical cases. By contrast in lower prevalence counties, fewer facilities are designated as AIDS care centers but will also more likely be to a higher-level facilities such as a town or county level center. Through this model optimizes healthcare access for the patient population at large, it also inevitably disadvantages a minority of patients unfortunate enough to live far from his or her designated HIV care center.

The conceptual model of healthcare access as a multifaceted interplay between client and system is complicated in China by the government's policy approach of channeling resources down to localities through the top-down state system. Although Chinese HIV patients without the economic means to pay for their healthcare at better care centers of choice, as a group they still exercise demand and choice, creating for a unique dynamic between patient demand for quality care and system supply of the "five A's--availability, accessibility, affordability, acceptability, and accommodation.[5] A better characterization of this dynamic is one of the key goals of Aim 2.

Drug Regimens of the Free ART Program

The earliest antiviral agents available to Chinese HIV/AIDS patients through the free ART program were generic forms of zidovudine, stavudine, didanosine, and nevirapine. Nearly 80% of early patients were given a treatment regimen consisting of zidovudine, didanosine, and nevirapine,, with the remainder on stavudine instead of zidovudine due to complications with the

former. As more antiviral agents came off patent domestically produced generic version of indinavir became available. In addition starting in 2005 the China Ministry of Health began to import branded versions of efavirenz and lamivudine.[6]

Aim 1 Study Design and Methods

Study Design

Our first aim was to determine the efficacy of ART on HIV transmission in serodiscordant couples in Henan who participated in at least two annual study visits between 2006 and 2012. We hypothesized that exposure to ART regimens by the index partner reduced the hazard of HIV seroconversion in the non-index partner as compared to couples whose index partners were exposed to ART.

Bias from differences in underlying risk rates between new and prevalent users of drug have been identified as key sources of bias in past pharmacologic analyses.[7] We found that ART users who had initiated ART before study enrollment had a slightly lower risk of HIV transmission (0.35 cases per 100 person years) than their counterparts who initiated therapy while under observation (0.47 cases per 100 person years). This difference can be attributed to lower adherence among new initiates of ART who may be more likely to experience adverse drug effects or prescription to suboptimal regimens. Inclusion of prevalent users in our study may therefore confer even greater protectiveness to ART exposure and exaggerate the estimates down and away from the null. Inclusion of these individuals would also mean forfeiting the ability to control for their baseline factors that are themselves affected by the treatment, such as CD4. Exclusion of the 369 prevalent users in our new user design reduced the number of couples by 7.1%. Due to low rates of treatment termination (1.2%), all new users of ART were assumed

to continue therapy until they were censored.

Primary exposure

The primary exposure was ART in the index partner, which was measured as a time varying variable in which changes in exposure status are reflected in the values in each time interval within which the exposure status remains constant. Information on patient ART regimen was extracted from the annual serodiscordant couple survey, and validated against information from the national treatment base. In cases where information from the two sources conflicted, preference was given to the data from the national database.

Primary Outcome

The primary outcome for this analysis was HIV seroconversion in the initially uninfected partner among enrolled couples who participated in at least two annual study visits between 2006 and 2012. Seroconversion was calculated as the midpoint between the date of the last HIV-negative or indeterminate antibody test, and three months before the date of the first positive HIV antibody test, to provide an average window period for seroconversion. Couples experiencing the outcome were censored in the interval in which estimated seroconversion occurred; those who remained discordant throughout the study were censored on the date of their last HIV negative test date. The outcome was validated by means of a manual review of results and dates of all HIV-positive test results in the national HIV surveillance database to which local and regional disease control authorities must report all newly identified cases of HIV infection. In cases where results differed between the two databases, preference was given to the records in the national surveillance database.

Statistical Analysis

A time-dependent marginal structural Cox proportional hazards model was used to estimate the causal effect of ART on HIV transmission in this cohort. Marginal structural models provide valid estimates of treatment effects from observational data when the effect of time varying exposures may be confounded by time-varying covariates that are simultaneously intermediate variables. The models are weighted with the inverse probability of each patient receiving treatment in order to eliminate associations between prior exposure and other risk factors for the outcome. By delinking the propensity for treatment initiation from the variables that predict both initiation and risk of the outcome, these weights can address confounding by indication when exposures and risk factors are both time-varying. As a consequence, these variables are implicated in confounding whether they are included or excluded from the final models Figure 3.2 provides a hypothetical example of how time-varying exposures and covariates can result in conflicting model building criteria, showing how possible causal pathways from ART_0 and ART_1 to HIV transmission travel through unconfounded and confounded pathways through $CD4_1$, respectively. For these reasons, whether or not the final model includes $CD4_1$, the estimates generated by a standard Cox model of the effect in question in above will be biased.

To eliminate time-varying confounding by indication, the contribution of each subject *i* to the risk set calculation at each time interval was calculated using the following stabilized weight formula:

$$sw_i = \frac{\prod_{k=0}^{k} \Pr(A_k = a_{ki} \,|\bar{A}_{k-1} = \bar{a}_{(k-1)i})}{\prod_{k=0}^{k} \Pr(A_k = a_{ki} \,|\bar{A}_{k-1} = \bar{a}_{(k-1)i}, \bar{L}_k = \bar{l}_{ki})}$$

where A_k represents time dependent treatment on day k, and L_k represents vector for all measured time dependent risk factors for the outcome, and overbars are used to represent

exposure ($\bar{L}$) or treatment history ($\bar{A}$). The stabilized weight itself therefore represents the degree to which the patient's observed treatment is explained by their prognostic indicators. By weighting the final model with the inverse of these weights, we are able to deemphasize the role in the risk set of subjects whose prognostic indicators strongly agree with their actual treatment experience, and emphasizing the role of those whose treatment is relatively independent of the prognostic indications. The resulting weighted "ghost" population therefore looks far more uniform in terms of their propensity to receive the exposure, in that the association between the prognostic indicators at time t, L(t) no longer predict treatment at time t, and the causal association between treatment and the outcome are the same as in the study population.

Pooled logistic regression models were then used to calculate the numerator and denominator of the subject specific weights separately:

Numerator: $Logit\ \Pr(A_k = 1|\bar{A}_{k-1} = \bar{a}_{k-1}) = \alpha_0 + \alpha_1 a_k + \alpha_2 a_{k-1}$

Denominator: $Logit\ \Pr\left(A_k = 1\middle|\bar{A}_{k-1} = \bar{a}_{k-1}, \bar{L}_k = \bar{l}_k\right) = \alpha_0 + \alpha_1 a_k + \alpha_2 a_{k-1} + \alpha_3 l_k + \alpha_4 l_{k-1} + a_5(a_{k-1} * l_k)$

Covariates making up L included age, sex, occupation, time, and disease stage. Appropriate scaling of age was assessed by comparing likelihood ratio tests for rescaled, log transformed, polynomial, and splines versions. The predicted values estimates by these two models are used to calculated sw_i for each subject using the formula given on the previous page.

The following time-dependent Cox proportional hazards model was then fit with the inverse standardized weights to provide a valid and unbiased estimate of the treatment effect on HIV transmission:

$$\log[h_i(t)] = \alpha(t) + \beta_1 a_i(t) + \beta_2 V(t)$$

where $\log[h_i(t)]$ is the hazard of HIV transmission at time t, $\alpha(t)$ is the baseline hazard of HIV transmission, β_1 is the unknown parameter representing the causal effect of ART on time to HIV transmission, and V are baseline covariates in the population. To accommodate subject-specific time-varying weights, the final model used pooled logistic regression models with time as a class variable to allow a separate intercept for each time, thus mimicking the baseline hazard in a Cox model.

Stratified Analyses

Measures of effect of ART on HIV transmission risk were estimated across the following subgroups: sex, age (≤45 vs >45), baseline CD4 cell count of index partners, type of regimen, and time period, with the inclusion of interaction terms.

For assessment of effect across strata of drug regimen, we compared the different exposure categories of "no ART," "ART without didanosine" and "ART with didanosine." These were coded using disjoint indicators, using "no ART" as the referent category.

Power and Sample Size

In order to test the hypothesis that ART treatment reduces the risk of sexual transmission, the following calculations describe the expected statistical power to detect a range of effects given our existing sample size. Based on the fewest number of couples to ever take part in the annual serodiscordant couple survey since 2006 we used a sample size of 3407, with an ART coverage rate consistent with that as reported in Study 2 of 85.7%. With a two-sided hypothesis with a Type I error rate of 0.05, and the rate of outcomes observed in the unexposed was 2.3 cases per 100 person years. Follow up time was calculated at 7 years, from 2006 to 2012, we estimated

having about 70% power to detect the same effect measure as reported in Study 1 (Figure

Aim 2 Study Design and Methods

The purpose of my second aim was to determine the impact of accessibility and quality of HIV-related care, measured in terms of 1) patient volume per clinician at the designated HIV care center, and 2) distance to one's designed HIV care center and on the preventive effect of ART on HIV transmission. The effect from healthcare access to HIV transmission risk was assumed to be connected through the pathway of viral suppression of index partners due to adherent use to ART. This pathway was hypothesized to operate through the improved clinical response expected among ART patients who more routinely seek care from their primary HIV care provider, thus increasing the likelihood of early identification of virological failure either through clinical or laboratory screening, by increasing frequency of adherence messaging, or by necessary adjustments of less tolerable or suboptimal drug regimens. Behavioral drivers of transmission including frequency of sex and condom use were not assumed to vary by level of access to healthcare and so were not considered in the final model. To isolate estimation to effects traveling through this pathway we restricted analysis of Aim 2 to the subset of couples whose index partner had ever receive ART between 2006 and 2012.

Primary exposures

Our second aim consisted of two separate exposures, patient load per clinician, and distance from treated index partner's village of residence to his or her designated HIV care center. To estimate patient load, clinic level characteristics of designated HIV care centers at which at least one patient from our study sample was assigned was collected in the form of a

survey distributed to the county level health authorities, through which information on clinic tier (village, town, or county), numbers of medical staff, and numbers of treated and untreated HIV patients per clinic were obtained. Patient load was calculated as the total number of HIV patients (regardless of ART status) at each HIV care center, divided by the total number of doctors and nurses at that care center. Both patient load and distance to clinic reflect the state of these measures as of 2012.

Patients' villages of residence were extracted from reported addresses in the most recent survey data in the serodiscordant couple database, or, if missing this information, from the national epidemiology or treatment databases. Addresses of designated HIV care centers were provided by county level health authorities who indicated the specific care center to which treated patients from villages in our sample were assigned. Chinese language addresses were uploaded into an online geomapping service to generate estimated latitudes and longitudes for each point, from which Euclidean distance in kilometers (km) was calculated using the GEODIST function in SAS 9.3 (SAS Institute, Cary, North Carolina, USA).

Primary Outcome

The measurement and coding of the outcome variable of HIV seroconversion in the initially uninfected partner was the same as was used for our first aim.

Statistical Analyses

Univariable Cox PH regression analyses were first used to determine the appropriate functional form of both exposures. Next, both variables were visually assessed by plotting these measures against risk of HIV transmission when measures were coded linearly, categorically,

and as a quadratic spline. The decision to bifurcate distance at ≤10km and >10km was further informed by informal observation of common modes of transportation in the study prefecture where access to electric bicycles, farm vehicles, and public buses were common. A validation sub-step was conducted for 200 randomly sampled individuals in which the geomapping service generated results were compared with manual entry of start and stop points in Google Earth.

The two exposures were assessed independently to estimate the effect of these two measures of healthcare access on HIV transmission. Multivariable causal models were built with the guidance of directed acyclic graphs[8] and informed by common adjustment practices identified in the literature.

For patient volume, causal models of its effect on HIV transmission took the following form of a Cox proportional hazards model:

$$h_i(t) = h_0 * e^{[\beta_1(patient\ volume)_i + \beta_2(V)_i]}$$

H_0: $\beta_1 = 0$; H_0: $\beta_1 < 0$. We hypothesize that receiving care at a village level facility will be associated with greater hazard of HIV transmission, controlling for distance and other factors believed the affect quality and HIV transmission at the same time.

The effect of distance on HIV transmission risk took the form of a standard Cox proportional hazards model as follows:

$$h_i(t) = h_0 * e^{[\beta_1(distance)_i + \beta_2(V)_i]}$$

H_0: $\beta_2 = 0$; H_0: $\beta_2 > 0$. We hypothesized that 1) higher patient load at one's designated HIV care center and 2) farther distance from a patient's residence to his/her primary AIDS care facility would both be associated with elevated HIV transmission risk, controlling for quality of care and other potential confounders. Regarding tiers of care, Based on the results of Ma et al, we expected that patients receiving care at village or township level clinics to experience less

ART efficacy than those receiving care at county hospitals based on a past study on virological failure in this population.[9] On the other hand results from our qualitative study suggested that patients receiving care at county hospitals may be less satisfied and due to the less personal nature of the care they receive there.

Stratification

Assumptions of multiplicatively of effects across sub-strata of tier of HIV care center were assessed using the following models:

$$\log[h_i(t)] = \alpha(t) + \beta_1 ART_i(t) + \beta_2(Type)_i + \beta_3(Distance)_i + \beta_4(Distance * Tier)_i(t)$$

$$\log[h_i(t)] = \alpha(t) + \beta_1 ART_i(t) + \beta_2(Type)_i + \beta_3(Patient\ load)_i + \beta_4(Load * Tier)_i(t)$$

H_0: $\beta_4 = 0$; H_0: $\beta_4 \neq 0$ (for both models). We hypothesized that the coefficient of the interaction between type of facility and ART, and distance to facility and ART would be significant. An alpha value of 0.20 was used in recognition of limited power in detecting significance in more finely stratified data. Stratified estimates for the effect of 1) distance and 2) patient volume on HIV risk were then calculated for each tier of HIV care center (village versus town and county) by interacting this variable with the exposure of interest, in order to estimate subgroup-specific measures of effect.

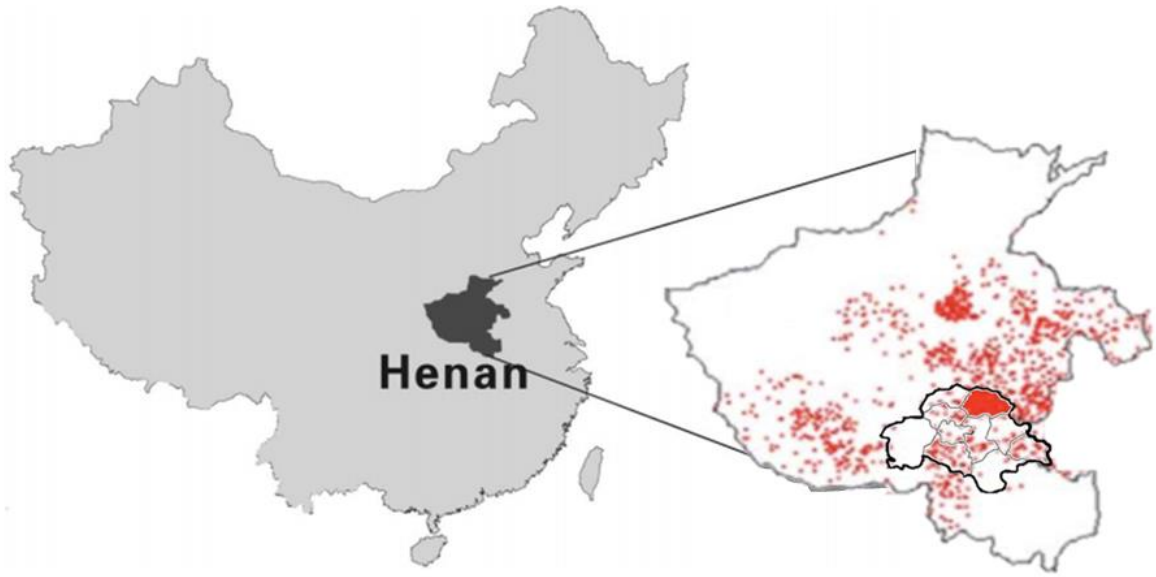
Tables & Figures

Table 3.1. Description of tiers of care in study prefecture

	Advantages	Disadvantages
Upper tier level HIV care centers (county hospitals)	• Best trained and specialized medical staff, most advanced medical equipment	• HIV care and ART prescriptions provided at separate facilities (county hospitals vs. county CDC's)
	• Widest availability of non-ART drug	• Longer wait times, less individualized care, more bureaucratic red tape
	• Shortest turnaround on CD4/VL results	• Care is only subsidized if patient is referred from lower tier HIV care centers
	• Widest availability of ART drug; regimens adjusted more easily	
Lower tier HIV care centers (township health centers, village clinics)	• More individualized care, socialization w other patients	• Most clinicians lack formal medical training and have no specializations, only basic medical equipment
	• Shorter wait times, less bureaucratic red tape	• Low availability of non-ART drugs
	• All AIDS related care is subsidized	• Longest turnaround time for CD4/VL results
		• Long process to change ART regimen

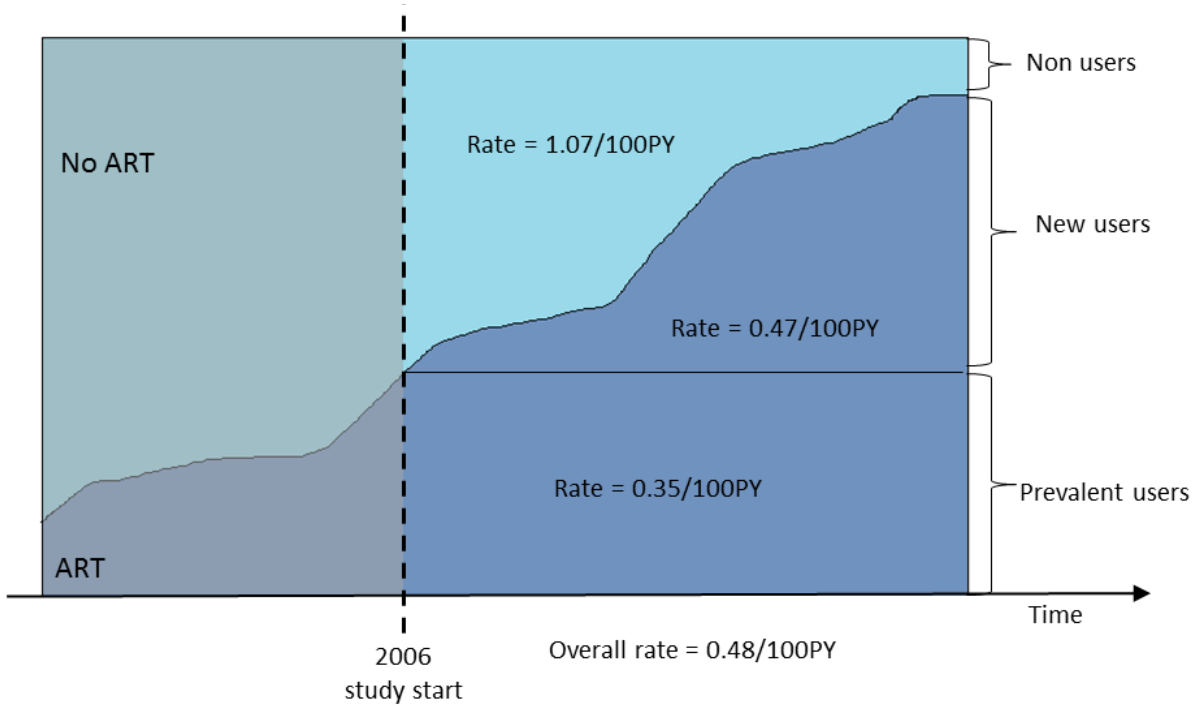
Caption: Figure 3.1: Advantages and disadvantages of care accessed at each type of AIDs care facility in Zhumadian.

Figure 3.1. Map of study prefecture



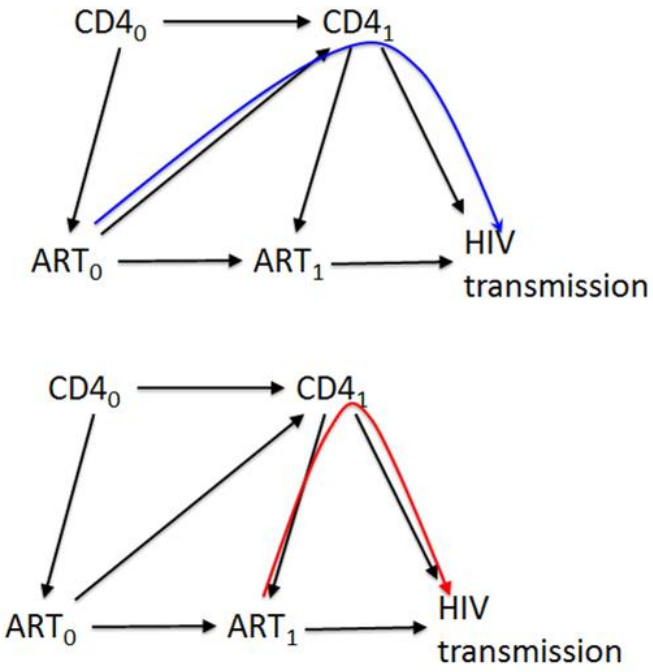
Caption: Figure 3.1: The relative location of Henan Province and the study prefecture outlined in black, within Henan province. Red dots show the geographic distribution of HIV cases among former plasma donors in the province. One red dot equals 20 infections (adapted from Dou et al[10]).

Figure 3.2. New User Design



Caption: Figure 3.2. The new user design excludes prevalent users from analysis, among whom underlying risk may be systematically different than that of new users, given time varying risk patterns over the course of drug exposure.

Figure 3.3. Theoretical causal graph demonstrating time-varying confounding



Caption: Figure 3.3: The graph illustrates the adjustment dilemma when a time-varying covariate is both a confounder and an intermediary of the exposure-outcome association. Adjustment of $CD4_1$ would block a direct pathway from ART_0 to the outcome (blue line) while simultaneously unblocking an indirect pathway from ART_1 to HIV transmission (red line).

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CHAPTER 4: AIM 1

Antiretroviral Therapy for Prevention of Sexual HIV Transmission in Serodiscordant Couples in Henan, China, 2006 to 2012

Introduction

Antiretroviral treatment (ART) administered in clinical trial settings can nearly eliminate heterosexual HIV transmission risk by suppressing the amount of virus in the blood and genital tract of the infected partner.[1] Whether this effect can be achieved outside of trial settings is a matter of debate.[2,3] Critics argue that the requirements of durable and reliable viral suppression—optimal drug regimens, routine lab monitoring, timely treatment for opportunistic infections and other concerns—make this strategy unrealistic in resource limited settings.[4–6] Supporters claim that the potential benefit of ART is already reflected in the collective experiences of several cohorts of HIV serodiscordant couples where only one partner is infected.[7] In two such studies from China[8] and Uganda,[9] however, HIV transmission persisted regardless of the infected partner's ART use. Details of the Ugandan cohort are forthcoming, but a more recent analysis of the same Chinese couples from Henan Province—hereafter the "Henan cohort"—found that ART was since highly protective against transmission,[10] raising further questions about the preventive potential of ART in non-trial settings[11]. Closer examination of these seemingly conflicting results of the Henan cohort is the subject of this report.

This cohort provides an important opportunity to examine the potential effect of ART on HIV as is likely to take place in the real world. The Chinese government provides free and universal ART to eligible patients through a decentralized system. Subsidized care and drugs

(mostly generic) are delivered to patients through the existing healthcare system, in many cases by nonphysician clinicians with minimal training.[12] The program's high coverage of the treatment eligible population[13] makes it a remarkably realistic version of "treatment as prevention" strategies proposed for resource poor settings.[14] Why fewer rural Chinese patients were able to sustain low enough viremia to afford their partners consistent protection may be less surprising than useful for highlighting important gaps between clinical science and the real world.

This analysis uses existing data collected for public health purposes to investigate the efficacy of ART in preventing HIV transmission in serodiscordant couples in Henan using all years of available data (2006-2012).

Methods

Study Setting and Data Sources

The Henan cohort is an artifact of a regional HIV epidemic largely attributed to unsanitary blood and plasma selling practices prevalent in the mid-1990's.[15] Government crackdowns ended these practices by 2000 by which time an estimated 50 to 170 thousand persons in the province were estimated to be living with HIV.[16,17] 38% of the HIV population of Henan live in the prefecture where this study is set.[8]

As part of the government's emergency response to the Henan HIV epidemic, in 2006 the prefectural disease control center began enrollment of an open cohort of HIV serodiscordant couples to track HIV transmission in married couples. According to local guidelines, eligible couples were 1) registered residents of the study prefecture, 2) over 16 years of age (the age of legal consent in China), 3) in a stable marriage (no separation nor divorce), 4) in a HIV serodiscordant couple at the time of enrollment and 5) willing to provide informed consent. HIV

status of both partners was confirmed at enrollment through enzyme-linked immunosorbent assay (ELISA; Lizhu, Zhuhai, Guangdong Province; Xinzhuang, Xiamen, Fujian Province) and positive test results were confirmed by Western Blot (WB) assay (Ou'ya, Hangzhou, Zhejiang Province), both of which were carried out carried out at the county or prefectural level disease control center laboratories.

Eligible couples participated in annual surveys consisting of private and separate face-to-face interviews for each partner in their native dialect with trained county-level disease control staff. Participants provided information on demographics and behaviors over the previous year including sexual contact within and without the primary partnership, diagnosis of STIs, drug use, and activities related to blood exchange (including injection drug use, blood selling, blood transfusions, use of blood products, or invasive medical procedures), and migration for work (seasonal migration for labor is common in this population). The initially HIV infected (or "index") partners provided additional medical history including ART use and initially uninfected (or "non-index") partners were screening for antibodies to HIV, with those testing positive referred to their local county disease control center for confirmatory testing and treatment eligibility screening.

Exposure, Outcome, and other Covariates

The primary outcome for this analysis was time to HIV seroconversion in the initially uninfected partner of couples participating in at least two annual study visits between 2006 and 2012. Seroconversion was calculated as the midpoint between the date of the last HIV-negative or indeterminate test, and three months before the date of the first positive-HIV test to provide an average window period for seroconversion. Couples experiencing the outcome were censored in

the interval in which estimated seroconversion occurred; those who remained discordant throughout the study were censored on the date of their last HIV negative test date. Seroconversion events were manually validated by comparing test results and dates in the national HIV surveillance database, a centralized web-based system[18] to which local disease control authorities report all newly identified HIV cases. If results differed between the two sets of records, information from the national surveillance database was used.

The primary exposure was time-varying ART use by the index partner. As with the outcome, we validated treatment status by comparing our records against those of the national ART database, and priority was given to national ART database information in the event of discrepancies. Additional index partner covariates including disease stage, AIDS related signs and symptoms, and laboratory indicators such as CD4 cell count and viral load were linked from the national epidemiology and treatment databases using a unique identifier.

Statistical Analyses

To minimize potential bias introduced by differential risk experienced across couples whose index partners initiate ART at different times, we restricted analysis to those who unexposed to ART at baseline. By excluding prevalent users, this "new user design[19]" eliminates the bias induced by 1) under-ascertainment of events likely to occur early in the course of therapy and 2) by our inability to control for baseline factors that are themselves affected by the treatment (e.g. CD4 cell count). Exclusion of the 369 "prevalent user" couples reduced the sample size by 7.1%. Due to low rates of treatment termination (1.2%), all new users of ART were assumed to continue therapy until they were censored. Variables for which information was missing for more than 20% of the sample were multiply imputed using Markov Chain Monte

Carlo simulation, and the resulting model estimates were combined using Rubin's formula.[20]

We used Cox proportional hazard models to estimate the association between index partner ART use and time to HIV seroconversion in non-index partners. To mitigate bias from time varying confounding variables that are also affected by prior treatment, we weighted our estimation of a marginal structural model (MSM) with the inverse probability of treatment and censoring to balance treatment groups at each time point.[21] Stabilization with baseline indicators yielded an appropriate weight distribution (mean, 1.04; standard deviation; 0.24; range, 0.27-13.02). The final model was estimated using pooled logistic regression using time as a class variable to allow a separate intercept for each time and for subject specific weight to vary by visit.

Hazard ratios from the MSM were compared with those of) unweighted models, both crude and adjusted; b) weighted models that adjusted for residual confounding by baseline variables identified by directed acyclic graphs;[22] c) a model weighted only for the inverse probability of treatment but not censoring, and d) a complete case analysis restricted to couples with complete data.

Additional analyses stratified estimates using interacting terms for index partner characteristics including sex, baseline CD4 cell count, ART regimen, and time period (2006-2008 versus 2009 onwards, to reflect periods before and after availability of second line ART). The assumption of proportional hazards was relaxed after inspection of the log-log survival curve by interacting our time and exposure variables.

Ethical Approval

All data used for this analysis were collected as part of prefectural disease control efforts. Ethical approval for the analysis of this data for research purposes was provided by the Institutional Review Board of the National Center for AIDS/STD Control and Prevention (NCAIDS) at the Chinese Center for Disease Control and Prevention.

Results

The final analysis included 4916 couples with a mean follow-up of 5.4 years (Table 4.1). The median age of index partners was 44 years (interquartile range: 40-49) and 52.3% were female. Half of index patients (46.8%) were initially infected through blood or plasma donation, and over 90% of them reported "farmer" as his or her primary occupation. Occupation and schooling were largely similar across partners, most (68.9%) of whom had six or fewer years of education. Of the 94.8% (N=4662) couples who reported any sex at most recent follow-up, 63.3% of them (N=3115) reported "always" using condoms. On their first study visits, only 8.4% of index partners had initiated ART, but by 2012, most (82.8%) were receiving therapy.

Few uninfected partners reported any behaviors that might increase subsequent HIV acquisition from outside the partnership. Thirty two (0.65%) reported any episode of extramarital sex in, and in all but once case perfect condom use was indicated in these relationships. Information on past diagnoses of STIs became available in the final year of the study (2012), which showed that 13 uninfected partners (0.4%) received such a diagnosis in the previous year.

In 26,389 total years of follow-up we observed 157 seroconversions (overall incidence, 0.59 cases per 100 person years; 95% confidence intervals (CI), 0.51-0.70). Of these seroconversions, 84 occurred when the index partner had already initiated ART (incidence 0.43

per 100 person years, 95% CI.0.35-0.53) and 73 when not on therapy (incidence 5.87 per 100 person years, 95% CI, 4.65-7.42; Table 4.2). Couples who seroconverted were more likely to be farmers, have had more reported sex over the past year, lower reported condom use, have an index partner whose baseline CD4 cell count below 250, have an index partner who was diagnosed more than five years ago, and who seroconverted in the earlier phase of follow-up (before 2009).

In earlier years of the study, generic drugs—some with known side effects such as didanosine—were used. However, didanosine exposure did not appear to elevate transmission risk (incidence 3.15, 95% CI, 2.29-4.32 versus 5.36, 95% CI, 3.90-7.35 among non-didanosine exposed person years). Viral load is only collected after HIV patients initiate ART; but using this information we assessed that 29.9% of index partners of seroconverting couples were virally suppressed at the time, versus 56.0% of those whose did not transmit to partners, measured at their most recent visit.

In crude analysis, ART reduced the risk of HIV in treated couples by 29% (HR=0.71, 95%CI: 0.34-1.45). Weighting couples by their inverse probability of treatment and censoring resulted in comparable estimates (HR=0.68; 95% CI, 0.34-1.39). Adjustment for residual confounding by baseline indicators of treatment and censoring (disease stage, sex, age, occupation) lowered estimates for the weighted and unweighted models to 0.45 (95% CI: 23-0.88) and 0.43 (95% CI: 0.22-0.84), respectively. In sensitivity analyses, weighting for treatment but not for censoring had little effect (HR=0.44, 95% CI: 0.22-0.86); as with restricting analysis to cases with complete information (HR=0.44, 95% CI: 0.28-0.69). Stratification by sex, index partner baseline CD4 cell count, ART regimen type, and time period showed that ART may be only slightly more protective for male rather than female index partners (HR=0.31, 95% CI,

0.14-0.76 versus HR=0.39, 95% CI, 0.16, 0.94) and for index partners initiating ART at CD4 cell count above 250. We did not observe a noticeable difference of ART efficacy based on if index partners were exposed to didanosine (HR=0.31, 95% CI, 0.13-0.71) or not (HR=0.49, 95% CI, 0.24-1.02).

In comparing transmission risk over time (Figure 4.2) we observed a substantial difference in the effect of ART between the early phase of follow-up (2006-2008) and more recent years (from 2009 onwards).Specifically, we observed no effect of ART in the early period (HR=1.27; 95% CI: 0.39-4.11) whereas ART was effective in the later period (HR=0.36, 95% CI: 0.19-0.68).

Discussion

Our report found that ART can reduce HIV transmission risk in serodiscordant couples in rural China. However the protective effect was neither perfect nor detectable in the early years of the government provided free ART program. The change in ART efficacy over time did not appear to be related to the drug regimen employed, even though in the early years drugs with more side effects were used. We speculate that the improved ART efficacy over time may be at least partially attributable to systems level factors over time, such as improvements in ART delivery systems[23] or increased medication adherence support.[24]

Our report expands on two previous analyses of the same population, the first of which reported no protective effect between 2006 and 2008;[8] and the second which reported that ART nearly eliminated transmission risk from 2007 to 2011.[10] To address possible sources of bias driving these results, our analysis used all available years of data (2006-2012) and validated exposure and outcome data against national disease control records. Our inclusion of more

eligible couples (3182 or 65% additional eligible couples in the same years of follow-up) mitigated potential selection bias and measurement of ART as a time varying exposure (versus status at last visit) captured shifting exposure distribution over time and minimized misclassification bias. Finally, by restricting analysis to couples already exposed to ART prior to enrollment in our new user design, we established clear temporality between baseline confounding variables, ART use, and transmission. These methodological strengths, together with weighting of models with visit-specific inverse probabilities of treatment and censoring to address time-varying confounding, allowed our estimates to more closely mimic those of a randomized trial.

Whether ART reduces HIV transmission risk in stable Chinese couples—which it does—may be secondary to the question of the magnitude and durability of this effect. We found that the hazard ratio of ART efficacy changed dramatically over time (Figure 4.2). Since hazard ratios average potentially time-varying period-specific hazard raios,[25] its magnitude can vary depending on the duration of follow-up, which is a likely explanation for the seemingly conflicting conclusions of the earlier[8] and later[10] observation periods of the Henan cohort. Moreover, dominant modes of HIV infection in China have shifted from blood and plasma selling to riskier sex,[26] resulting in notable changes in baseline characteristics of new ART patients over time.[23] For this reason the 26% relative reduction of HIV transmission risk from ART use reported by authors who analyzed a nationally representative sample of over Chinese 38,000 couples over eight years[27] may in fact averaging over a series of highly diverse effects over time and across patient populations. Stratified analyses provided by these authors hint at the disparity of effects embedded in their large sample; for example, the relative risk reduction from ART use was far greater for couples whose index partner was infected through heterosexual

contact (50%) rather than blood or plasma selling (33%); or for couples followed for shorter periods of time. A smaller study of about 1000 couples in Yunnan Province reported a strong protective effect in virologically linked transmissions from 2009 to 2011,[28] though higher overall transmission rates in couples in Yunnan relative to Henan (1.5 versus 0.5 cases per 100 person years) indicate the need for strategies capable of adapting to local habits and treatment barriers.

China's scale-up of free ART and HIV care to over 100,000 patients by the end of 2011 is nothing short of remarkable, and vastly improved survival rates even among the earliest beneficiaries in rural Henan.[29] Decentralization of ART delivery to rural community health centers and task shifting of primary HIV care responsibilities to nonphysician doctors was key to rapid program rollout, but more resource intensive services such as routine laboratory monitoring or adherence counseling programs have developed more slowly over time. The type of healthcare facility where patients receive care and travel time to clinics have been cross-sectionally associated with outcomes such as poorer adherence[24], virological failure[30], and drug resistance.[31] The interdependence of systems-level factors and the suppressive ability of ART to protect sexual partners of treated patients is the subject of an ongoing analysis. Scale up of ART in areas of low coverage may therefore do well to bear in mind the differential time scales on which direct services (drugs) and ancillary services (adherence counseling, viral load testing) develop, especially when program implementers are forced to prioritize services due to resource constraints.

The Henan couples make up a unique cohort particularly well suited for assessing effects of ART on HIV prevention. The relatively long observation period captures the effects of ART over a historically significant period of treatment scale-up in China. Many resource poor areas where treatment as prevention is expected to have the greatest impact have yet to achieve

Chinese ART coverage levels, and successful programs will need full grasp of potential trade-offs in preventive efficacy during early stages of implementation. Moreover the HIV population of Henan is largely made up of older individuals with low reported rates of drug use or sexual promiscuity[23] (corroborated by low rates of syphilis or reported STI-like symptoms in our cohort); as such, the seroconversions we observed are likely true representations of HIV transmission between primary partners, a hypothesis that could ideally be confirmed through phylogenetic linkage analysis had useable samples of stored plasma been unavailable. In addition results from this cohort are generalizable to the 13% or 56,000 persons diagnosed with HIV in China every year who report a stable relationship with uninfected partners.[27]

Virtually all current normative guidelines call for immediate treatment of the infected case in a stable discordant couple as soon as possible after diagnosis to prevent a transmission event.[32,33] The preventive role of suppressive ART makes it an appealing solution to the dual problem of equitable drug access and effective HIV prevention. On the basis of our observations, ART is an effective method for reducing HIV transmission risk in stable couples in China. China's proposed strategy to strengthen universal and immediate ART for the prevention of HIV,[34] may benefit from monitoring system to identify in real time groups at higher risk of treatment failure.

Tables & Figures

Table 4.1. Characteristics of the 4916 HIV serodiscordant couples included in the final analysis

	Seroconversion	No seroconversion	Total
	N=157	N = 4759	N = 4916 (%)
Sex of index partner			
Male	69	2177	2246 (45.7%)
Female	86	2487	2573 (52.3%)
Missing	2	95	97 (2.0%)
Age of index partner			
<45	73	2504	2577 (52.4%)
≥45	84	2255	2339 (47.6%)
Index partner HIV transmission route			
Blood/plasma donation	101	2301	2302 (46.8%)
Blood transfusion	10	705	715 (14.5%)
Injection drug use	4	122	126 (2.6%)
Hetero or homosexual sex	18	1270	1288 (26.2%)
Missing	24	461	485 (9.9%)
Index partner occupation			
Farmer	153	4307	4460 (90.7%)
Non-farmer	2	352	354 (7.2%)
Missing	2	100	102 (2.1%)
Index partner education level			
Primary or less	86	3299	3385 (68.9%)
More than primary	58	948	1006 (20.5%)
Missing	13	512	525 (10.7%)
Monthly average frequency of sex			
0-2	11	1429	1440 (29.3%)
3 or more	140	3209	2249 (45.7%)
Missing	6	272	278 (5.7%)
Condom use			
Always	36	2871	2907 (59.1%)
Sometimes	11	156	167 (3.5%)
Never	7	23	30 (0.6%)
Missing	103	1709	1812 (36.9%)
Index partner baseline CD4			
<250	66	1520	1586 (32.3%)
≥250	66	2735	2801 (57.0%)
Missing	25	504	529 (10.8%)
Time since index HIV diagnosis			
<5 years	5	496	501 (10.2%)
≥5 years	133	4158	4291 (87.3%)
Missing	19	105	124 (2.5%)
Index ART use (ever)			
Yes	101	3851	3952 (80.4%)
No	56	908	964 (19.6%)

Table 4.2. Incidence of HIV seroconversion in non-index partners by key covariates

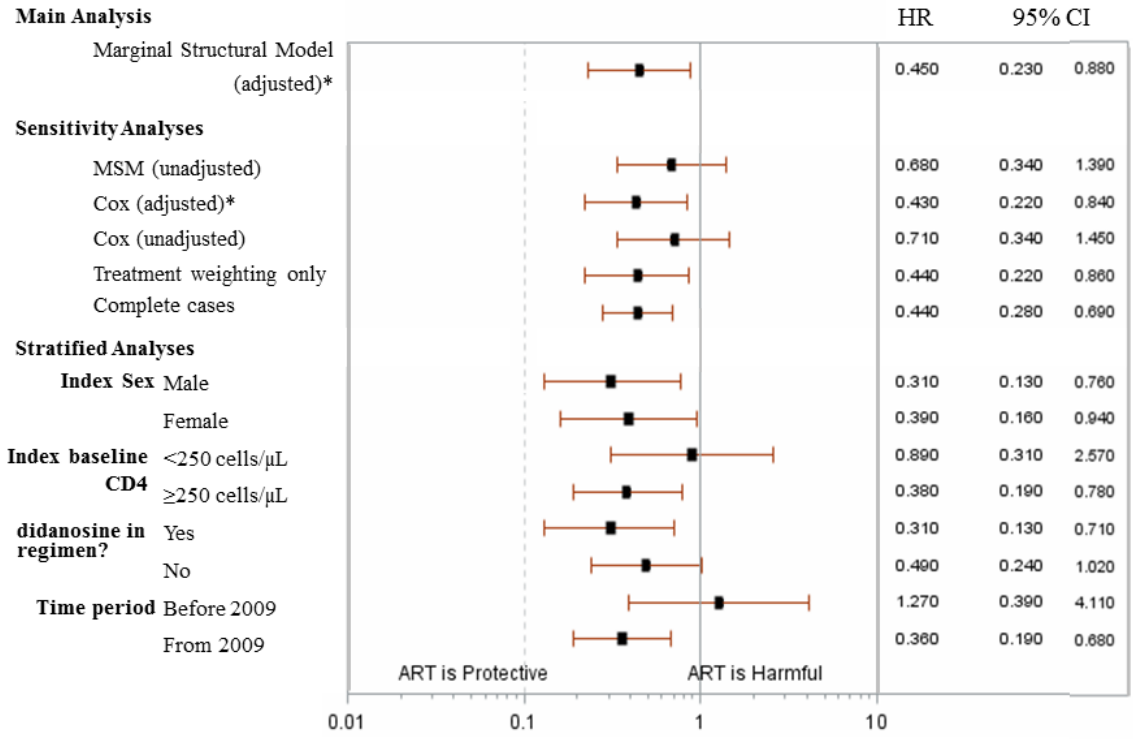
	Events	Person Years	Cases/1000PY (95% CI)	
Sex of index partner				
Male	69	12045	0.57	(0.45-0.72)
Female	86	13915	0.62	(0.50-0.76)
Missing	2	429	0.47	(0.12-1.86)
Age of index partner				
<45	73	14072	0.52	(0.41-0.65)
≥45	84	12317	0.68	(0.55-0.84)
Index partner HIV transmission route				
Blood/plasma donation	101	12115	0.83	(0.69-1.01)
Blood transfusion	10	4084	0.24	(0.13-0.45)
Injection drug use	4	710	0.56	(0.21-1.50)
Hetero or homosexual sex	18	7294	0.25	(0.16-0.39)
Missing	24	2186	1.10	(0.73-1.63)
Index partner occupation				
Farmer	153	24015	0.64	(0.54-0.75)
Non-farmer	2	1923	0.10	(0.02-0.42)
Missing	2	451	0.44	(0.11-1.77)
Index partner education level				
Primary or less	73	18454	0.40	(0.31-0.50)
More than primary	13	2699	0.48	(0.28-0.83)
Missing	71	5236	1.36	(1.08-1.71)
Average monthly frequency of sex in the past year				
0-2	124	15456	0.80	(0.67-0.96)
3 or more	29	9370	0.31	(0.22-0.45)
Missing	4	1563	0.26	(0.10-0.68)
Condom use				
Always	54	15981	0.34	(0.26-0.44)
Sometimes	16	736	2.17	(1.34-3.53)
Never	9	104	8.65	(4.63-16.16)
Missing	78	9568	8.15	(0.65-1.02)
Index partner baseline CD4				
<250	66	8651	0.76	(0.60-0.97)
≥250	66	15747	0.42	(0.33-0.53)
Missing	25	1991	1.26	(0.85-1.85)
Estimated time of index HIV diagnosis				
<5 years	5	1923	0.26	(0.10-0.62)
≥5 years	133	22978	0.58	(0.49-0.69)
Missing	19	488	3.89	(2.51-6.05)
Index ART user (ever)				
Yes	90	20769	0.43	0.35-0.53)
No	66	1124	5.87	(4.65-7.42)
ART status				
Regimen contains didanosine	5	1589	0.31	(0.13-0.75)
Regimen does not contain didanosine	79	14749	0.54	(0.43-0.67)
Not treated (naïve or terminated)	73	10051	0.73	(0.58-0.91)
Time period				
2008 and earlier	86	10160	0.85	(0.69-1.04)
After 2008	71	16229	0.44	(0.35-0.55)

Table 4.3. Hazard ratios comparing HIV transmission risk in ART exposed and unexposed serodiscordant couples

	HR	95% CI	
Main analysis (crude)			
Weighted	0.68	0.34	1.39
Unweighted	0.71	0.34	1.45
Sensitivity Analyses (adjusted)			
IPTW only	0.44	0.22	0.86
Complete case	0.44	0.28	0.69
Weighted	0.45	0.23	0.88
Unweighted	0.43	0.22	0.84
Stratified Analyses (weighted and imputed)			
Sex of index partner			
Male	0.31	0.13	0.76
Female	0.39	0.16	0.94
Index baseline CD4 cell count (weighted w/ CD4)			
<250	0.89	0.31	2.57
≥250	0.38	0.19	0.78
ART regimen			
ART with didanosine vs no ART	0.31	0.13	0.71
ART without didanosine vs no ART	0.49	0.24	1.02
Time period			
2008 and earlier	1.27	0.39	4.11
2009 onwards	0.36	0.19	0.68

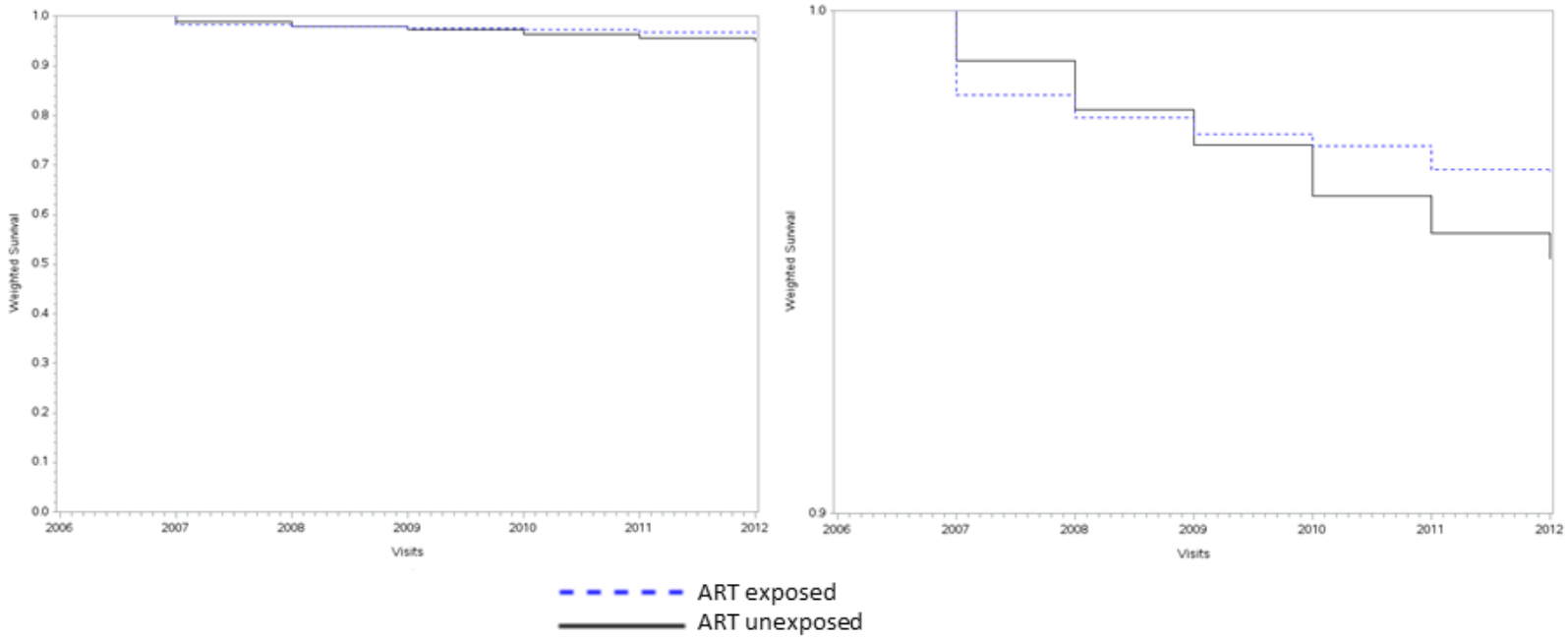
Caption: Table 4.3: Adjusted models included variables for occupation, index partner age, index partner disease stage, index partner sex, and time period. IPTW, inverse probability of treatment weighting. IPCW: inverse probability of censorship weighting. MI: multiple imputation.

Figure 4.1. Hazard ratios and 95% confidence intervals for effect of ART on HIV transmission



Caption: Figure 4.1: *Adjusted for baseline prognostic indicators, including baseline disease stage, occupation, age, and sex.

Figure 4.2. Weighted Kaplan Meir survival curves



Caption: Figure 4.2: Inverse probability of treatment and censoring weighted Kaplan Meir survival curves comparing treated and untreated experiences of couples. The same curves are shown on two different scales (0 to 1 on the left and 0.9 to 1.0 on the right) to better illustrate the divergence.

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CHAPTER 5: AIM 2

Efficacy of Antiretroviral Therapy for Sustained Viral Suppression in Henan, China: Implications for Healthcare Delivery Systems

Introduction

Universal antiretroviral therapy (ART) coverage has become a central pillar of the global HIV agenda,[1–3] propelled by the twin goals of equitable drug access for individuals and disease eradication through transmission prevention.[4] Clinical challenges of helping patients sustain low enough viral levels to protect their sexual partners are considerable, particularly in developing settings constrained by limited laboratory resources, frequent interruptions to the drug supply, and inadequate adherence counseling.[5,6] In a recent report [K Muessig et al., *AIDS,* in press] of 13 studies assessing ART efficacy for preventing HIV transmission in discordant couples, only two, from Uganda[7] and Henan Province, China[8], found no protective effect. The cohort in Henan arises from a well-studied population of HIV patients who were the earliest recipients of ART through China's free public sector treatment program. The comparatively long and ongoing follow-up of these Henan couples provides useful insight in to factors dictating the effectiveness of ART for prevention in resource poor healthcare settings.

As victims of regional blood selling scandals in the 1990's—to which an estimated 30 thousand HIV infections have been attributed[9]—the Henan couples were among the earliest recipients of a government administered free ART program to treat all HIV/AIDS patients regardless of infection route.[10] What began as a pilot program among 100 patients in Henan was

rapidly scaled up to a nationwide network treating over 52,000 patients by 2008. The program today is notable for its size and scale – about 78.5% of the estimated population of eligible patients are currently on treatment, and for its success – mortality rates among treated patients have fallen from 39.3 to 14.2 deaths per 100 person years from 2000 to 2009.[11]

Success of the Chinese ART program has been largely attributed its use of the existing three-tiered healthcare infrastructure (healthcare centers at village, town, and county levels) which allows uniform HIV care to be dispensed even to remote rural commuinties.[12] To adapt the existing system to HIV care needs, health authorities have designated a subset of healthcare entities to specialize in HIV care based on geographic distribution of patients in each county. Under this system, antiretroviral drugs (and after 2005, relevant laboratory tests and treatment for opportunistic infections) are provided free of charge to patients only at their designated HIV care clinics—which could be a village, town, or county level care center (Table 5.1)—and those seeking care outside the referral chain must bear medical costs themselves. The resulting model has successfully lowered AIDs related mortality rates across China, but results presented in Chapter 6 indicate that efficacy ART for HIV prevention in places like Henan may have been less effective during earlier years of program scale-up. Our hypothesis that characteristics of the healthcare delivery system may affect protective efficacy of ART, is informed by findings from our qualitative sub-study presented in Chapter 2, as well as from past studies identifying tier of HIV care clinic as a salient predictor of virological failure[13] and development of drug resistance.[14]

To explore the impact of specific factors on ART protectiveness in rural China, we used locally collected data of the Henan couples whose infected (or index) partners received ART between 2006 and 2012. Additional information about the local healthcare system was included

to complete the assessment of features of the China's rural ART delivery system on risk of HIV transmission.

Methods

Data Sources

Since 2006, disease control centers in the ten counties that make up our study prefecture in Henan province have followed a cumulative total of 5285 HIV patients and their uninfected spouses to monitor HIV transmission. Eligible couples meet the following criteria:1) registered residents living in the study prefecture, 2) over 16 years of age (the age of legal consent in China), 3) in a stable marriage (no separation or divorce), 4) one partner confirmed to be HIV seropositive and the other seronegative, and 5) willing to provide informed consent. HIV status of both partners is confirmed at enrollment through enzyme-linked immunosorbent assay (ELISA, Lizhu, Zhuhai, Guangdong Province; Xinzhuang, Xiamen, Fujian Province) conducted by county-level CDC's, and positive test results are confirmed by western blot assay (Ou'ya, Hangzhou, Zhejiang Province) carried out at the prefectural CDC laboratories.

Cohort enrollees were contacted annually to participate in individual face-to-face interviews. Trained staff from county disease control centers interviewed partners in their native dialect to collect information on demographic characteristics and HIV related risk factors including sexual behaviors within and without the primary partnership, history of STIs and activities related to blood exchange such as injection drug use or blood donation or transfusion. At each survey, initially infected (or index) partners were tested for CD4 cell count and viral load and they provided updated information on ART treatment history and new incidents of opportunistic infection.

Exposure, Outcome and Other Covariates

We assessed two primary factors of interest: median clinician patient load at each clinic, and distance from couples' villages to their designated HIV care center. Patient load was calculated using additional information on HIV care centers provided by county level health officials, including tier of each HIV care center, numbers of medical staff, and numbers of treated and untreated HIV/AIDs patients, all as of 2012(Table 5.2).

Distance from patients' village of residence to their designated HIV care center was determined using patient addresses found in the serodiscordant couple database (or if missing, from the national epidemiology or treatment databases) and addresses of designated HIV care clinics extracted from clinic rosters provided by county health officials. Baidu maps geomapping software (http://map.yanue.net/) was used to generate estimates of latitude and longitude of each patient's designated HIV care center and the geometric midpoint of his or her village of residence, from which Euclidean distance in km was calculated using the "GEODIST" function in SAS 9.3 (SAS Institute, Cary, North Carolina, USA). Optimal coding of both exposure variables was based on visual inspection of plots of these values against HIV transmission risk and comparing relative model fit using the Akaike information criterion. In addition, field notes from our qualitative sub-study indicated that most participants in our study area had access to some mode of transportation (whether an electric bicycle, car, or public bus), suggesting that distances over 10 km might be far enough away to incur a more substantive effort to reach the healthcare settings. The primary outcome of interest was HIV transmission, assessed through annual HIV antibody screening for initially uninfected partners. Those who screened positive were contacted for confirmatory testing, post-test counseling, and evaluation for treatment eligibility.

Statistical Analyses

Couples included in our analysis were those with at least two study visits between 2006 and 2012, and whose index partner was exposed to ART. We excluded couples whose index partners were already exposed to ART before study enrollment to eliminate bias induced by under-ascertainment of events that tend to occur earlier in therapy (due to factors such as incomplete viral suppression in inexperienced ART users) and from the inability to control for baseline factors (such as CD4) that are themselves affected by the treatment.[15]

Couples experiencing the outcome were censored in the interval in which the seroconversion occurred; those who remained discordant throughout the study were censored on the date of their last HIV negative test date. Outcomes were validated by comparing our results with those in the national HIV surveillance database using a unique identifier or when missing, a combination of name, date of birth, and residential address. When results diverged across database, preference was given to details in the national surveillance database. Seroconversion date was calculated as the midpoint between the date of the last HIV-negative or indeterminate test, and three months before the date of the first positive-HIV test, to provide an average window period for seroconversion.

For variables missing information for more than 20% of the sample on any given study year, we used Markov Chain Monte Carlo simulation to impute the missing data, and results from five imputations were combined using Rubin's formula.[16]

Hazard ratios to assess impact of healthcare access indicators on HIV transmission risk were estimated using Cox proportional hazards models. Plots of the hazards over time stratified by distance subgroups were examined to assess proportionality of hazards over time, and an interaction term with time was assessed using a likelihood ratio test. We used directed acyclic

graphs to identify the minimally sufficient of potential confounders of the association between healthcare exposures and HIV transmission.[17] Statistical analyses was conducted using SAS 9.3 (SAS Institute, Cary, North Carolina, USA)

Ethical Approval

All data used for this analysis were collected as part of Zhumadian CDC local disease control efforts. Ethical approval for the analysis of this data for research purposes was provided by the Institutional Review Board of the National Center for AIDS/STD Control and Prevention (NCAIDS) at the Chinese Center for Disease Control and Prevention. The current analysis relied on an agreement between the Institutional Review Boards of NCAIDS and the University of North Carolina, Chapel Hill.

Results

Overall, 3939 treated HIV patients and their spouses contributed a total of 22,787 person-years (Table 5.3). Median age of index partners was 44 years, slightly more than half (55.8%) of whom were male. About half (51.3%) of index partners (regardless of sex) reported blood or plasma selling as their initial route of HIV infection. In their first year on therapy, 71.7% of index partners with a viral load value achieved viral suppression.

Overall, 46 HIV transmission events occurred over the course of the study, for an incidence rate of 0.20 cases per 100 person years. In unadjusted bivariable analyses, HIV transmission rates were higher for couples whose index partners had the following characteristics: male sex, infected with HIV through blood/plasma selling (couples missing this information also

had higher rates), "farmer" as their primary occupation, and had a designated clinic with a greater than 100 patient volume.

Clinic tier and distribution varied widely by county (Figure 5.1). Patients lived a median distance of 5.3 km from their designated clinic, with most (85.1%) living within 10 km and a small minority (N=89) living over 25 km away. In most cases, index partners were assigned to village level HIV care centers (63.4%); the remainder was assigned to township health centers (34.7%) or county hospitals (2.0%). Village clinics tended to have a higher median number of patients than township health centers (45 versus 22) and slightly higher patient burden (13.8 patients per clinician versus 7.3, respectively; Table 5.3). Only one county hospital operated as a designated HIV care site to 178 patients from our study. The large staff size of this entity (6 physicians and 9 nurses) meant that its patient burden of 11.9 patients per clinician was comparable to other tiers of healthcare.

Effects of Patient Volume of HIV Care Center on HIV Transmission

Unadjusted models of the effect of patient volume of HIV care centers on HIV transmission risk showed that couples assigned to HIV care centers with more than 100 patients per clinician had 60% higher risk of transmission (HR=1.59, 95% CI 1.01-2.49) compared to those at centers with lower patient volume. The effect was preserved when potential confounders were included in the model, though adjustment moderated the effect towards the null (HR=1.24, 95% CI, 0.76-2.03). Mean time to HIV transmission among those assigned to clinics with high patient volume was shorter than for those at town or county HIV care centers (3.1 versus 3.7 years; Table 5.5).

When stratified by tier of care center, in unadjusted models patient volume per clinician more than doubled risk of HIV transmission in those assigned to village care centers (HR=2.20, 95% CI, 1.25-3.87), an effect that was only slightly changed by adjustment for confounders (HR=2.26, 95% CI, 1.27-4.03). The effect among those assigned to town or county level clinics was too imprecise to ascertain an effect, given the low case count in this subgroup (HR=0.66, 95% CI, 0.04-11.23).

Effects of Distance from HIV Care Center on HIV Transmission

In unadjusted Cox models, living more than 10km from a designated HIV care site was associated with lower HIV transmission risk (HR=0.56, 95% CI, 027-1.17). This relationship changed little after adjustment for potential confounders (HR=0.52, 95% CI, 0.22-1.22). Mean time to HIV transmission was shorter among those living farther than 10km from their designated clinic (3.2 versus 4.2 years for those living $\leqslant$10km), and was shorter among couples assigned to HIV care at village clinics (3.3 versus 4.2 years for those assigned to town or county level centers; Table 5.5).

Stratification of these unadjusted estimates resulted in divergent patterns across tiers of care. Among those assigned to town or county level HIV care centers, farther distance was associated with lower HIV transmission risk (HR=0.50, 95% CI, 0.15-1.69), whereas this same risk was elevated among those assigned to village care centers (HR=1.18, 95% CI, 0.44-3.15). Adjusted models produced results mirroring those of unadjusted stratified analyses with higher risk for those living farther from their designated village care centers (HR=1.22, 95% CI, 0.46-3.27) and lower risk for living father from town or county care centers (HR=0.18, 95% CI, 0.02-1.36). Estimates of the effect of distance on HIV transmission were all highly imprecise.

Discussion

We observed that higher patient volume was strongly associated with elevated risk of HIV transmission in our population. When stratified, this effect was magnified among couples assigned to village level HIV care centers but no association could be found for those at town and county centers. The relationship between distance to HIV care center and HIV transmission risk was less pronounced but may have varied by tier of HIV care center.

The relationship between our two exposures—travel distance and patient load—and HIV transmission risk are linked in our study by way of the reinforcing role of routine healthcare access on suppressive capacity of ART. Regular access to quality healthcare can help treated HIV patients sustain viral suppression through greater exposure to adherence counseling, earlier identification of virological failure, and maintenance of optimal drug regimens. Though behavioral factors such as frequency of sex or condom use also predict HIV transmission, these behaviors are not thought to be associated with how far patients live from their HIV care centers, nor with any features distance of those centers, suggesting that suppressive capacity—rather than risk behaviors—better explain observed differences in HIV transmission rates across subgroups. Moreover, using the very limited viral load data available, we found that median viral loads in the first year of ART exposure were higher for those assigned to village (470 copies/μL) than those at town or county care centers (50 copies/mL), further supporting our hypothesized pathways. Interpretations regarding viral load data should be interpreted with caution given the high and nonrandom missingness of the original data before imputation.

Strong associations between higher patient volume and risk of HIV transmission suggest that adequate visit time with clinicians and clinic resources may play an important role in helping patients sustain viral suppression. This was particularly the case in village HIV care centers

where patient load is generally higher (Table 5.2) and where laboratory monitoring services can only be accessed by shipping samples to higher tiers of care. The impact of patient-provider relationships on patient satisfaction and improved medication adherence are well known.[18] In addition, a survey of Chinese HIV care providers has found that those perceiving strong institutional support from their workplace–in the form of things like HIV related medical trainings or prophylactic equipment to minimize occupational HIV exposure—have less discriminatory attitudes towards their HIV infected patients.[19] Our finding that higher patient volume increased risk of HIV transmission in village level HIV care centers suggests that targeting new resources to lower-tier sites strained by large patient numbers may yield high marginal returns in the form of reduced HIV transmission.

That distance to clinic was a less salient predictor of HIV transmission may not be surprising in light mixed findings from past studies.[20-22] However, the fact that stratified estimates of this effect moved estimates to opposite sides of the null value suggests that the underlying mechanism linking distance and routine medical care may differ by the type of healthcare center. Past research has found that among rural Chinese patients, concerns about provider expertise and reputation drive choice of provider more than barriers imposed by cost of care or travel distance to a specific clinic.[23,24] Among Chinese HIV patients specifically, views on physician expertise and quality of clinics have both been linked to patient satisfaction and medication adherence.[25] Patients' faith in their own healthcare system may therefore alter minimum thresholds of distances they may be willing to travel for this care. Though we did not directly measure perceptions of care quality in our participants, less favorable impressions of village clinics would not be surprising given the marked contrasts in available resources found at these sites (Table 5.1).

Though still preliminary, findings from this analysis support several modest recommendations. First, interventions to ease the work burden of clinicians at HIV care centers with high patient load—particularly at lower tier care centers—could have an immediate and disproportionate impact on treatment outcomes and transmission risk among patients at these centers. Low cost interventions might include adherence counseling programs administered by non-physician staff,[24] or uptake of technological innovations such as point of care viral load testing, could have a substantial benefit for enhancing both the therapeutic and preventive effects of HIV.[27,28] Second, since perceived quality may be a stronger motivator than proximity in terms of care seeking, cost effective ways to alter patient perceptions of care quality and clinicians competence may not improve patient willingness to seek more routine care, but also substantively improve quality of care they receive.[25] Concentrating financial resources into a subset of sites may be politically difficult in the short term, but initiatives such routine field visits by respected HIV physicians or regular trainings for village clinicians could signal stronger intent on the part of health officials to close gaps in health disparities. Last, the three-tier rural healthcare system through which the Chinese government delivers ART was optimized for an era of highly restricted mobility in rural populations.[29] Today, migration among China's rural population is the most extensive documented in human history;[30] as such, an ART delivery system capable of centralized, real-time reporting could enhance case management and streamline drug supply chain management.

Results of this analysis must be interpreted in the context of China's unique healthcare delivery model; however insights into drivers and barriers of routine medical care among HIV patients are widely applicable to many HIV affected populations globally. Our choice of Euclidean distances is an improvement upon self-reported measures;[22] however, a validation of

our geomapping software measures against manually inputting start- and end-addresses found that our measure may slightly overestimate these distances.

The success of China's decentralized HIV care model to rapidly expand coverage and reduce mortality in resource limited settings is nothing short of remarkable.[31] Task-shifting and decentralization has long been advocated by the WHO,[32,33] for rapid roll out of HIV care in resource limited settings. Direct generalizations of guidelines from wealthier settings in places with far fewer resources,[5] however, may require more careful exploration of how features of local healthcare systems may facilitate translation of this evidence into practice.

Tables and Figures

Table 5.1. Characteristics of the healthcare system in study prefecture

	Village clinic	Township health center	County hospital
Services	Basic health services including physical examination and drug dispensation by non-physicians.	Primary healthcare and supervision of village clinics. Full time pharmacists.	Larger medical center with referral and specialty services. Full time pharmacists
Medical Staff	One full-time or several part-time nonphysician clinicians.	Several full time physicians.	Full time physician clinicians; usually staffed within an infectious disease ward.
Laboratory testing capacity	No on site laboratory; lab samples are transported to higher level laboratories for testing.	Some CD4 cell count testing capacity.	Full CD4 and VL monitoring capacity.

Caption: Table 5.1: Descriptions of the three tiers of healthcare entities providing HIV care in the study prefecture.

Table 5.2. Characteristics of each tier of HIV care centers in the study prefecture

	Village clinic	Township health center	County hospital
Total number in Zhumadian	91	75	1
Treated patients per clinic (median)	45	22	178
Medical staff per clinic (median)	3	3	15
Patients per clinician (ratio)	13.8	7.3	11.9

Caption: Table 5.2: Statistics of the three tiers of healthcare entities providing HIV care in the study prefecture.

Table 5.3. Characteristics of the 3939 HIV serodiscordant couples included in the final analysis

	HIV Transmission N (%)		No HIV Transmission N(%)		PY	Cases per 100PY (95% CI)	
Total	46	(1.2)	3893	(98.8)	22787	0.20	(0.15-0.27)
Sex of index partner--N(%)							
Female	16	(0.9)	1726	(99.1)	10109	0.16	(0.10-0.26)
Male	30	(1.4)	2167	(98.6)	12678	0.24	(0.17-0.34)
Age of index partner--N(%)							
<45	19	(0.9)	2038	(99.1)	12110	0.16	(0.10-0.25)
≥45	27	(1.4)	1855	(98.6)	10677	0.25	(0.17-0.37)
Index partner HIV transmission route--N(%)							
Blood/plasma donation	38	(1.9)	1983	(98.1)	11251	0.34	(0.25-0.46)
Blood transfusion	1	(0.2)	605	(99.3)	3657	0.03	(0.00-0.19)
Injection drug use	0	(0)	76	(100)	492	0.00	--
Sexual contact	1	(0.0)	1080	(99.9)	6454	0.02	(0.00-0.11)
Missing	6	(3.9)	149	(96.1)	933	0.64	(0.29-1.43)
Index partner occupation--N(%)							
Farmer	45	(1.2)	3582	(98.8)	20989	0.21	(0.16-0.29)
Non-farmer	1	(0.3)	311	(99.7)	1798	0.06	(0.01-0.39)
Clinic Tier--N(%)							
Village	38	(1.6)	2273	(98.4)	12890	0.29	(0.21-0.40)
Township	6	(0.4)	1359	(99.6)	8275	0.07	(0.03-0.16)
County	0	(0)	75	(100)	441	0.00	--
Missing	2	(1.1)	186	(98.9)	1181	0.17	(0.04-0.68)
Distance from designated clinic							
≤10 km	43	(1.3)	3311	(98.7)	19361	0.22	(0.16-0.30)
>10km	3	(0.5)	582	(99.5)	3426	0.09	(0.03-0.27)
Patient volume of designated clinic							
≤100 patients per clinician	25	(0.9)	2712	(99.1)	15950	0.16	(0.11-0.23)
>100 patients per clinician	18	(1.9)	940	(98.1)	5312	0.34	(0.21-0.54)
Missing	3	(1.2)	241	(98.7)	1525	0.20	(0.06-0.61)
Index partner baseline CD4--N(%)							
≤250 cells/μL	14	(1.2)	1204	(98.9)	7131	0.20	(0.12-0.33)
>250 cells/μL	32	(1.8)	2689	(98.8)	15656	0.20	(0.14-0.29)

Caption: Table 5.2: PY, person years. CI, confidence intervals.

Table 5.4. Hazard ratios comparing HIV transmission risk in serodiscordant couples by distance to, and patient load of, HIV care center

Effect of patient load per clinician at designated clinic on HIV transmission risk	Unadjusted HR (95% CI)		Adjusted HR* (95% CI)	
Overall				
>100 patients	1.59	(1.01-2.49)	1.24	(0.76-2.03)
≤100 patients	1.00	--	1.00	--
Village tier HIV care center**				
>100 patients	2.20	(1.25-3.87)	2.26	(1.27-4.03)
≤100 patients	1.00	--	1.00	--
Town or county tier HIV care center**				
>100 patients	0.68	(0.04-11.64)	0.66	(0.04-11.23)
≤100 patients	1.00	--	1.00	

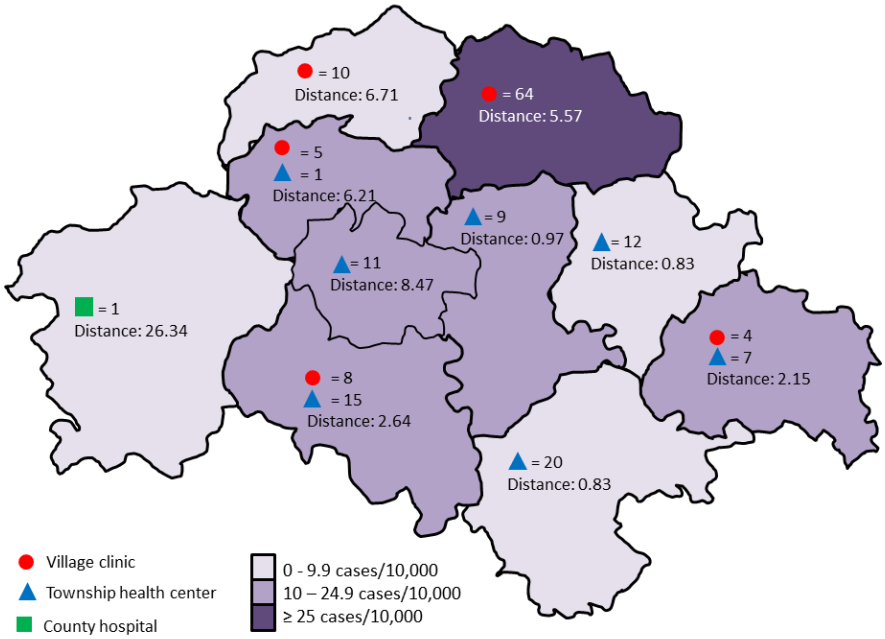
Effect of distance in km to designated clinic on HIV transmission risk	Unadjusted HR (95% CI)		Adjusted HR* (95% CI)	
Overall				
>10km	0.56	(0.27-1.17)	0.52	(0.22-1.22)
≤10km	1.00	--	1.00	--
Village tier HIV care center**				
>10km	1.18	(0.44-3.15)	1.22	(0.46-3.27)
≤10km	1.00	--	1.00	--
Town or county tier HIV care center**				
>10km	0.50	(0.15-1.69)	0.18	(0.02-1.36)
≤10km	1.00	--	1.00	

Caption: Table 5.4: HR, hazard ratio. CI, confidence interval. *Adjusted models included variables for clinic type, distance from clinic (if not already included as the exposure), patient volume (if not already included as the exposure), age, sex, and occupation. *Stratified analyses show results of the unadjusted and adjusted models using interaction terms for clinic type (village level vs. town or county level)

Table 5.5. Mean time to HIV transmission among serodiscordant couples

Subgroup	Mean time to HIV transmission
Clinic tier	
Village	3.24
Town or county	4.22
Distance from clinic	
>10km	3.44
≤10km	4.75
Patient volume per clinician	
>100 patients	3.10
≤100 patients	3.67

Figure 5.1. Distribution of HIV care centers and median distance by county in study prefecture



Caption: Figure 5.1: Counts of each tier or AIDS care clinic and median distance from patient homes to clinic are indicated for each county. Number of people living with HIV/AIDS per 10,000 population in 2012 is indicated by the shaded color of each county.

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CHAPTER 6: DISCUSSION

The primary goal of this dissertation was to estimate the protective effect of ART on HIV transmission risk in serodiscordant couples. This research was motivated both by the need for better insight into effectiveness of suppressive ART in real world settings, as well as to resolve a puzzling set of results from two past analyses of this study population.[1,2] Our secondary goal was to assess the relationship between systems-level mechanisms of ART delivery and HIV transmission risk in this population.

Aim 1: ART to prevent HIV transmission

Our study identified a protective effect of ART on HIV transmission in serodiscordant couples in Henan, China from 2006 to 2012 (HR, 0.55) after adjustment and weighting for time-varying confounding. This effect was stronger than that of Study 1 which had reported no protective effect between 2006 and 2008 (HR, 0.76),[1] but was less in magnitude than the effect reported in the subsequent Study 2 from 2007 to 2011 (HR, 0.05).[2] While varying methodological approaches likely explain some of these differences, a key finding of this dissertation was the time-varying nature of ART efficacy in this population. This confirms that the protective effect of ART was likely nonexistent in early years of the program, after which a strong protective effect took hold in about 2009, thereby corroborating the effects reported by Study 1 and 2. That 2009 coincides with the beginning of systemization of China's ART administrative program structure, massive scale-up of resources including for laboratory monitoring, and introduction of free second line therapies is likely not a coincidence. The time-

varying nature of ART efficacy is not only substantively meaningful, but also highlight the futility of interpreting summary hazard ratios given their tendency to average over time-varying effects, thus masking changes along the way. Hazard ratios may also over-represent the experiences of persons who survive until the end of the study.[3]

Findings from this dissertation contribute to an ongoing investigation of treatment as prevention in Chinese settings (Table 6.1). A national database-driven analysis of over 38,000 couples in China,[4] for example, has found that ART efficacy was lower in former blood plasma donors relative to other groups, further supporting our hypothesis that early ART in Henan was fundamentally different than the standardized care that was rolled out in Henan and nationwide by 2009. Contrasts of our study estimates with other serodiscordant couples studies in China are best considered alongside a comparison with methodological differences across studies.

Limitations of Aim 1 are can guide interpretation and generalization of these results. Primary among these is our assumption that all HIV infections in non-index partners were acquired within the primary partnership. Sociological and epidemiological data on rural Chinese populations[5] and former plasma donors[6] suggest that this is not an unreasonable assumption, but the ideal method of verification through phylogenetic linkage of paired viral samples was hindered by availability of useable stored plasma samples.

Another limitation was the high and nonrandom missingness of viral load data. Though the biologic pathway from ART to sexual HIV transmission in sexual partners is presumed to pass through viral suppression, an explicit effort to verify its role as the primary indicator of transmissive potential would have strengthened our findings. Such data could have also potentially identified predictors of high risk subgroups in the absence of transmission events. Although our multiple imputation of this variable accounted for the time dependence and prior

information about data distribution, problems with the original data undermined veracity and interpretability of in-depth analyses using imputed viral load data.

The primary strength of this analysis was our ability to assess HIV transmission events, made possible by the participation of serodiscordant couples. By being able to assess risk factors for both transmission and acquisition, this study design provided insight into a logistically challenging—yet epidemiologically meaningful —type of outcome. Our analysis also benefitted from validation of both outcome and exposure data with national level databases. Since local clinicians and disease control staff face high administrative burdens in reporting case information to multiple entities, health experts at the national center for disease control verified cases by phone and routine site visits. By comparing our data to records stored in the national database, this analysis minimized potential bias from misclassification error. Our restriction of analysis to new users of ART also helped establish a clear temporality between baseline confounding variables, ART use, and transmission. Finally, our use of marginal structural models to address time-varying confounding by variables that were also affected by prior exposure, helped address this source of confounding common to longitudinal observation of pharmacologic effects.

Aim 2: Distance and Patient Volume on HIV Transmission

Estimates obtained for our second aim showed that higher patient load per clinician at HIV care centers was associated with elevated risk of HIV transmission among treated couples in our population, particularly at village level centers. Adequate time with clinicians and availability of clinic resources may play an important role in helping patients sustain long term suppression. The association between distance to clinic and HIV transmission risk was far less consistent, though we may have detected a possible elevation of risk associated with living father

from village level HIV care centers but a *lower* risk among those living far from town or county level centers. Though it is possible that patient perceptions of care quality may alter their willingness to travel for this care, the lack of precision limits interpretability of these results.

The primary limitation of our second aim was the validity of our assumption that distance from a patient's home to his or her designated HIV care center was representative of distance to care centers where care was actually sought. Though most participants in our study reported being farmers—a population with per capita income of 5000RMB or about 600 US dollars in 2013—and are therefore less likely to be able to afford fee based care at non-designated clinics, a few may still opt to attend other care centers where they feel care quality is better or where they can avoid inadvertent HIV status disclosure in their local communities. In addition although our study prefecture is set in a flat plains region and where communities are connected by a modern network of paved roads and highways, we were not able to account for the presence of two large reservoirs in our distance calculations and thus may have underestimated actual distances for participants who traveled farther to circumnavigate these bodies of water in real life.

Our lack of other information on patients' health seeking behaviors or on salient details of healthcare centers also limited our inability to develop a more nuanced view of the interplay between good access and reliable quality of healthcare.

Our inability to assess impact of our exposure on useable viral load data was for reasons similar to those described above for Aim 1.

Future Directions for Public Health Policy

Intense interest has mounted over the potential for HIV treatment as prevention to slow and eventually stop the HIV epidemic.[7] Enthusiasm for this strategy has been attributed not only

to the unprecedented success of HPTN 052[8] relative to other large scale HIV prevention trials, but also to lags in vaccine development,[9] collective frustration at the futility of existing behavioral interventions[10] and the broader availability of increasingly tolerable and inexpensive drugs even in the developing world.[11] The promise of this tool, however, is not without substantial risks and tradeoffs. With scale-up to treat more and individuals at higher CD4 cell counts may come concomitant rise of drug resistant HIV strains, as increasingly healthy individuals will be referred to ART among whom adherence may not be strong. The potential for improved ART access to stimulate riskier sexual behaviors, a phenomenon known as risk compensation, has already been documented in some populations with high ART coverage.[12] Effective "treatment as prevention" strategies will also need to consider the disproportionate contribution of acutely infected individuals to onward transmission, given their elevated potential for transmission and inherent difficulty in identifying these individuals.[13]

Research to inform effective, cost efficient, and locally acceptable implementation of treatment for prevention that are well suited for resource constrained environments is underway in the form of several large scale community randomized trials.[14] However, policy may be outpacing the evidence that can be provided by such slow-moving and expensive trials. One goal of this dissertation is to close the gap between science and policy by harnessing observational data to assess effectiveness of ART for preventing HIV transmission in real world settings.

Findings from this study underscore the fact that ART is a potentially powerful but imperfect tool for HIV prevention. ART programs in resource poor areas may have an immediate impact on HIV mortality, but may not immediately be able to achieve the population-level protective benefits cited in developed settings.[15,16] Combination implementation to sustain multifaceted strategies that harness biomedical and behavioral interventions[17] must therefore

continue to be advanced up lists of priority policies. With these limitations in mind, however, methods to harmonize therapeutic and preventive goals of suppressive ART may have multiplier benefits across the system. Phasing out CD4 testing in favor or more frequent virological testing, for example (current protocol in China and other resource poor settings dictates a single annual viral load test), might be considered in not in spite of, but rather because of, the high costs and labor intensiveness associated with the test. Concentrating available resources in the gathering of viral load data can help clinicians with few other means more reliability identify patients who are failing therapy and provide them with immediate assistance whether in the form of more counseling to resuppress or by altering their drug regimen. It could also function as a counseling aid for unsuppressed patients to prioritize adherence or consider condom use in order to protect their sexual partners.

Long term suppressive ART is borne out of a partnership between patients and their healthcare systems. Quality of healthcare therefore matters greatly, as does patients' trust in their healthcare system. Initiatives to improve perceptions can improve patient satisfaction and with it, health outcomes. Incorporation of patient feedback regarding barriers to care may improve delivery while empowering patients to advocate for their needs as patients.

Future Directions for Research

One critical question remaining after this research is about prevalence of unlinked transmission in Chinese serodiscordant couples. To date only one study in China has assessed phylogenetic similarity in viral samples from seroconverting couples, among whom all events were linked.[18] Several more data points would deepen understanding of behaviors in Chinese couples and better inform future couple-based intervention strategies. This information will also

provide much needed inputs to form key parameters for mathematical models estimating treatment as prevention impact.

Another area for further research is documentation of healthcare service and delivery indicators. Routine data gathering of resources expended in healthcare services can be paired with information about virological failure or drug resistance, two outcomes linked to low healthcare quality in past studies[19,20] could better characterize not only ways to prevent new infections but also patterns and key subgroups that drive population level spread of HIV. Two key parameters identified by this dissertation that can measure healthcare system's abilities to deliver effective ART for prevention include patient perceptions of care quality and the nature of interactions between patients and physicians.

Finally, future comparisons of ART efficacy in the real world must account for the high probability that underlying risks may vary over time. Large scale shifts in treatment environments are to be expected, particularly in settings like China that are undoing rapid social and economic change. Summary hazard ratios may be useful as a cursory tool for comparison across studies, but we recommend additional methods to present results including adjusted survival curves[21] or supplementary statistics from flexible parametric alternatives to Cox model.[22]

Summary

Widespread access to ART and HIV testing in China make it an ideal candidate for controlling the HIV epidemic through population level ART. Its ability to establish an ART treatment environment in even the most rural and resource constrained areas bode well for treatment as prevention in the developing world. However the protective effect was neither

constant nor perfect, and was itself closely linked to other features of the how the healthcare was delivered. Findings from this research hope to inform initiatives of Chinese health officials who have already taken decisive steps towards national roll-out of a treatment program whose primary goal is HIV prevention .[23] Moreover China's experience can provide timely insight and guidance for other resource constrained communities that are also weighing strategies to mitigate the effects of HIV in their populations.

Tables & Figures

Table 6.1. Comparison of serodiscordant couple studies on treatment as prevention in China

Author [year]	Time Period	Study Design	Results	Conclusion
Wang Lu (2010)[1]	2006-2008	Zhumadian CDC serodiscordant couple cohort. N = 1927 couples.	Overall incidence: 1.17/100PY. Crude estimate for effect of ART on HIV in negative partner: HR= 0.76 (95% CI, 0.45-1.28).	ART did not prevent HIV seroconversion in negative partners.
Wang Lan (2013)[2]	2007-2011	Zhumadian CDC serodiscordant couple cohort. N = 4499 couples.	Overall incidence: 0.82/100PY. Crude estimate for effect of ART on HIV in negative partner: HR=0.36 (95% CI, 0.24-0.55). Adjusted estimate: 0.05 (95% CI, 0.01-0.16)*	ART exposure was highly protective against HIV seroconversion in negative partners. Durability of ART protective benefit wanes after 7 years.
He N (2013)[18]	2009-2011	Dehong, Yunnan serodiscordant couple cohort. N = 813. 48% of index cases were IDU, virological linkage confirmed for all seroconversions	Overall incidence: 1.5/100PY. Crude estimate for effect of ART on HIV in negative partner: HR=0.34, 95%CI=0.12-0.97. Adjusted estimate: HR=0. 30 (95% CI, 0.10-0.86)**	ART as associated with a 66% reduction in risk of HIV transmission in these couples.
Jia Z (2013)[4]	2003-2011	Retrospective cohort assembled from national epidemiology and treatment databases. N = 38,863.	Overall incidence: 2.6/100PY. Crude estimate for effect of ART on HIV in negative partner: HR=0.61, 95%CI=0.55-0.67. Adjusted estimate: HR=0. 74 (95% CI, 0.65-0.84)*** Stratified by transmission route find FPDs HR = 0.91, (95% CI, 0.72-1.14)	ART exposure was highly protective against HIV seroconversion in negative partners. Durability of ART protective benefit wanes after 4 years.

Caption: Table 4.4: *Adjusted for duration of follow-up, sex, age, education, marital status, occupation, route of HIV infection, and baseline CD4 cell count of the index patient; ** Adjusted for education, sexual frequency, condom use, last recorded CD4 cell count, AIDS diagnosis, last recorded viral load, and ever being exposed to ART; *** Adjustment for age, sex, education, seropositivity for herpes simplex virus 2, and frequency of sex.

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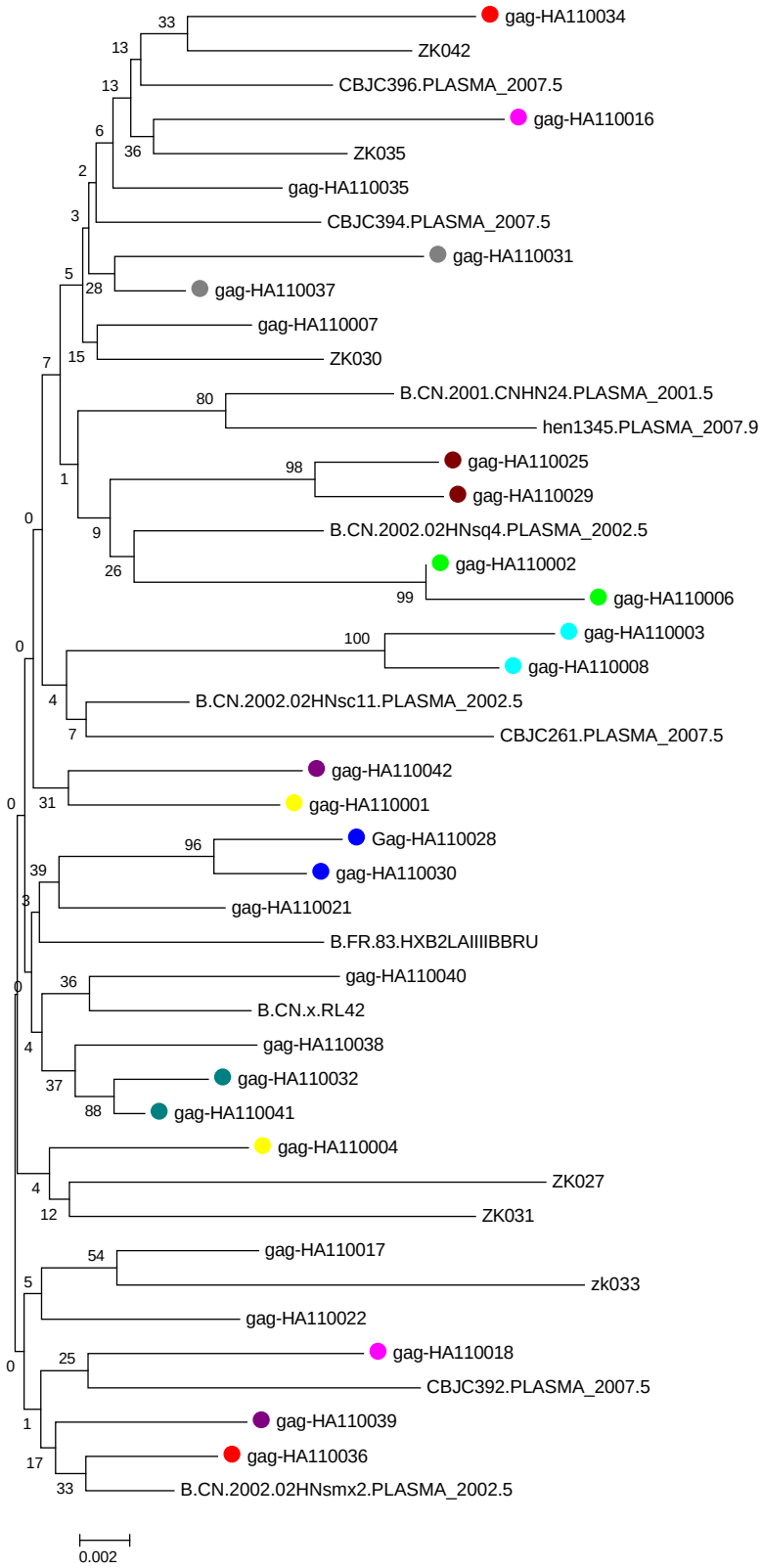
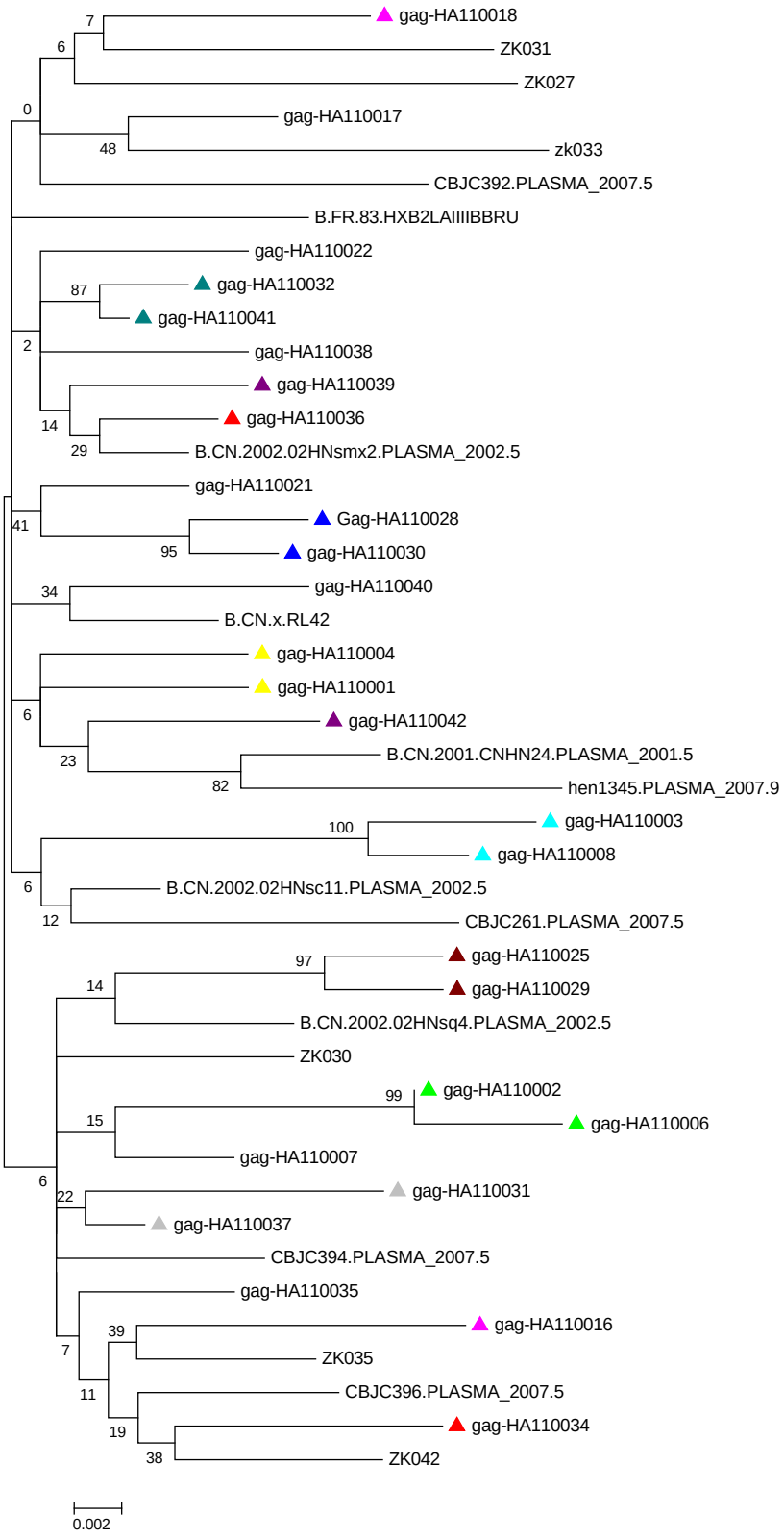
APPENDIX 1. Neighbor Joining Tree



Caption: Appendix 1: Neighbor joining tree documenting 10 transmission events based on an analysis of gag sequences from index-partner pairs (marked with colored dots). The tree also includes 17 subtype-matched reference sequences (ZK--, CBJ--, B.CN--) and 6 local controls (gag-HA110007, --17, --21, --22, -38, --40). Bootstrap values are shown for the grouping of index and partner sequences for each event based on 500 bootstrap replications.

APPENDIX 2. Maximum likelihood tree



Caption: Appendix 2: Maximum likelihood tree documenting 10 transmission events based on an analysis of gag sequences from index-partner pairs from Zhumadian (marked with colored dots). The tree also includes 17 subtype-matched reference sequences (ZK--, CBJ--, B.CN--) and 6 local controls (gag-HA110007, --17, --21, --22, -38, --40). Bootstrap values are shown for the grouping of index and partner sequences for each event based on 500 bootstrap replications.

APPENDIX 3. Patient Interview Guide

Date of Interview: _____

Location of Interview: _____

Interviewee ID #: _____

Section 1. Obtain information about the diagnosis experience, changes in transmission related risk behaviors since diagnosis, and treatment experience.

Warm Up Questions

- How many people are in your family?
- How did your family come to live in this town?
- How do you and your family make a living?
- Can you tell me about your experience participating in the discordant couple study?
- How long have you been taking part in the study?

HIV Related History

- Were you already diagnosed with HIV before the study began?
- Can you tell me more a bit more about the first time you were diagnosed?
- Where and by whom were you diagnosed?
- What do you remember discussing with your doctor/provider at the time?
- Can you describe the process by which your partner learned about your results?

Post Diagnosis

- Some couples experience a change in their sexual behaviors after one of them learns that he/she is HIV positive. How would say your sexual behaviors have changed since learning your status?
- How have your feelings about sex changed if at all?
- How has the frequency of sex with your partner changed, if at all?
- Can you talk about any changes that you and your partner made to your sex life to avoid possible HIV infection?
- Can you describe any prevention methods that are commonly recommended for couples in your situation?
- Some couples have difficulty using these methods every time they have sex. Can you think of any reasons why they have trouble? [If appropriate, can ask if participant has ever personally experienced any of these difficulties]

Treatment History

- Can you tell me about your experience on HIV treatment?
- How did you decide to start treatment?
- What do you remember discussing with your doctor about treatment?
- Can you describe your ART regimen? (Names of drugs, doses, etc.)

Section 2. Goal is to solicit as many barriers to treatment success as possible with the following statement, then follow-up on any mentioned items with the probes below.

"We know that people who are HIV infected can live longer, healthier lives by keeping the levels of virus in their body as low as possible. Usually this is achieved by adhering to medication every day. But there are many reasons why this might be difficult for people. Some examples include the difficulty of remembering to take one's medicine every day, or the fact that the drugs sometimes have uncomfortable side effects. What are some example of things that you think can make it difficult for people to adhere to their medicines?"

1. Individual Level: Memory, Routine, etc.

Any mention of forgetting, losing track of schedule, disruptions to routine, etc

- Can you tell me more about why you have trouble remembering to take your medications?
- Can you tell me about the most recent time you missed a dose?
- Can you describe your routine in a typical day? Is it difficult to take your medicine at the same time each day?
- What are some ways you think people can overcome some of these barriers? (Prompts: alarm clocks, recruiting family members to remind them, coordinating it with another routine like tooth brushing, etc.

2. Individual Level: Drug Side Effects

Any mention of ever having experienced side effects from ART

- Can you tell me about the worst/most recent side effects you've experienced? What did you do in that case?
- Have you experienced side effects in the past year?
- Can you describe the conversations you had with your providers about side effects prior to starting ART?
- Have you ever had to stay overnight at a hospital/clinic due to side effects?
- Does your current regimen (or termination of ART) reflect the changes made as a result of side effects?

3. Relationships: Social Support

Any mention of outside perceptions of the participants or the attitude of people regarding one's HIV infection.

- How many people in your family or among your close friends know your status?
- In what ways do you think friends and family can help an HIV patient stay healthy and regularly take their medicines?
- In what ways have your family and friends been supportive and helped you maintain good health? (Prompts: pick up drugs, accompany to appointments, remind to take drugs)

4. Relationships: Provider Interactions

P*roviders can play an important role in a patient's long-term health and ability to regularly take their medications. Providers can provide helpful information and encourage patients.*

- Can you describe your relationship with your primary HIV care provider?
- In what ways has he/she/they helped you adhere to your medication (prompts: coaching better adherence, effective management of side effects, etc.)?
- Have you ever had an instance where your doctor wasn't able to help solve a medical problem you had? What happened? How did this affect your relationship?
- How easy is it for you to meet with your primary doctor, or a doctor who has seen you before?

5. Relationships: Stigma & Social Discrimination

Sometimes it can be difficult to make sure you have enough medication to ensure that you don't miss any doses. Have you ever had difficulties on this front?

- Do you think stigma towards HIV patients is a problem in your community?
- If you have ever experienced stigma or discrimination either in the community or healthcare setting, can you describe what happened?
- What would it mean for you if neighbors & friends learned about your status

6. HC Systems Level: Clinic Access

Being able to reach your get to your clinic or pharmacy in a timely manner is very important part of staying healthy.

- Do you have more than one place where you seek medical care? If so, how do you decide which HC center you go to?
- Can you describe any preparations you make to see your doctor (prompts: scheduling appointments, arranging transportation, arranging for childcare or missing work, etc.)
- Can you describe the process of traveling to the HC center, including how long it takes, how much it costs, and any other notable things?
- Have you ever not been able to access care or prescription refills because of the clinic or pharmacy hours?
- Have you ever not been able to fill a prescription because the pharmacy had run out of medication?

7. HC Systems Level: Economic Factors

Healthcare costs can be

- How much money do you spend in a month (half year? year?) for your healthcare?
- How concerned are you about paying for your healthcare?
- Where does the money for your healthcare come from (prompts: household income, savings, borrowing from friends/family, borrowing from bank, etc.)
- Do you have health insurance? If so, what kind (prompts: public, private)?
- In your view how much of your medical needs is covered by your health insurance?
- How has the Four Frees, One Care program affected you and your family? If you could change one thing about the program, what would it be?

Section 3.

Research has found that patients who take their medications every day may be less likely to infect their partners. But others think that preventing HIV this way can be very difficult. Do you think this method would be effective for you and your partner? How about for other couples in this town?

APPENDIX 4. Provider Interview Guide

Section 1. Basic Information

1. Sex [record gender as observed]

2. What is your current age?

3. What is your primary health care center (HCC) of employment? How many other staff work at this HCC full time (n =) and part time (n =)?

4. How long have you worked in the medical profession? What is your specialty?

5. What is your current position, and how long have you served in this position?

6. How did you first become involved in HIV care?

Section 2. Training

7. Can you explain any HIV specific medical training you have received?
   Probes:
   - What organization provided the training?
   - How was the training paid for?
   - What skills did you gain at through the training?

8. If you could participate in any sponsored training for HIV providers, what skills would you like to develop? (e.g. pharmacology, home based care, behavioral counseling, mental health management, surveillance, research, etc.)

Section 3. Resources

Please describe any resource constraints you experience in terms of the following:

9. Medical supplies or equipment (e.g. lab supplies, diagnostic tests, hospital beds, emergency transportation measures)
10. Drugs (ART, or for side effects of opportunistic infections)
11. Support staff (nurses, pharmacologists, psychiatrist/counselors, etc.)
12. Time: what is your current patient load (i.e. how many patients would currently consider you their primary care provider?). Do you feel pressed for time when meeting with your patients?

Section 4. Psycho-Social Factors

13. In some places, providers avoid working with HIV positive patients for a number of reasons. What are some reasons that some providers might do this? (e.g. fear of getting infected, feel a lack of professional qualification, discomfort working with possible sex workers or drug users, etc.). Have you ever experienced such feelings in the past?

14. In some places providers who work with HIV patients have experienced discrimination by other healthcare providers. Have you or anyone you know ever experienced this?

Section 5. Treatment Challenges

15. What portion of your treatment eligible patients are currently receiving ART? What do you think is the primary reason that the remainder are not on treatment (prompts: fearful of side effects, cannot afford the testing, patient doesn't think it's necessary, etc.)?

16. What portion of your patients on treatment do you think are currently suppressed? What do you think is the primary reason that those who are not cannot achieve suppress (prompts: poor adherence, suboptimal regimens, side effects, drug resistance, etc.)?

17. What do you typically discuss when you meet with patients? How often do you have lab monitoring (CD4, VL, drug resistance testing) results available? How do you assess a patient's health when you don't have lab results?

18. HIV patients in other developing areas have many difficulties maintaining viral suppression. What do you think some of them are? Do you think your patients face similar challenges? If you could initiate a program to help patients overcome these challenges, what would you do?