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Treatment as Prevention for HIV Infection: Current Data, Challenges, and Global Perspectives

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Abstract

In 2008, the Swiss National AIDS Commission issued a statement about the safety of HIV treatment in terms of reduced transmission in serodiscordant couples to reduce transmission in serodiscordant couples. This was subjected to debate until 2011 when the HIV prevention trial network 052 published the first randomized study about HIV transmission in serodiscordant couples, where no transmission was observed when the infected person was under effective antiretroviral treatment (ART). Later, the Partners of People on ART-A New Evaluation of the Risks (PARTNER) and the opposites attract studies, which first involved a large number of men who have sex with men (MSM), also showed no transmission, even in condomless receptive anal intercourse (CLAI). In this article, we first review the major studies' data showing the efficacy of ART in HIV transmission in serodiscordant couples at public health scale. Second, we discuss the implications and challenges behind the treatment as prevention strategy regarding the 90-90-90 UNAIDS targets to end the HIV epidemic.We now have strong evidence that ART reduces the risk of transmission of HIV from a positive partner to their negative partner. However, far beyond ART, combining prevention policies is crucial to avoid a new increase in the overall HIV incidence. **(AIDS Rev. 2018;20:131-140)**

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Key words

HIV. Serodiscordant couples. Sexual transmission. Treatment as Prevention (TasP). 90-90-90.

Introduction

Background

Thanks to the progress made in the past decades, AIDS-related deaths have been dramatically reduced so has the mother-to-child transmission rates[1]. Actually, the life expectancy of people living with HIV (PLWHIV) has increased and tends to reach that of the general population[2,3]. However, the incidence of the epidemic is stalling in adults and has increased by <1% between 2010 and 2015[4]. In 2016, still, 1.8 million people be-

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came infected[5]. Serodiscordant couples play a role in maintaining the global HIV epidemic. In high prevalence areas like Sub-Saharan Africa (SSA), approximately half of PLWHIV has seronegative partners, and in low prevalence settings, this proportion may be as high as 75%[6]. A 2013 modeling study among 20 countries in SSA estimated that 29% (range 10-52%) of new infections occurred within stable serodiscordant couples[7]. An estimation for Zambia alone 60.3-94.2% of all new heterosexual HIV infections is seen in serodiscordant married or cohabitating couples[8]. Among MSM, an estimated 33-67% of new HIV infections occur within a primary partnership[9,10]. In 2011, the UNAIDS established the 90-90-90 goals to fight HIV for 2015: 90% of PLWHIV have to be aware of their status, 90% of those people have to be on treatment, and 90% of treated persons have to be undetectable. These targets are actually postponed to 2020 because of the difficulties in accomplishing them[4].

History of ART for the prevention of HIV transmission in serodiscordant couples

Since 2015, ART initiation is recommended in all PLWHIV irrespective of the CD4 cell count[3,11-14]. In 2008, the Swiss Federal AIDS commission made a statement that an HIV-positive person who is virologically suppressed for at least 6 months under effective ART, has no other sexually transmitted infection, and is under medical supervision will not sexually transmit the HIV[15]. They founded their declarations on the previous studies of Castilla et al.[16], Melo et al.[17], and Barreiro et al.[18] They were conscious that a negligible risk existed, but they estimated it much lower than 1 for 100,000[15]. However, these findings had been subject to debate. A systematic review published in 2009 found that there was no HIV transmission in heterosexual couples when the HIV-positive partner (HPP) was virologically suppressed in contrary to couples that were not on ART[19]. In contrast with the Swiss Statement, they pointed out that the data were compatible with 1 HIV transmission in 79 person-years (PY), with a 95% confidence limit of 1.27/100 PY that meant that the risk was not negligible. The risk in real life continued to be debated on until 2011 when a large randomized study, the so-called HIV prevention trial network (HPTN) 052, showed a 96% risk reduction of HIV in serodiscordant couples[20]. Despite the findings, a doubt maintained concerning men who have sex with men (MSM) for whom scientific evidence remained insufficient. Now two studies, the Partners of People on ART-A New Evaluation of the Risks (PARTNER) and the opposites attract studies have been published concerning MSM and confirm the reduction of HIV transmission in this high-risk population[21-24].

Objectives

In this paper, we first review the major studies showing the efficacy of ART in HIV transmission in serodiscordant couples and on a public health scale. Second, we discuss the implications and challenges behind the treatment as prevention (TasP) strategy in regard to the 90-90-90 Unaids targets to end the HIV epidemic.

Major Studies

Partners in Prevention HSV/HIV Transmission Study

Donnell et al.[25] published in 2010 a prospective cohort study where 3381 heterosexual HIV-1 serodiscordant couples were eligible. Median sexual frequency was 4 acting per month (interquartile range [IQR] 2-8), and 29% of couples reported unprotected (no use of condoms) sex during the month before enrollment. ART was initiated by 349 (10%) HIV-1-infected participants following local guidelines. A total of 103 linked HIV-1 transmission events occurred during study follow-up where ART use was known (incidence 2.15/100 PY). An additional 39 unlinked transmissions occurred during study follow-up (incidence 0.81/100 PY). Among the 103 linked HIV-1 transmissions, 102 occurred in couples in which the HIV-1-infected partner had not yet initiated ART (incidence 2.24/100 PY). Only 1 HIV-1 transmission event was observed in 349 couples after the HIV-1-infected partner had initiated ART (incidence 0.37/100 PY). That infection occurred within 4 months after ART had been started, and the infected partner was probably still viremic. Thus, ART use by the HIV-1-infected partner was associated with a 92% reduction in risk of HIV-1 transmission, an effect that was statistically significant (adjusted incidence rate ratio [IRR] 0.08, 95% confidence interval [CI] 0.002-0.57, $p = 0.004$).

HPTN 052 study

Cohen et al.[20,26] led a randomized control study over a 10-year period in which 1763 mostly heterosexual (97%) serodiscordant couples were enrolled. They were randomly assigned in two groups: one group got

ART at enrolment (CD4 count between 350 and 550 cells/mm^3) and the other one when CD4 cell count decreased to <250 cells/mm^3 or who developed an illness related to AIDS. During the week before enrollment, 5% of HIV-infected participants and 6% of non-infected participants reported having unprotected sex. Condom use in this study was high (>93%). The interim result was already spectacular with a decrease of 96% in HIV transmission with early treatment, motivating to the proposal of immediate ART in every HPP[12]. At the end of the study, they documented 46 genetically linked HIV infections, 3 in the early-ART group, and 43 in the delayed-ART group (incidence: 0.5%). Only 8 of them occur after treatment initiation. Four infections occurred because there was a failure in the treatment and the other 4 occurred because the partner had been treated for <90 days and was probably still viremic at the time of the transmission. They concluded that early ART was associated with a 93% lower risk of linked partner infection compared to delayed ART (hazard ratio, 0.07; 95% CI, 0.02-0.22). No linked infections were observed when HIV-1 infection was well suppressed by ART in the index participants[26].

Partners of People on ART-A New Evaluation of the Risks (PARTNER) study

This is a prospective observational study, in which Rodger et al.[21] evaluated the rate of within-couple HIV transmission in heterosexual and MSM couples who had condomless sexual intercourse when the HPP had an undetectable viral load[21]. Among 888 couples, 548 heterosexual (61.7%) and 340 MSM (38.3%) partners provided 1238 eligible couple years of follow-up (CYFU). At baseline, couples reported condomless sex for a median of 2 years (IQR, 0.5-6.3). Condomless sex with other partners was reported by 108 HIV-negative MSM (33%) and 21 heterosexuals (4%). During follow-up, condomless sex couples reported a median of 37 times per year (IQR, 15-71), with MSM couples reporting approximately 22,000 condomless sex acts and heterosexuals approximately 36,000. Although 11 HIV-negative partners became HIV-positive (10 MSM, 1 heterosexual, and 8 reported condomless sex with other partners), no linked HIV transmissions occurred, giving a rate of within-couple HIV transmission of zero, with an upper 95% confidence limit of 0.30/100 CYFU. The upper 95% confidence limit for condomless anal sex was 0.71/100 CYFU.

Opposites attract study

Recently in July 2017, the final results of this observational prospective longitudinal cohort study by Bavinton et al. and Grulich et al.[22,23] were released[24]. This study examined HIV transmission in MSM serodiscordant couples only. They particularly targeted men in a new relationship with 39% of relationship that lasted < 1 year. By the end of 2016, 358 homosexual male HIV serodiscordant couples were enrolled from Australia, Thailand, and Brazil. There were 591 calculated CYFUs in 343 couples, of whom 57.4% reported anal sex with outside partners during any point in follow-up. At baseline, 79.9% of HPP were on ART and 77.9% had undetectable viral load. The baseline CD4 cell count was not mentioned. There were a total of 16,889 acts of condomless anal intercourse (CLAI) reported. Three new HIV infections occurred but no linked transmission. The overall upper 95% confidence limit of the transmission rate when CLAI was reported was 1.16/100 CYFU, and it was 1.56/100 CYFU when there was an undetectable viral load.

Table 1 summarizes the main characteristics and results of these studies.

Implications for Guidelines

In terms of prevention, the national and international guidelines have been updated[3,11-14] not only based on the HPTN 052[20,26] and PARTNER study[21] but also on previous prospective studies and meta-analysis[19,22-24]. They all agree that there is enough evidence that transmission is significantly reduced if the HPP is under effective ART (consistently undetectable viral load)[3,11-14]. The International AIDS Society, the European AIDS Clinical Society, the Department of Health and Human Services, the World Health Organization (WHO), and the British HIV Association recommend the initiation of ART as soon as possible in an PLWHIV for individual risk to reduce transmission risk (for partners as well as mother to child)[2,11-14].

Challenges of TasP

Real-life effectiveness

There are concerns that controlled trial environments overestimate the “real-life” effectiveness of TasP, especially in regions where the medical system is suboptimal, where psychosocial barriers prevent HPP from

Table 1. Summary of major studies of treatment as prevention

Authors	Donnell et al.	Cohen et al.	Bavinton et al.	Rodger et al.
Design	Observational prospective cohort study	Randomised cohort study	Observational prospective cohort study	Observational prospective study
Study period	2004-2007	2005 – 2015	2012-2016	2010-2014
Number of couples, total	3381 couples at enrolment; 349 (10%) in wich ART was initiated	1763 couples (886 in the early and 877 in the delayed-ART group)	358	888
HIV-positive partner's sex (%)	68% female 32% male	50% female 50% male	100% male	68% (609) male 31% (279) female
Partnership duration	4,6 years (> 50% of couples)	not mentioned	< 1year in 39% of couples	not mentioned
Follow-up of couples (years)	2	10	not mentioned	1,3 (0,8-2)
Couple-Year of follow-up, total	273	8509	591	1238
Sexual orientation	heterosexual	97% heterosexual 3% MSM	MSM	548 (61,7%) heterosexual 340 (38,3%) MSM
Median Age (year)	32	26-40	36	40-45
Origin of the participants	7 African countries (Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, Zambia)	9 countries in America, Asia and Africa	Australia, Thailand, Brazil	14 European countries
Baseline CD4 count (cells/mm3)	198[i]	428 (delayed treatment group) 442 (early treatment group)	not known	≥ 350 (≥84% of patients)
Baseline Viral load (cp/ml)	4,1 log10	4,4 log10	77,9 % of patients: VL <200	<200
Sexual activity (nb/month)	4 (IQR 2-8)	4	5-6 of CLAI	3 - 3.52[ii]
Unprotected sex acts	29% (in the month prior to enrolment)	5-6% (in the week prior to enrolment)	NA	100% unprotected sex for a median of 2 years (0,5-6,3)
Condom use (%)	at least 93% during the study	95-96%[iii]	42%	0
Extra-conjugal transmission	(39) 28%	30%	(3) 100%	(11) 100%

(Continue)

Table 1. Summary of major studies of treatment as prevention *(Continued)*

Authors	Donnell et al.	Cohen et al.	Bavinton et al.	Rodger et al.
Within-couple transmission when the HPP is under ART	1 (< 4 month of ART)	8 (4 because of virologic failure, 4 within 3 month of ART)	0	0
Within-couple transmission with undetectable VL	0	0	0	0
Risk reduction compared to couples not on ART	92%	93%	NA	NA
Strength	– comparative study – benefit of ART irrespective of CD4 count	– controlled randomized trial – very long follow-up	– MSM – important number of CLAI	– condomless sex – MSM – long follow-up
Weakness				

HPTN 052: HIV Prevention Trial Network 052, CLAI: condomless anal intercourse, MSM: Mem who have Sex with Men, VL: viral load, ART: antiretroviral treatment, NA: not applicable, PARTNER: Partners of People on ART-A New Evaluation of the Risks, NA: not availaible
[i]median CD4 count when treatment was started
[ii]3/month in heterosexual couples; 3.5/month in MSM
[iii]95-96% of participants reported 100% condom use

revealing their HIV status, and where adherence is more difficult. Oldenburg et al.[27] evaluated data from a longitudinal survey of households in KwaZulu-Natal, South Africa, to assess the ability of ART in preventing HIV transmission in the "real life" (outside of a clinical trial or observational study). The authors noted a 77% reduction in HIV transmission in serodiscordant couples that they ascribed to ART provided to the HPP. In this study, the source of HIV infection in household partners was not known, which made it difficult to assess the real impact of ART on HIV transmission. Although this reduction in transmission was high, it was less than that of HPTN 052[26] randomized cohort study or that of partners in prevention study Donnell et al.[25] where risk reduction was 93% and 92%, respectively.

On the other hand, Tanser et al. reported that, for every 1% increase in ART availability, a 2% decrease in HIV incidence was observed in community settings in KwaZulu-Natal, South Africa[28]. The experience of San-Francisco, between 2004 and 2008, showed that the HIV incidence was reduced by 50%, thanks to public health measure in reducing the community viral load[29]. In British Columbia, a widespread availability of ART for intravenous drug users appeared to reduce HIV incidence as well.[30]

Recently, the ARNS12249 study[31] tried to find the effectiveness of an HIV TasP intervention on a population in an African community profoundly burdened by HIV; no measurable effect on HIV incidence over the course of the trial was found. This cluster-randomized controlled trial in rural Kwazulu-Natal included 28,153 people in 11 control clusters and 11 intervention clusters. In term of new HIV infection, overall 495 new HIV infections were recorded, over 22,434 PYFU. This equates to an annual incidence of 2.21%. The incidence did not differ between the intervention clusters (2.13%) and the control clusters (2.27%). The delays in linkage to care (49.2% and 46.0%) could have meant that individuals with recent HIV infection disproportionately contributed to onward transmission[31]. It should be noted that community-based clinical trials of TasP are underway[32].

Unlinked transmission outside of the partnership

Polygamy is usual in some cultures and sexual intercourse with multiple partners common in some circles. In the opposites attract study, 57.4% of participants reported anal sex with outside partners[24]. Transmissions from outside of the partnership are not unusual: 30% of transmission events in the HPTN 052[26] and 28% in the partners in prevention study Donnell et al.[25], and all transmissions in the PARTNER and the opposites

attract study were attributable to external events[21-24]. In a recent modeling study of extra-couple HIV transmission in SSA, researchers estimated that 27-61% of all HIV infections among men and 21-51% of infections among women were attributable to extra couple events[33]. Early treatment of all PLWHIV will probably reduce this effect, assuming that the HIV partner outside of the couple is on effective ART. Pre-exposure prophylaxis (PrEP) for persons with a high risk of transmission of HIV is another important preventive measure that we will not discuss in detail here.

Identification of people infected or at high risk of acquiring HIV

Identifying infected and uninfected people at high risk is challenging because many people are difficult to reach and/or resistant to testing.

Globally, only 40% of infected men in 2015 were getting ART and only 30% of HIV tests were performed among them[4]. Some regions of the world contribute to the tendency of HIV incidence (Eastern Europe, Eastern Mediterranean, Central and West Africa, and Asia)[4]. Living in Africa, being young (15-24 years) and female are risk factors for acquiring HIV since 30% of them lack knowledge about HIV transmission[1]. Overall, 16% of PLWHIV are undiagnosed in the European Union. People who are unaware of their HIV infection are estimated to contribute up to 50–90% of new HIV infections, and they are unable to benefit from HIV treatment[5].

Treat early all HIV-infected patients

Despite well-established guidelines, it is not easy to convince all people to be treated early with ART, especially those with high CD4 cell count and low viral load[34]. In the HPTN 052 study, despite that ART was offered to all participants with intermediate results showing a 96% HIV incidence reduction at 1 year, there were still 17% of participants who did not choose to start treatment. Their arguments being that their CD4 count was too high, they felt too healthy to start treatment, or they feared side effects[26]. In a study of 1958 HIV-infected partners in Kenya and Uganda, 50.1% of those eligible for ART had not started therapy within 6 months of determined eligibility. Even at 24 months, 12.4% of those eligible still had not started therapy. The factors associated with delay were an age below 25, a higher CD4 count, higher education level, and poor income[35].

Linkage and retention to care

Assuming that the HIV-infected population is diagnosed early and put under ART (test and treat), one of the cornerstones will be to retain them to care for a long duration. Shah et al.[33,36,37] stated that if HIV-care strategies do not change, there will be an estimated 1.39 million (95% uncertainty range [UR], 0.91-2.2 million) new HIV infections over two decades. In contrast, couple testing and linkage to care could reduce HIV incidence by 54% (95% UR, 37-68%) and mortality rate by 64% (46-78%), at a cost-effectiveness ratio of $45 300 per quality-adjusted life year gained $27,800-72,300. Their results suggest that the most important priority in reducing the incidence and mortality of HIV is linkage and retention in care, which is essential for virological suppression[37]. The modeling analysis of Skarbinski et al.[38] estimated that 61.3% HIV infections in the USA in 2009 were acquired from HIV-diagnosed people who did not retain to care. The impossibility of ANRS 12249 trial to show the impact of the test and treat strategy was probably attributable to the delays in linkage and retention to care[31] possibly due to the stigma and the prevailing models of care and population attitude. Recently, combination intervention including point-of-care CD4 testing at the time of diagnosis, accelerated ART initiation, and short message service (SMS) health-care messages and appointment reminders have shown effectiveness in improving linkage and retention in care following HIV diagnosis in Mozambique and Swaziland.[39,40]

Long-term adherence and resistance

Resistance to ART is steadily increasing and has actually reached 29% following the recent WHO report about HIV resistance[41]. Successful TasP requires consistent high medication adherence, a constant challenge in daily practice. Strict adherence is one of the conditions that PLWHIV must respect if unprotected sexual intercourse is considered in a serodiscordant relationship. Even now, adherence is far from perfect, and some patients discontinue for a variety of reasons, including behavioral, psychosocial, and structural barriers[42]. Adherence depends also on the health-care structure, and it supports the provider-patient relation and the drugs side effects[42]. In the trial HPTN 052, through pill-count, they noted that 82% of participants were adherent at 1 month and 83.3% at 1 year. Mental health was the only psychosocial variable associated with adherence[43]. Bijker et al. reported 13,001 adher-

ence assessments in 3934 participants during the first 24 months of ART in Africa and Asia, of which 6.4% (837) were suboptimal, with 7.3% (619/8484) in the African cohort versus 4.8% (218/4517) in the Asian cohort ($p < 0.001$). The reasons for suboptimal adherence in Africa were male sex, younger age, use of concomitant medication, and attending a public facility. In Asia, adherence was lower in intravenous drug users. Risk of suboptimal adherence decreased with longer ART duration in both the regions. Participants in low- and lower-middle-income countries had a higher risk of suboptimal adherence, compared to those in upper middle- or high-income countries[44]. Suboptimal adherence was strongly associated with virological failure, in Africa and Asia[44]. In a recent published paper (subanalysis of ANRS 12249), Iwuji et al. found no evidence that higher CD4 count at ART initiation was associated with suboptimal ART adherence in the first 12 months. Among 900 individuals who initiated ART ≥ 12 months before the end of the study, adherence was suboptimal in 14.7% of visits as measured by a visual analog scale and 20.7% by pill counts[45].

Evidence from Africa indicates that the proportion of ARV recipients with resistance mutations has increased each year since ARV roll-out[46]. Etta et al. reported a high level of HIV-1 drug resistance in patients with unsuppressed viral load in rural Northern South Africa[47]. The prevalence was significantly higher than those reported in urban settings in South Africa, and the amount of mutations was higher in patients taking ART for more than 5 years[47].

Behavioral risk compensation

Behavioral risk compensation negating the prevention benefits of earlier ART initiation is possible. However, a study among 957 participants in Ivory coast did not support this concern as no significant difference was found in sexual behavior risk among early versus standard initiators[48]. In addition, in cases of viral replication suppression, risky behaviors are unlikely to result in HIV transmission as shown in the results of the PARTNER and the opposites attract studies where even in CLAI no linked HIV transmission occurred[21-24].

Global cost

The real costs linked to TasP and other prevention policies, and the costs saved from treating PLWHIV with opportunistic infections and those related to the increase in HIV incidence, are difficult to estimate. TasP had been shown to be cost saving. Walensky et al.[49], using data from the HPTN 052 study, showed that early ART in comparison to delayed ART would be cost-effective: in South Africa and in India, it would save $590 and $530 per life year, respectively.

On the other hand, to achieve the 90-90-90 UNAIDS goals, there will be a huge increase in global cost. For example, Shah et al.[36] estimated that successful attainment of all three of these goals will require an additional $105 billion over 10 years, mostly to pay for additional ART at the cost of $32,000 per person per year. In sensitivity analyses with ART costs of $10,000 and $45,000 per person per year, the additional costs associated with achieving the NHAS goals were estimated at $26 billion and $152 billion, respectively.

Implications for Prevention and the Response to AIDS Epidemic

TasP for serodiscordant couples

ART as a preventive measure in serodiscordant couples has shown to be effective in randomized studies and prospective observational cohorts[21-26]. Supervie et al.[50] in a meta-analysis of six studies noted one transmission that happened in a time interval of 0-12 months. The HPP being undetectable at 6 months, the transmission probably happened before the 6th month of treatment that raises the question of when the partners can have unprotected sexual intercourse. The within-couple transmissions in the HPTN052 and in the partner in prevention study happened within 3 and 4 months, respectively, probably because the HPPs were still viremic. The newer ART such as integrase inhibitors will probably reduce this window of 3 or 4 months by decreasing more quickly the viral load.

Combining prevention measures

Several studies demonstrate the benefits of combining intervention strategies. Williams et al.[51] in a model showed that, if 60% of men in a given population were circumcised and 80% of infected men and women were taking ART, the risk of someone becoming infected would drop by 55%. Reducing risk by 85% would require 90% of infected people on ART, 10% on daily PrEP, 80% male circumcision, and 25% of uninfected women using a vaginal microbicide before and after sex[51]. Veermeersch et al.[52], in a model taking into account Belgian

epidemiology and literature data, indicate that, without explicit new efforts, the number of new HIV diagnoses in Belgium is expected to increase by 33% in 2030 when compared to 2015. They demonstrated that combining TasP, outreach, and PrEP could reduce the incidence by 51% (down to 65% of the 2015 number of new diagnoses). Furthermore, it would lead to an expected budgetary savings of €33.7 million in 2030 alone.

In real life, however, beyond ART, there are a lot of other strategies for HIV prevention in serodiscordant couples[34] which are not sufficiently implemented: Actually, in Africa, condom use is approximately 50% of the estimated need[1]. Even if male circumcision had known a big expansion in the past years, it declined in some countries in 2015[1]. PrEP, the newest tool in reinforcing the prevention policies, is still not largely implemented worldwide[1].

Test and treat strategy

Mathematical modeling studies have suggested that widespread use of ART could substantially reduce HIV incidence[53,54]. In a model constructed by Lima et al.[55], increasing ART coverage beyond the current 50% of those with a CD4 count <200 cells/mm^3 to 75%, 90%, and 100% in the setting of stable adherence would decrease HIV incidence by 37%, 54%, and 62%, respectively, as well as per capita lifetime treatment costs. Granich et al.[56] argued that the HIV epidemic in Africa could be ended with universal annual HIV testing and immediate treatment. Obviously, empiric data derived from mathematical model are absolutely required to demonstrate a public health benefit from ART. The broadest coverage would result from the initiation of ART regardless of CD4 cell count, the "Test and Treat" strategy. The HPTN O71 is a universal testing and treatment intervention to improve HIV control. The 1-year result showed that acceptance of HIV testing among those consenting to the intervention was high, although linkage to care and ART initiation took longer than expected. Knowledge of HIV-positive status increased steeply after 1 year, almost attaining the first "90 target" in women and approaching it in men. The second "90 target" was more challenging, with approximately three-quarters of known HIV-positive individuals on ART by the end of the annual round[57].

Perspectives

In comparison to the Swiss statement which already affirmed the absence of risk transmission in serodiscordant couples, we now have evidence from randomized studies (HPTN 052) and prospective observational cohorts (PARTNER study and opposites attract study) that are crucial in the field of HIV transmission in serodiscordant couples[20-24,26]. For physicians in daily clinical practice, there is enough evidence now to support condomless sex in serodiscordant couples under certain conditions: the HPP must be under well-conducted ART for at least 6 months with perfect adherence and have undetectable viral load and no other STI. It is evident that the final decision to have, or not, condomless intercourse depends on the HIV-negative partner. It is the role of the physicians to follow-up closely these couples and to give them all the information they need[13,14].

After HPTN052 which brings to light a reduction of HIV risk transmission for heterosexual couples[20,26], now the PARTNER study and the opposites attract study bring to light information about MSM serodiscordant couples; furthermore, in these high-risk populations, they detected no transmission in CLAI when the HPP was under effective ART and the viral load was undetectable[19-24].

The results of TASP strategy have been obtained in well-conducted studies. Furthermore, we have not enough information on the effectiveness of TasP on real-life conditions, and it might be not comparable to the efficacy obtained in clinical trials. If mathematical modeling studies have suggested that widespread use of ART could substantially reduce HIV incidence, empiric data are absolutely required to demonstrate a public health benefit from ART. Studies in that field are still ongoing and they are necessary to determine the validity and cost-effectiveness of such an approach[31,49].

Furthermore, we need to realize, in view of the current epidemiological data, that the TasP strategy alone will not suffice to fight HIV epidemic. TasP needs to be integrated in a global prevention strategy combining different tools (early testing of high-risk population, PrEP, PEP, TasP and Comdom, circumcision, and others…).

Concerning the UNAIDS 90-90-90 goals, there are still some gaps in the HIV care cascade which we must focus on. For TasP to be efficient, PLWHIV needs to be reached (early testing and outreach) and treated. In the western countries, the greatest barrier to achieve the UNAIDS goals is the undiagnosed PLWHIV mostly MSM and people from SSA origin (late presentation). In Europe, there are still 16% of undiagnosed PLWHIV. This represents the greatest drop in the HIV care cascade[58,59]. Efforts need to be made to improve the awareness of their status. Strategies need to be implemented

to test not only people at risk of acute HIV infection[60,61] but also late presenters. To do so, decentralized and demedicalized testings need to be expanded and anonymous testing needs to be available[62]. In the southern part of the world psychosocial barriers, care infrastructures and behavior of health-care personnel seem to be a problem for linkage and treatment. Recently, combination intervention including point-of-care CD4 testing at the time of diagnosis, accelerated ART initiation, and SMS canal for health messages and appointment reminders have shown effectiveness improving linkage to and retention in HIV care following diagnosis[39,40]. Resistance to ART is a terrible consequence of HIV program failure. This is why new-generation of ART with high genetic barrier and easy to take (injectable, single tablet) should be widely used in developing countries[63]. Health-care programs need to be reinforced and local medical staff sensitized to the barriers that local population deals with. However, even in some industrialized countries, linkage is poor because health care is insufficiently guaranteed for the poorest people. Linkage to care is essential for viral suppression, and medical staff and patient-care provider relationship is essential as well. The question of cost plays a big role, of course. Even if it has demonstrated that there will be a huge increase in costs to achieve the UNAIDS goals[36], TasP has shown to be cost saving[49], and at the end, it will be beneficial to all. Thus, national policies need to be encouraged to use their resources wisely.

If we do not act at all scales of HIV care continuum and if we do not combine preventive measure, the HIV epidemic will continue to escalate[33,34,50].

Conclusions

Thanks to the recent studies, we have now strong evidence that there is a reduced risk of HIV transmission of HPP under effective ART to their seronegative partners[21-26], which was already claimed by the Swiss statement in 2008[15]. Even in MSM, for whom scientific evidence had been lacking until now, the preventive effects of ART have been recently shown[21-24]. Beneath the individual-based benefits of ART, it is now recognized as an important armamentarium for prevention at a public health scale. This strategy so-called TasP has been shown to be effective to reduce HIV transmission and to be cost saving[49]. Obviously, empiric data are absolutely required to demonstrate public health benefit from ART. Studies in the field are ongoing[31]. Even if most western European countries are approaching the UNAIDS goals for 2020[58,59], many countries are still far away from reaching them by 2030[58] despite widespread use of ART. Several progresses have been made; however, HIV incidence is actually stalling and several challenges remain in fighting HIV epidemic[1].

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