PRESIDENZA DEL CONSIGLIO DEI MINISTRI
Dipartimento Politiche Antidroga

REGIONE VENETO
ULSS 20
VERONA

Regione del Veneto - Azienda ULSS 20
Dipartimento delle Dipendenze

ADDICTION NCCN National Coordination Center for NIDA Collaboration

Accordo di collaborazione scientifica ITALIA - USA

Screening and treatment of HIV and drug related diseases among drug users: a scientific update

Safe Conception for couples living with HIV/AIDS: the changing scenario

State of the art and our experience

Marina Malena

Verona 3rd April 2014

Background
HIV/AIDS epidemic

More than 35 million: people living with HIV

Around 10 million: people who has access to antiretroviral therapy, which also has prevention benefits.

Close to 26 million: are eligible for antiretroviral therapy (under WHO 2013 consolidated ARV guidelines).

- Worldwide, women constitute more than half of all people living with HIV/AIDS and the majority of those women are of child-bearing age.

- Women are at least twice as likely to acquire HIV from men during sexual intercourse than vice versa.

What has changed

.

- The face of the HIV/AIDS epidemic has changed dramatically since its emergence in the 1980s. Far from its origins as an illness of homosexual men, HIV/AIDS is increasingly affecting women around the world.

- In 2011, nearly 60% of pregnant women living with HIV in low- and middle-income countries received effective drug regimens to prevent new HIV infections among children.

- Number of new HIV infections has dropped by 33% in 2012 compared to 2001, and AIDS-related deaths have been reduced by 30% compared to 2005
- (Data of the UNAIDS report on the global AIDS epidemic 2013)

- Recent efforts have largely focused on expanding access to HIV diagnosis and counseling , as well as treatment with highly-active antiretroviral therapy (HAART).

What must be changed

- Providing reproductive health services to women/couples living with HIV is crucial to improving their overall health.
- Preparing for the pregnancy, whether planned or unplanned, is an important component of care.
- Preventing unplanned pregnancy allows a woman with HIV to optimize her own health and has the potential to decrease maternal-to-child trasmission of HIV (MTCT).
- Promoting and protecting women's human rights, increasing education and awareness among women and encouraging the development of new preventive technologies such as pre/post-exposure prophylaxis and microbicides.

An epidemic of women

The HIV/AIDS epidemic has had a unique impact on women, which has been exacerbated by their role within society and their biological vulnerability to HIV infection.

Additionally, millions of women have been indirectly affected by the HIV/AIDS epidemic. Women's childbearing role means that they have to contend with issues such as the MTCT of HIV. The responsibility of caring for AIDS patients and orphans is also an issue that has a greater effect on women.

http://www.avert.org/women-and-hiv-aids.htm#sthash.D81KVevP.dpuf

Let us consider how the "HIV factor" impacts on....

- Relationships
  - Existing relationships
  - Formation of new relationships
  - Sero-different relationships
- Contraceptive options
- Fertility and reproduction
- Management of pregnancy

Update on Sexual transmission

Rates of heterosexual transmission of HIV

- The likelihood of HIV transmission to women in serodiscordant couples has been reported to be more than twice that of men: 3.8 for women and 1.7 for men per 100 person-years (data reported in one African study[1])

- Male circumcision can decrease the risk of male infection [2,3]

1. Mugo N, et al. International Microbicides Conference Pittsburgh, 2010. Abs 8
2. Baeten JM, et al. J Infect Dis2005;191:546–53
3. Quinn TC, et al. N Engl J Med 2000;342:921–29

The first emerging literature that exonerates natural conception

- HIV-discordant couples and parenthood: how are we dealing with the risk of transmission? Vernazza et al, AIDS 2006,20:000-000.
- Reproduction decision Making for Couples Affected by HIV: A review of the Literature. Thornton et al, Top HIV Med 2004; 12(2): 61-67.
- Reproduction Options for HIV-Serodiscordant Couples. Barreiro et al, AIDS Reviews 2006; 8:158-70.
- HIV and reproductive care-a review of current practice. Gilling-Smith et al, An International Journal of Obstetrics and Gynaecology 2006.
- Is natural conception a valid option for HIV-serodiscordant couples? Barreiro et al, Human Reproduction 2007; 22,9: 2353-2358.
- Consejo reproductivo en parejas serodiscordantes para el virus de la inmunodeficiencia humana. Labarga et al, Med Clin (Barc.) 2007; 129(4):140-8)

The Swiss Recommendations

"HIV-positive individuals without additional sexually transmitted diseases (STDs) and on effective antiretroviral therapy are sexually non-infectious."

The Swiss National AIDS Commission

CFS — AUTRES GROUPEMENTS ET INSTITUTIONS

Les personnes séropositives ne souffrant d'aucune autre MST et suivant un traitement antirétroviral efficace ne transmettent pas le VIH par voie sexuelle

Pietro Vernazza[a]; Bernard Hirschel[b]; Enos Bernasconi[c]; Markus Flepp[d]

Commission fédérale pour les problèmes liés au sida (CFS), Commission d'experts clinique et thérapie VIH et sida de l'Office fédéral de la santé publique (OFSP)

a Prof. Dr méd., président de la Commission fédérale pour les problèmes liés au sida (CFS) et responsable de la Division des maladies infectieuses et de l'hygiène hospitalière de l'Hôpital cantonal de St-Gall

b Prof. Dr méd., membre de la Commission d'experts clinique et thérapie VIH et sida de l'OFSP et responsable de l'unité VIH-SIDA des Hôpitaux Universitaires de Genève

c Dr méd., membre de la Commission d'experts clinique et thérapie VIH et sida de l'OFSP et responsable de la Division des maladies infectieuses de l'Ospedale Regionale Sede Civico à Lugano

d Dr méd., président de la Commission d'experts clinique et thérapie VIH et sida de l'OFSP et praticien spécialiste des maladies infectieuses et de la médecine interne

Après avoir pris connaissance des faits scientifiques, à la demande de la Commission d'experts clinique et thérapie VIH et sida (CCT) de l'Office fédéral de la santé publique (OFSP) et après avoir longuement délibéré, la Commission fédérale pour les problèmes liés au sida (CFS) arrive à la conclusion suivante:

Une personne séropositive ne souffrant d'aucune autre MST et suivant un traitement antirétroviral (TAR) avec une virémie entièrement supprimée (condition désignée par «TAR efficace» ci-après) ne transmet pas le VIH par voie sexuelle, c'est-à-dire qu'elle ne transmet pas le virus par le biais de contacts sexuels.

Cette affirmation reste valable à condition que:
- la personne séropositive applique le traitement antirétroviral à la lettre et soit suivie par un médecin traitant;
- la charge virale (CV) se situe en dessous du seuil de détection depuis au moins six mois (autrement dit: la virémie doit être supprimée depuis au moins six mois);
- la personne séropositive ne soit atteinte d'aucune autre infection sexuellement transmissible (MST).

Introduction

Une des tâches de la CFS consiste à rendre pu-

prouvent pas qu'un TAR efficace empêche toute infection au VIH (en effet, il n'est pas possible de prouver la non-survenance d'un événement certes improbable, mais théoriquement envisageable). Reste que du point de vue de la CFS et des organisations concernées, les informations disponibles à ce jour sont suffisantes pour justifier ce message. La situation est comparable à celle de 1986, lorsqu'il a été communiqué publiquement que le VIH ne se transmet pas par un baiser avec la langue. Si cette constatation n'a jamais pu être prouvée, plus de vingt années d'expérience du VIH ont néanmoins permis d'étayer sa forte plausibilité. Cependant, les faits et critères scientifiques soutenant l'affirmation selon laquelle les personnes séropositives ne souffrant d'aucune autre MST et suivant un traitement antirétroviral efficace ne transmettent pas le VIH par la voie sexuelle sont nettement plus favorables qu'en 1986. En conséquence, la CFS et les organisations concernées sont d'avis que les informations disponibles actuellement sont suffisantes pour justifier ce message.

Il s'agit ici d'évaluer le risque de transmission du virus lorsqu'une personne suivant un TAR efficace a des rapports sexuels non protégés.

Données épidémiologiques

Dans le cas de couples sérodifférents (une personne VIH positive et une personne VIH

Pietro Vernazza et al. *L Bulletin des médecins suisses.* 2008;89:165-169.

Guidelines state that the risk of HIV transmission during sex without a condom is less than 1:100,000 if the HIV-infected individual:

- Is fully compliant with the antiretroviral therapy
- Evaluated regularly by the treating physician
- Has a viral load that has been undetectable since at least six months (< 40 copies/mL)
- Has no additional sexually transmitted diseases present

Pietro Vernazza et al. *L Bulletin des médecins suisses.* 2008;89:165-169.

A meta-analysis of studies of heterosexual discordant couples observed no incidences of transmission in patients treated with ART and with VL <400 copies/mL

Attia S, et al. AIDS 2009;23:1397–1404

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 11, 2011 VOL. 365 NO. 6

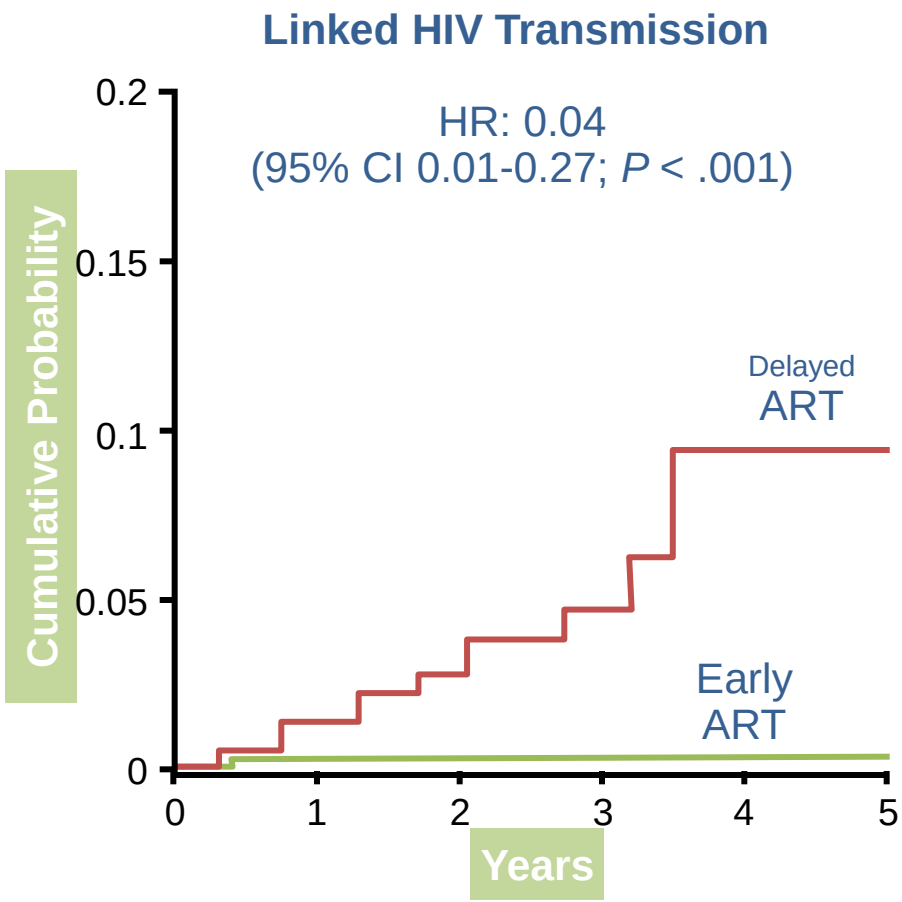
Prevention of HIV-1 Infection with Early Antiretroviral Therapy

Myron S. Cohen, M.D., Ying Q. Chen, Ph.D., Marybeth McCauley, M.P.H., Theresa Gamble, Ph.D., Mina C. Hosseinipour, M.D., Nagalingeswaran Kumarasamy, M.B., B.S., James G. Hakim, M.D., Johnstone Kumwenda, F.R.C.P., Beatriz Grinsztejn, M.D., Jose H.S. Pilotto, M.D., Sheela V. Godbole, M.D., Sanjay Mehendale, M.D., Suwat Chariyalertsak, M.D., Breno R. Santos, M.D., Kenneth H. Mayer, M.D., Irving F. Hoffman, P.A., Susan H. Eshleman, M.D., Estelle Piwowar-Manning, M.T., Lei Wang, Ph.D., Joseph Makhema, F.R.C.P., Lisa A. Mills, M.D., Guy de Bruyn, M.B., B.Ch., Ian Sanne, M.B., B.Ch., Joseph Eron, M.D., Joel Gallant, M.D., Diane Havlir, M.D., Susan Swindells, M.B., B.S., Heather Ribaudo, Ph.D., Vanessa Elharrar, M.D., David Burns, M.D., Taha E. Taha, M.B., B.S., Karin Nielsen-Saines, M.D., David Celentano, Sc.D., Max Essex, D.V.M., and Thomas R. Fleming, Ph.D., for the HPTN 052 Study Team*

Early ART Reduces Risk of Transmission

Cohen MS, et al. *N Engl J Med.* 2011;365:493-505.

- Early ART associated with 96% reduction of sexual HIV transmission in serodiscordant couples
- Linked HIV transmissions to HIV-negative partner (n = 28/1763)
  - Early therapy (n = 1): 0.1/100 PYs
  - Delayed therapy (n = 27): 7/100 PYs
- Median follow-up: 1.7 yrs
- HIV-1 RNA < 400 copies/mL
  - Early ART: 90%
  - Delayed ART: 93%



Kaplan-Meier estimates for the cumulative probabilities of linked HIV-1 transmission between partners

Treatment as prevention and Pre-exposure prophilaxis (PrEP):where are we going?

DHHS 2013

Initiating Antiretroviral Therapy in Treatment-Naive Patients (Last updated February 12, 2013; last reviewed February 12, 2013)

Panel's Recommendations

- Antiretroviral therapy (ART) is recommended for all HIV-infected individuals to reduce the risk of disease progression.

  The strength and evidence for this recommendation vary by pretreatment CD4 cell count: CD4 count <350 cells/mm^3 **(AI)**; CD4 count 350–500 cells/mm^3 **(AII)**; CD4 count >500 cells/mm^3 **(BIII)**.

- ART also is recommended for HIV-infected individuals for the prevention of transmission of HIV.

  The strength and evidence for this recommendation vary by transmission risks: perinatal transmission **(AI)**; heterosexual transmission **(AI)**; other transmission risk groups **(AIII)**.

- Patients starting ART should be willing and able to commit to treatment and understand the benefits and risks of therapy and the importance of adherence **(AIII)**. Patients may choose to postpone therapy, and providers, on a case-by-case basis, may elect to defer therapy on the basis of clinical and/or psychosocial factors.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

DHHS

Reproductive Options for HIV-Concordant and Serodiscordant Couples

Panel's Recommendations

- For serodiscordant couples who want to conceive, expert consultation is recommended so that approaches can be tailored to specific needs, which may vary from couple to couple **(AIII)**. It is important to recognize that treatment of the infected partner may not be fully protective against sexual transmission of HIV.
- Partners should be screened and treated for genital tract infections before attempting to conceive **(AII)**.
- For HIV-infected females with HIV-uninfected male partners, the safest conception option is artificial insemination, including the option of self-insemination with a partner's sperm during the peri-ovulatory period **(AIII)**.
- For HIV-infected men with HIV-uninfected female partners, the use of sperm preparation techniques coupled with either intrauterine insemination or *in vitro* fertilization should be considered if using donor sperm from an HIV-uninfected male is unacceptable **(AII)**.
- For serodiscordant couples who want to conceive, initiation of antiretroviral therapy (ART) for the HIV-infected partner is recommended (**AI** for CD4 T-lymphocyte (CD4-cell) count ≤550 cells/mm^3, **BIII** for CD4-cell count >550 cells/mm^3). If therapy is initiated, maximal viral suppression is recommended before conception is attempted **(AIII)**.
- Periconception administration of antiretroviral pre-exposure prophylaxis (PrEP) for HIV-uninfected partners may offer an additional tool to reduce the risk of sexual transmission **(CIII)**. The utility of PrEP of the uninfected partner when the infected partner is receiving ART has not been studied.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

DHHS

For serodiscordant couples who want to conceive, expert consultation is recommended so that approaches can be tailored to specific needs, which may vary from couple to couple.

Before attempting to conceive, both partners should be screened for genital tract infections. If any such infections are identified, they should be treated because genital tract inflammation is associated with genital tract shedding of HIV.[1, 2] Semen analysis is recommended for HIV-infected males before conception is attempted because HIV, and possibly antiretroviral therapy (ART), may be associated with a higher prevalence of semen abnormalities such as low sperm count, low motility, higher rate of abnormal forms, and low semen volume. If such abnormalities are present, the uninfected female partner may be exposed unnecessarily and for prolonged periods to her partner's infectious genital fluids when the likelihood of getting pregnant naturally is low or even nonexistent.[3-6]

Recommendations for Initiation of ART in HIV-positive Persons without Prior ART Exposure[i]

EACS European AIDS Clinical Society
2013

Recommendations are graded while taking into account both the degree of progression of HIV disease and the presence of, or high risk for, developing various types of (co-morbid) conditions

Present condition/circumstance	Current CD4 count[ii,iii]	
	350-500	> 500
Asymptomatic HIV infection	C	C
To reduce transmission of HIV	C	C
Symptomatic HIV disease (CDC B or C conditions) incl. tuberculosis	R	R
Primary HIV infection	C	C
Pregnancy (before third trimester)	R	R
Conditions (likely or possibly) associated with HIV, other than CDC stage B or C disease:	R	R
• HIV-associated kidney disease	R	R
• HIV-associated neurocognitive impairment	R	R
• Hodgkin's lymphoma	R	R
• HPV-associated cancers	R	R
• Other non-AIDS-defining cancers requiring chemo- and/or radiotherapy	C	C
• Autoimmune disease – otherwise unexplained	C	C
• High risk for CVD (> 20% estimated 10-yr risk) or history of CVD	C	C
Chronic viral hepatitis:		
• HBV requiring anti-HBV treatment	R	R
• HBV not requiring anti-HBV treatment	R[iv]	C
• HCV for which anti-HCV treatment is being considered or given	R[v]	C
• HCV for which anti-HCV treatment not feasible	R	C

i,ii **ART is always recommended in any HIV-positive person with a current CD4 count below 350 cells/µL.**
For persons with CD4 counts above this level, the decision to start ART should be individualized and considered, especially if a person is requesting ART and ready to start, has any of the conditions mentioned above and/or for any other personal reasons. Priority should be taken to treat persons with CD4 counts below 350 cells/µL and for persons with higher CD4 counts if they suffer from one of the above-mentioned conditions before placing resources into treatment as prevention.
Time should always be taken to prepare the person, in order to optimize compliance and adherence.
Genotypic resistance testing is recommended prior to initiation of ART, ideally at the time of HIV diagnosis; otherwise before initiation of ART. If ART needs to be initiated before genotypic testing results are available, it is recommended to include a ritonavir-boosted PI in the first-line regimen. Before starting treatment, the HIV-VL level and CD4 count should be repeated to obtain a baseline to assess subsequent response.

iii R use of ART is recommended
C use of ART should be considered and actively discussed with the HIV-positive person; under these circumstances, some experts would recommend starting ART whereas others would consider deferral of ART; this clinical equipoise reflects that whereas certain data, such as hypotheses on pathophysiology and chronic immune activation, supports starting ART, this needs to be balanced against the risk of known or undiscovered adverse drug reactions from use of ART, and hence the risk/benefit ratio for use of ART under these circumstances has not yet been well defined.

iv See figure page 63 for indication of HBV treatment in HBV/HIV co-infected persons

v Initiation of ART is recommended to optimize the outcome of HCV treatment.

BIHVA 2012

British HIV Association
BHIVA
CLINICAL
GUIDELINES

Women: when to start

We recommend therapy-naïve HIV-positive women who are not pregnant start ART according to the same indicators as in men (see Section 4: When to Start)

We recommend that potential pharmacokinetic interactions between ARVs, hormonal contraceptive agents and hormone replacement therapy be checked before administration (with tools such as: http://www.hiv-druginteractions.org).

2.1.3 What to start (Section 5)

5.1 We recommend therapy-naïve patients start ART containing two nucleos(t)ide reverse transcriptase inhibitor (NRTIs) plus one of the following: a ritonavir-boosted protease inhibitor (PI/r), an NNRTI or an integrase inhibitor (INI). 1A

Summary recommendations for choice of ART:

	Preferred	Alternative
NRTI backbone	Tenofovir and emtricitabine	Abacavir and lamivudine*†
Third agent	Atazanavir/ritonavir	Lopinavir/ritonavir
	Darunavir/ritonavir	Fosamprenavir/ritonavir
	Efavirenz	Nevirapine†
	Raltegravir	Rilpivirine†

*Abacavir is contraindicated if HLA-B*57:01 positive.
†Nevirapine is contraindicated if baseline CD4 cell count is greater than 250/400 cells/μL in women/men.
‡Use recommended only if baseline VL <100 000 copies/mL: rilpivirine as a third agent, abacavir and lamivudine as NRTI backbone.

We suggest starting ART in HIV-positive patients with cervical cancer.

We suggest starting ART in HIV-positive patients with non-AIDS-defining malignancies (NADMs).

- We recommend following discussion, if a patient with a CD4 cell count >350 cells/μL wishes to start ART to reduce the risk of transmission to partners, this decision is respected and ART is started (GPP).

- The use of ART to reduce transmission risk is a particularly important consideration in serodiscordant heterosexual couples wishing to conceive and it is recommended that the HIV-positive partner be on fully suppressive ART.

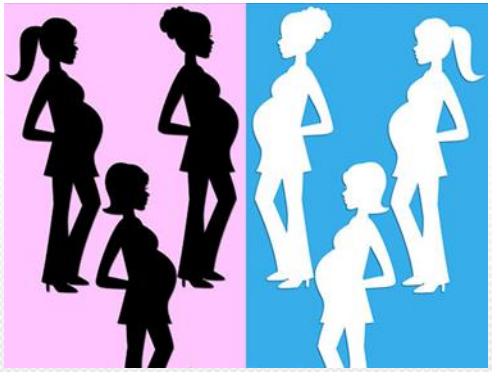
ITALIAN GUIDELINES 2013

Tabella 3 - Paziente con infezione cronica.

CONDIZIONE CLINICA	CONTA DEI LINFOCITI T CD4+	INDICAZIONE AL TRATTAMENTO	RACCOMANDAZIONE (FORZA/EVIDENZA)	RIFERIMENTI BIBLIOGRAFICI
AIDS.	Qualsiasi valore.	Sempre.	[AI]	[1-6]
Gravidanza.	Qualsiasi valore.	Sempre.	[AI]	[7-8]
Nefropatia HIV associata (HIV AN)	Qualsiasi valore.	Sempre.	[AII]	[9-12]
Neoplasie non-AIDS.	Qualsiasi valore.	Sempre.	[AII]	
HIV-associated Neurocognitive Disorders (HAND).	Qualsiasi valore.	• Sempre per HIV-Associated Dementia (HAD) o Mild Neurocognitive Disorder (MND); • Da considerarsi per (Asymptomatic Neurocognitive Impairment) ANI.	[AII] [BII]	[13-15]
Epatite cronica HBV che necessita del trattamento*.	Qualsiasi valore.	Sempre e con farmaci ad azione sia su HIV sia su HBV.	[AII]	[16-18]
Prevenzione della trasmissione secondaria: coppie sierodiscordanti e altri casi.	Qualsiasi valore.	Sempre in caso di solida motivazione da parte del paziente.	• Coppie sierodiscordanti: [AI]; • Rapporti non protetti ripetuti; patologie acute a trasmissione sessuale [AII].	[19-22]
Asintomatico.	T CD4+ ≤ 350 cellule/µL.	Sempre.	[AI]	[1-6]
	T CD4+: 350-500 cellule/µL.	Sempre.	[AII]	[1,2,22-30]
	T CD4+ > 500 cellule/µL.	Sempre, in presenza di: • Decremento di T CD4+ ≥ 100 cellule/µL ogni anno; • HIV-RNA > 100.000 copie/mL. Da considerarsi, in presenza di: • Età del paziente > 50 anni; • Epatite cronica da HCV**; • Rischio cardiovascolare elevato: diabete mellito o pregressi accidenti cardiovascolari, o rischio > 20% nei successivi 10 anni (stima tramite l'algoritmo di *Framingham*).	[AII] [AII] [BII] [BII] [BIII]	[31,32] [33-34] [30]

* = Nei casi in cui vi sia indicazione di trattamento con analoghi nucleosi(ti)dici.
** = In caso di mancata eradicazione con terapia anti-HCV.

Reproductive counselling



REPRODUCTIVE COUNSELING: a two way interaction

Should begin at the first visit for any HIV-infected patient

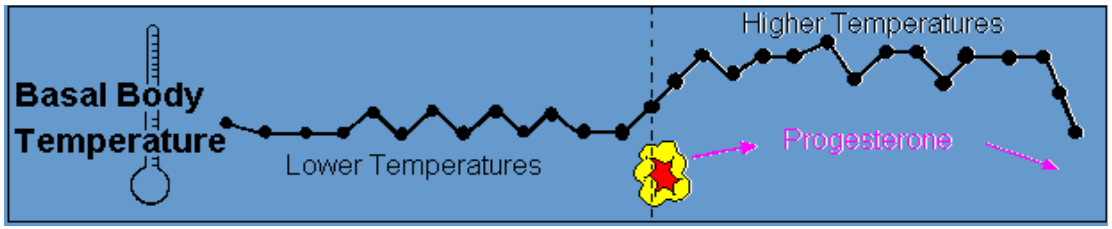
(of potentially child-bearing age)

- Avoid undesired pregnancy/use of effective contraception (family planning)
- Avoid potential teratogens (e.g. efavirenz, ribavirin, but also tobacco, alcohol, drugs)
- Maximize physical and mental health before pregnancy
- Discuss reproduction options that are safe to partner
- Discuss use of HAART in pregnancy
- Perform properly exams, pap smear, and sexually transmitted disease screening, fertility disorders, treat abnormalities
- Encourage sexual partners to receive HIV testing, counselling, and care

With access to optimal management, giving birth to a healthy, HIV negative baby is possible for the vast majority of women of childbearing age

Woman preconception counseling

- If pregnancy is planned while on ART: attain maximal virologic suppression prior to pregnancy
- If pregnancy is planned in women not on therapy: obtain resistance testing and make a decision on choice and timing of ART
- Prescribe folic acid or prenatal vitamins before conception for planned pregnancies
- Review diet and avoidance of alcohol, drugs and cigarettes
- Educate about ovulation and fertility



Reproductive options

Prevention of horizontal transmission

- Different clinical scenarios:
  - HIV+ woman with HIV- man (serodiscordant) or who is single or in same sex relationship
  - HIV+ man and HIV- woman (serodiscordant)
  - HIV+ man and HIV+ woman (seroconcordant)
  - HIV+ man who is single, or in same sex relationship, or a couple seeking egg donation or a surrogate mother

Different clinical scenarios have different risk of and require different strategies to prevent horizontal transmission

Different strategies

HIV+ man & HIV- woman

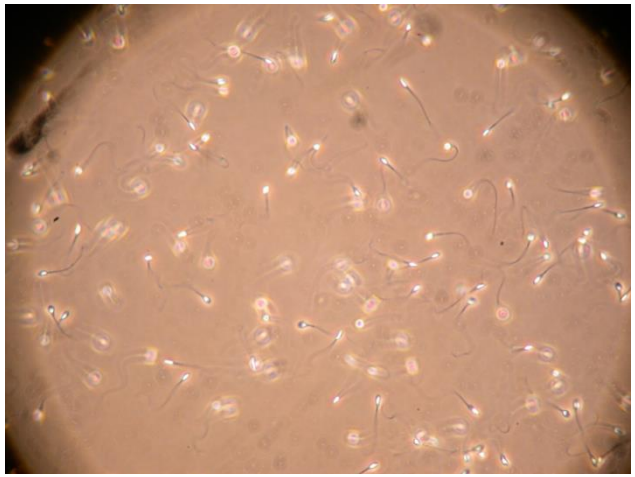
- IUI, IVF or ICSI following sperm washing
- Natural conception (if effective viral suppression)
- Insemination of donor sperm at ovulation
- Pre-Exposure Prophylaxis (PrEP)
- Adoption

HIV+ woman & HIV- man

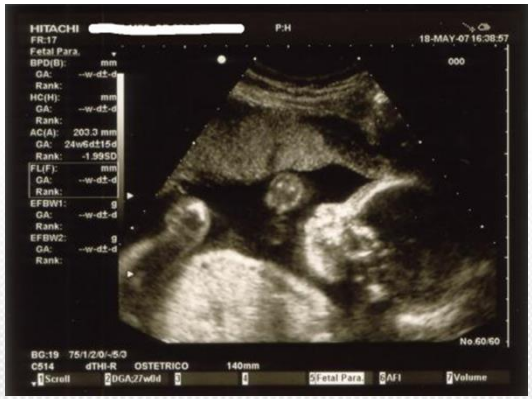
- Insemination of partner's sperm at ovulation (if not on ART / detectable viral load)
- Natural conception (if effective viral suppression)
- Assisted reproduction in case of fertility disorders
- Adoption

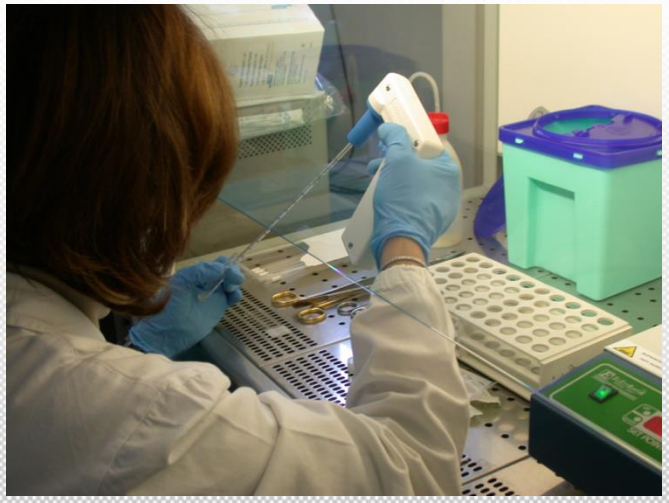
HIV+ man & woman

- Insemination of donor sperm or sperm washing to prevent superinfection
- Natural conception
- Assisted reproduction in case of fertility disorders



OUR EXPERIENCE





OUR INITIAL PROJECT

AIM

We started our activity of assisted reproduction in 2002 with the aim of reducing the risk of sexual HIV transmission within serodiscordant couples, during attempts to conceive. We applied intrauterine insemination (IUI) of HIV-negative women with semen from their HIV- infected partners incorporated in a multidisciplinary approach. Indeed, in order to gain insight into the couple's reproductive decision-making and behaviour, we included in our program an accurate evaluation of social, cultural, and psychological areas of the couples.

TECNIQUE

The semen was processed in order to separate motile spermatozoa from HIV-infected seminal plasma and cells (combining density-gradient centrifugation with swim-up of spermatozoa). After HIV testing, the final sperm fraction was used for IUI. Unfortunately only men with good semen qualities qualified for treatment.

LIMITS

To overcome subfertility or infertility problems after sperm preparation, the assisted reproductive techniques available could also include, besides intrauterine insemination (IUI), embryo-tranfer after either in vitro fertilization (IVF) or after intracytoplasmic sperm injection (ICSI), but there were not available in our Centre.

Our multidisciplinary network

CONSULTANTS AND SCIENTIFIC SUPERVISION:
Enrico Semprini MD Director of
Centro Ricerche Semprini
MILANO

Prof. Franco Diani
Cattedra di Fisiopatologia della Riproduzione
Clinica Ostetrica e Ginecologica University of Verona

CENTER OF PREVENTIVE AND COMUNITARY MEDICINE
AZIENDA ULSS 20 DI VERONA
UNIT OF SAFE ASSISTED REPRODUCTION FOR HIV COUPLES
Marina Malena MD
Roberta Frighetto (Social worker)
Marco Faccio MD (PSYCHIATRIST)
Veronica Scolari (NURSE)

CENTER OF ASSISTED REPRODUCTION TETHYS (Verona)
Patrizia Pezzini MD (DIRECTOR)
Laura Bosaro (BIOLOGIST)

LABORATORIES:
CLINICAL IMMUNOLOGY (University of Verona)
Azienda Ospedaliera di Verona
Prof. Giuseppe Tridente (Director)
Dunia Ramarli MD (Consultant)

UNITA' OPERATIVA AUTONOMA DI LABORATORIO ANALISI
Azienda ULSS 20-VERONA (Ospedale S. Bonifacio)
Bonadonna MD (Director)
Sandro Consolaro MD (Consultant)

DEPARTMENT OF OBSTETRICIA E GYNECOLOGY
OSPEDALE AZIENDA ULSS 20 -SAN BONIFACIO
Umberto Tosadori MD (Director)
Aldo Valentini MD (Consultant)

The european network CREAThE

CENTRES FOR REPRODUCTIVE ASSISTANCE TECHNIQUES IN hiv-INFECTED INDIVIDUALS IN EUROPE.

Is a not for profit network incorporating the major centres offering reproductive treatment services to couples with HIV. Thanks to its unique composition, the CREAThE network can rely on a timely access to systematically and prospectively collected data on a large number of HIV positive men and women accessing a range of reproductive treatments in over ten countries including: Italy, Germany, Switzerland, UK, Belgium, Denmark, France, Spain, Israel, South Africa and the US:

Data and features of the couples in the first period of activity: from 2002 to 2009

From January 2002 to October 2009 150 couples have included in the programme

IVDA: 86 % of man had previous drug abuse as risk factor for HIV infection

HCV: 70 % were HCV coinfected
History of drug abuse and HCV infection was present in 15% of women.

Social/cultural features: 75 % of female partners reported having high school education or university, a proportion significantly high compared to the 16 % of male
These couples were tipically in a stable relationship, steadily employed, and of medium-high socioeconomic status

Lost to follow-up: The giving up rate after the first interview was about 18%

Fertility: about 50% of the couples required in vitro fertilization

Etnicity: we observed in the last years of the described period an increasingly proportion of mixed-race, and foreign couples, mostly african

138 IUI attempts have performed in 49 women (96 with fresh semen and 42 with frozen semen *).

22 babies were born, 4 miscarriages have occurred

Pregnancy rate per IUI cycle was 15.9% #

Pregnancy rate per couple was 44.8 % #

* The capacitation techniques applied to sperm specimens improved the number of the motile spermatozoa of the samples, but the freezing process decreased significantly this value.

Pregnancy rates in our study per IUI cycle and, per couples are in accordance to those reported in 5 other series (Semprini *et al.*, 1992; Marina (A) *et al.*, 1998; Bujan (A) *et al*., 2004; Gilling-Smith *et al*., 2000; Weigel *et al*., 2001). Data from these studies show rates of pregnancy after IUI procedures ranging from 14.8 to 30.6 % per cycle, or 31.3 to 66.1 % per couple.

Our following activity: features and challenges

Since 2009 we have started to accept serodiscordant couples in which the female is positive and seroconcordant couples for counseling and reproductive assistance, according to the that time European Guidelines.

Then supported from the progress of the HIV prevention science in the most recent years we have started to assist the couples which opt for spontaneous conception.

The natural method carries an inconsistent unknown risk of transmission in couple in which the man's viral load is undetectable, thanks to the use of highly effective antiretroviral medication.

Nevertheless we prefer to apply a more safe alternative, while respecting couples' reproductive choice. This new method that we call "natural guided conception" consists in the combination of pre-exposure prophylaxis to the woman with timed unprotected intercourse, after exclusion of any STD and after the assessment of fertility in both partners. In this way we may further reduce the risk of transmission during spontaneous conception attempts.

In the HIV discordant couples where the woman is positive the risk of sexual transmission to the man is eliminated either by self insemination or by the use of ART when infertility factors exist.

CONCLUSIONS

Safer conception counseling for HIV couples is a reproductive right and should be included as a public health strategy to reduce HIV incidence among men, women and their children. Integrating effective HIV prevention strategies into comprehensive reproductive counseling is a rational step to protect uninfected partners and their children and to make progress towards eliminating HIV.

The different situations that affect HIV couples present different prevention and fertility issues and require specific reproductive counselling and care.

Several projects suggest the feasibility and acceptability of this new ARV-based safer conception option. While the number are too small to draw conclusion about safety the complete “package” (ART, PrEP, timed conception, STI treatment) is likely to confer nearly zero risk oh HIV transmission when the adherence is high.