Fondazione Icona

ITALIAN COHORT NAIVE ANTIRETROVIRALS

newsletter

JUNE 2023

By ICONA Foundation Scientific Secretary

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01 | Introduction

Dear Collegues,

it is a great pleasure to submit to your attention the first edition of ICONA Foundation Newsletter, an online report of the ICONA Cohort activities.

Actually, the idea of a newsletter focused on ICONA report and research findings was launched by professor Mauro Moroni in 2015, but at that time all the energies were dedicated to implementing the ICONA data base and to finding new centers collaborating and grants to bring forward the scientific production of the Cohort.

Many years have passed and now, at the 26th year of the Cohort, we can definitely say that ICONA has substantially contributed to HIV clinical research, being an open window on the real world of persons living with HIV in Italy: indeed, ICONA patients are enrolled when naives to antiretroviral therapy, and their follow-up lasts lifelong. The topics studied by ICONA are all-embracing the HIV research area, from virological and immunological issues, to clinical, therapeutic ones and, most important, to patients' related outcomes.

All this is done thanks to dedicated persons, data managers and statisticians, but, first of all, to the everyday work of clinical centers registering patients' data, and, more recently, to community members who focus on patients' needs and quality of life. All these entities are coordinated by the 14-member Scientific Secretary and a 48-member Scientific Board, that has to propose and evaluate new projects; finally, the Board of Directors controls fund raising and spending.

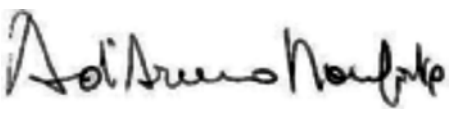
Why an ICONA newsletter now?

We think that is time to disseminate the data from ICONA, including the yearly report of ICONA Cohort - till now available only for members and centers of ICONA - containing information on new enrolled patients, their characteristics, coinfections, comorbidities, antiretroviral therapy regimens and outcome.

We also intend to include in the newsletter a brief summary of several published papers from the past 2 years, that are considered a milestone in HIV clinical research.

The newsletter is planned to be published yearly, any suggestions and comments are welcome.

Hoping that this initiative will be appreciated and useful, we thank all of you for your attention.



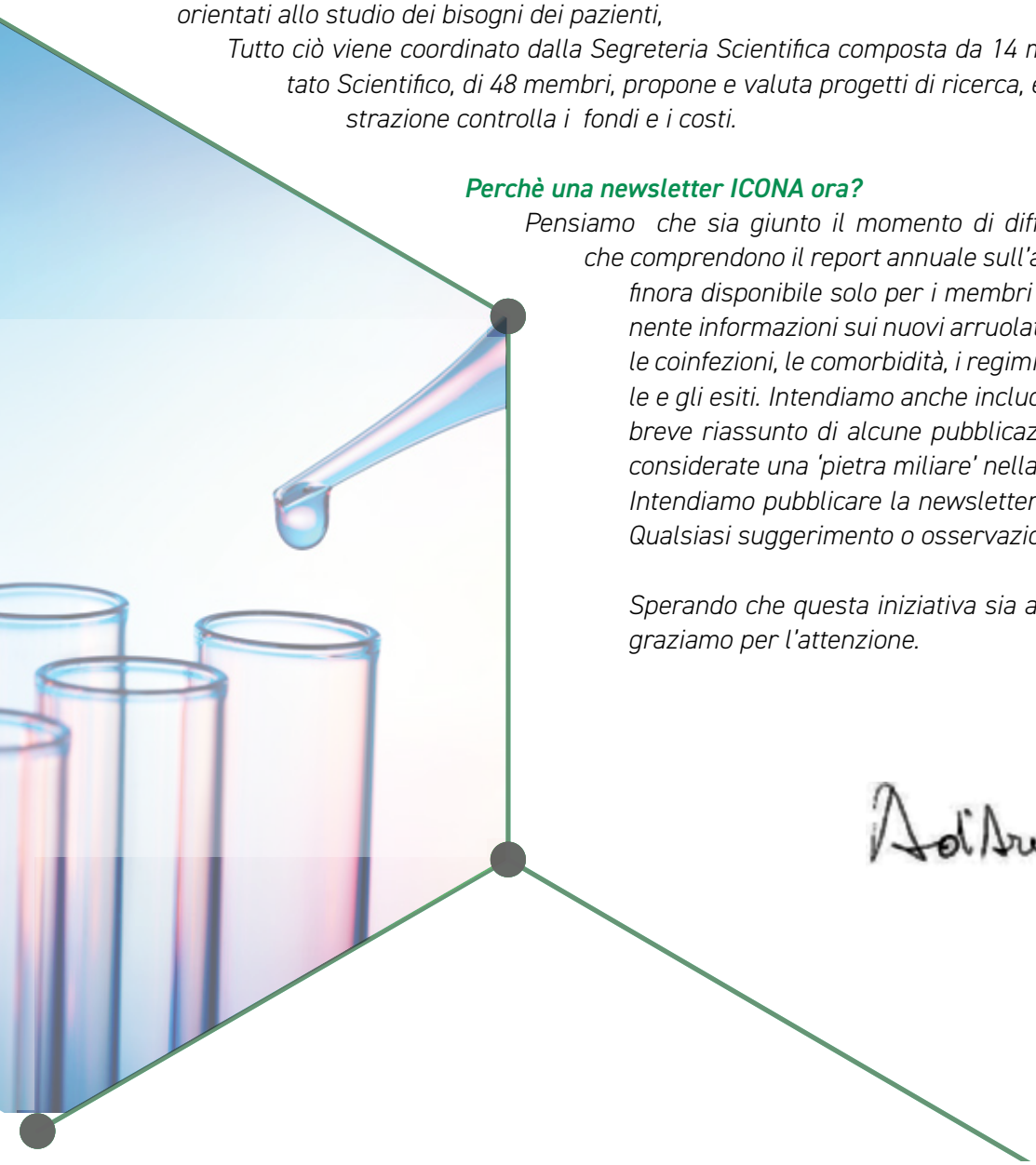
Care Colleghe e cari Colleghi,

è con grande piacere presentare il primo numero della Newsletter della Fondazione ICONA, che vuole essere un report annuale delle attività di ICONA.

Per la verità, l'idea di una newsletter di ICONA centrata sul report e sulle pubblicazioni della Coorte era stata proposta dal prof. Mauro Moroni nel 2015, ma all'epoca le energie erano tutte dedicate alla implementazione del database e a cooptare nuovi centri e fondi per portare avanti la produzione scientifica della Coorte.

Sono passati molti anni e ora, al 26° anno della Coorte, possiamo certamente affermare che ICONA ha contribuito in maniera sostanziale alla ricerca clinica su HIV, e rappresenta una finestra aperta sul mondo reale delle persone che vivono con HIV in Italia; infatti, i pazienti sono arruolati in ICONA quando sono naives e vengono seguiti per tutta la vita. Le linee di ricerca di ICONA comprendono diverse aree, virologica e immunologica, clinica, terapeutica, e soprattutto la ricerca 'patient-oriented' sul vissuto dei pazienti. Tutto questo grazie a persone dedicate, data managers, statistici, ma soprattutto dal lavoro quotidiano dei centri clinici che registrano i dati dei pazienti e ai membri della community, orientati allo studio dei bisogni dei pazienti,

Tutto ciò viene coordinato dalla Segreteria Scientifica composta da 14 membri, mentre il Comitato Scientifico, di 48 membri, propone e valuta progetti di ricerca, e il Consiglio di Amministrazione controlla i fondi e i costi.



Perchè una newsletter ICONA ora?

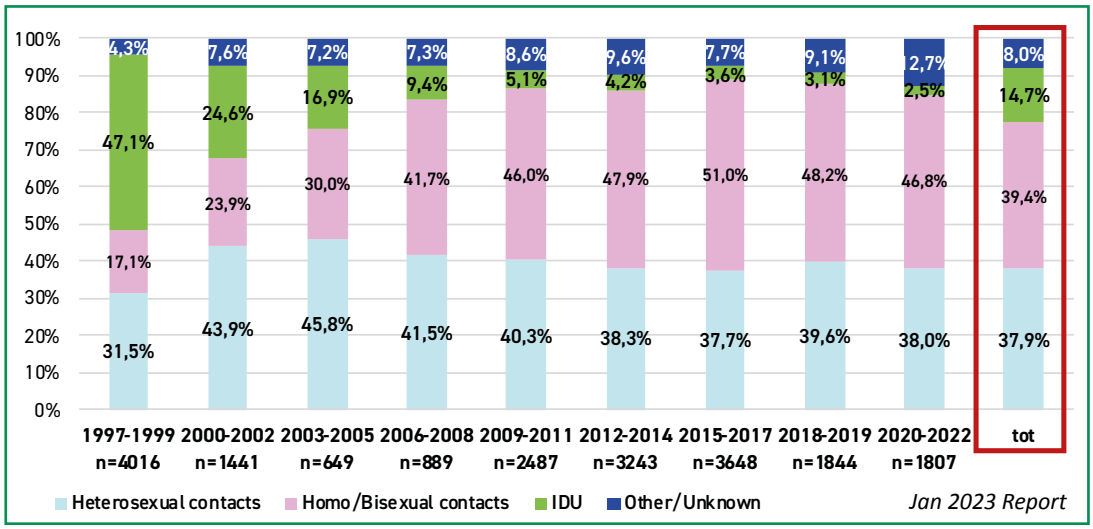
Pensiamo che sia giunto il momento di diffondere i dati di ICONA che comprendono il report annuale sull'andamento della Coorte, finora disponibile solo per i membri e i centri ICONA, contenente informazioni sui nuovi arruolati, le loro caratteristiche, le coinfezioni, le comorbidità, i regimi di terapia antiretrovirale e gli esiti. Intendiamo anche includere nella newsletter un breve riassunto di alcune pubblicazioni degli ultimi 2 anni, considerate una 'pietra miliare' nella ricerca clinica di HIV.
Intendiamo pubblicare la newsletter con scadenza annuale.
Qualsiasi suggerimento o osservazione è più che gradito.

Sperando che questa iniziativa sia apprezzata e utile vi ringraziamo per l'attenzione.

02
Data from the yearly ICONA report

02 | Data from the yearly ICONA report

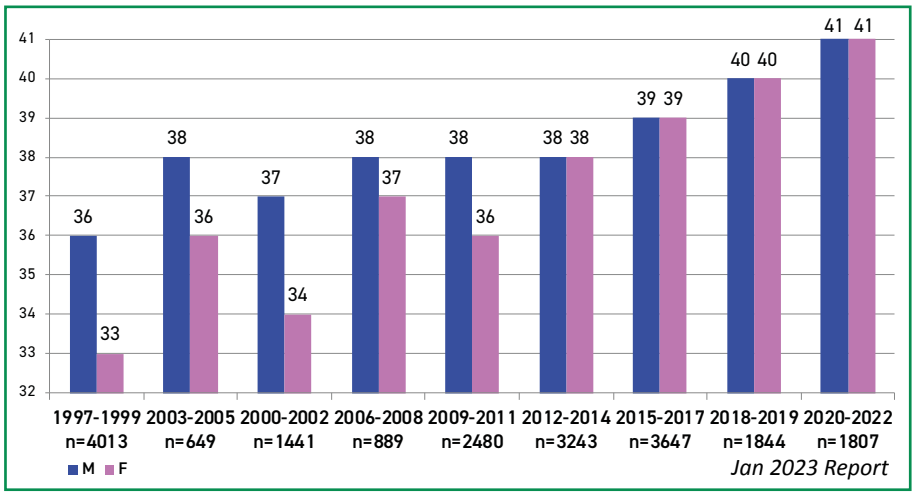
Mode of HIV transmission according to calendar year of enrolment in the ICONA cohort among 20012 persons living with HIV



Sexual contacts (77.3%) are the main mode of transmission of HIV infection in the cohort.
Except for the first period, when IDUs represented nearly half of the modes of transmission of HIV, sexual intercourses have always been the most frequent mode of transmission. In particular, men-to-men sexual intercourses represent around 50% of cases diagnosed in the last 10 years. Furthermore, the percentage of IDUs decreased sharply from 1997 until 2010, and continues to decrease, albeit more slowly, until today (from 47,1% to 2,5%). In general, the modes of HIV transmission remain pretty stable from 2010 until today.

La principale via di trasmissione dell'infezione è rappresentata da quella sessuale (77.3%). Come mostrato nel grafico, fatta eccezione per il primo periodo, quando l'uso di sostanze per via endovenosa rappresentava circa la metà dei casi, la trasmissione per via sessuale è sempre stata la principale via di trasmissione. In particolare, la trasmissione uomo-uomo rappresenta circa il 50% dei casi negli ultimi 10 anni. Inoltre, è evidente come la percentuale di trasmissione attraverso l'uso di sostanze per via endovenosa sia diminuita rapidamente dal 1997 al 2010, e stia continuando lentamente a diminuire anche negli ultimi anni (dal 47,1% al 2,5%). In generale, le modalità di trasmissione del virus sono rimaste relativamente stabili dal 2010 ad oggi.

Median age according to calendar year of enrollment and gender

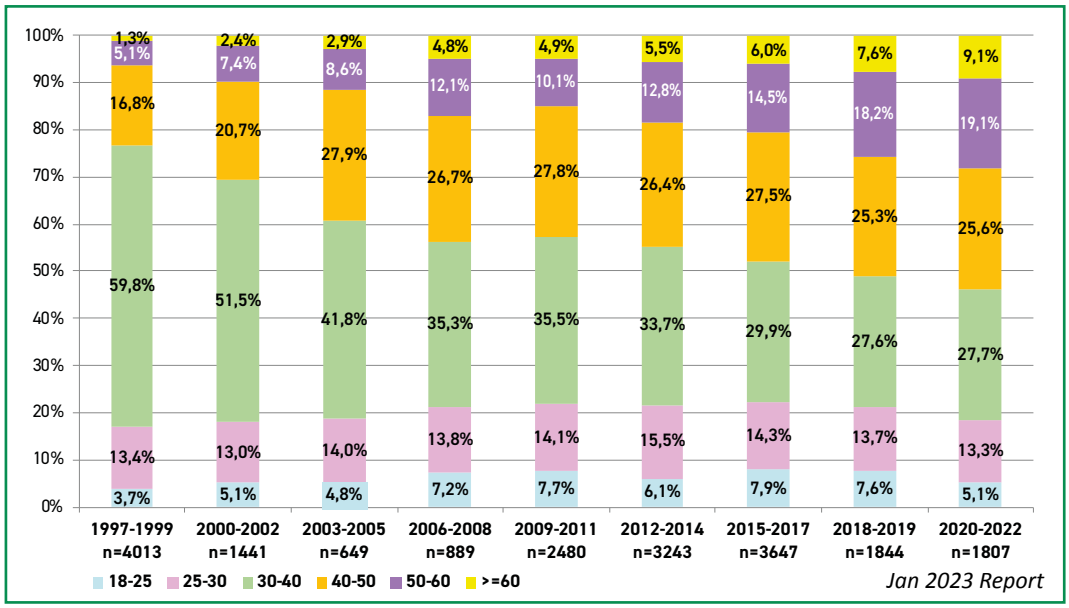


The median age of HIV positive antiretroviral naive people enrolled in the ICONA Cohort has increased in the last years, expecially from 2012, in both sexes. In 1997-2011 women with a new diagnosis of HIV were younger than in the last 4 calendar years; the median age of men was stable until 2014, but it has increased in the last 3 calendar years. It is worth noting that the ages of men and women with new infections at enrollment are identical to each other in the last 10 years.

L'età media delle persone HIV positive naive arruolate nella coorte ICONA sta in genere aumentando negli ultimi anni, soprattutto dal 2012, senza differenza di genere. Nel 1997 fino al 2011 le donne con nuova diagnosi di HIV erano più giovani rispetto agli ultimi 4 periodi di calendario; l'età media degli uomini è rimasta pressochè stabile fino al 2014, mentre sta aumentando negli ultimi 3 periodi di calendario. È da notare che l'età di uomini e donne con nuova infezione all'arruolamento in ICONA è tra loro identica da circa 10 anni.

Age strata at enrolment according to calendar period

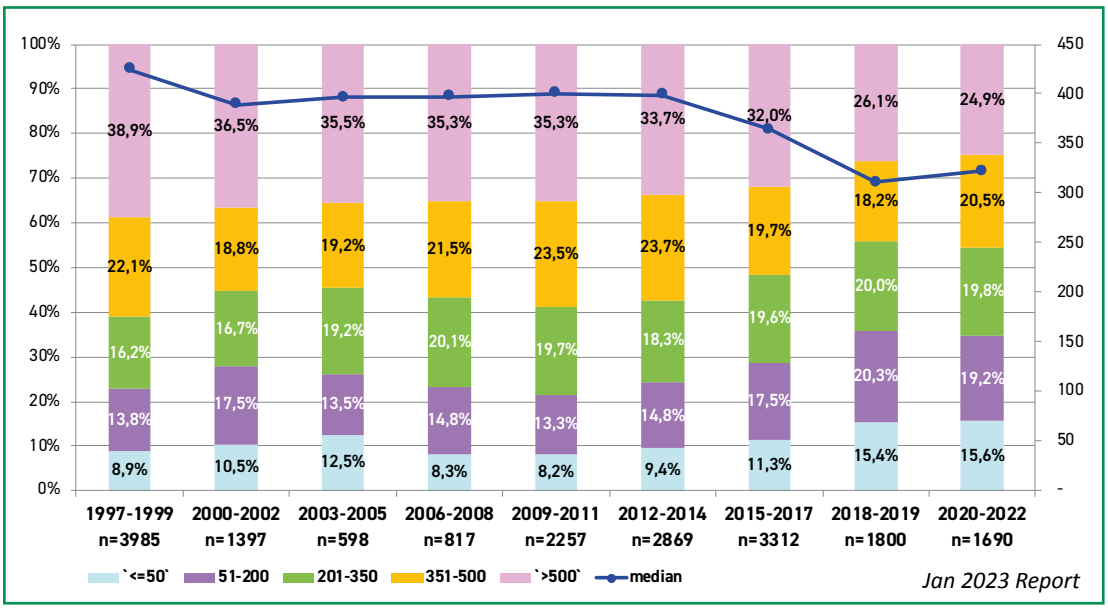
The median age of naive people enrolled in ICONA Cohort has increased in the last years. This results in an increasing percentage of persons diagnosed with HIV ageing over 50 and in particular over 60, representing 18-19% of all the enrolled patients in 2018-22, while new infections in the 30-40 age strata have decreased from 50% in 2000 to 28% in 2018-22.



L'età media delle persone naive arruolate nella coorte ICONA negli ultimi anni sta aumentando. In particolare, sta aumentando la percentuale di soggetti con diagnosi infezione da HIV di età superiore ai 50 anni, in particolare nella fascia oltre i 60, che rappresenta il 18-19% dei pazienti arruolati nel 2018-22, mentre stanno diminuendo le nuove diagnosi nella fascia di età compresa tra 30 e 40 anni, che rappresentano il 50% circa degli arruolati nel 2000 e il 28% nel 2018-22.

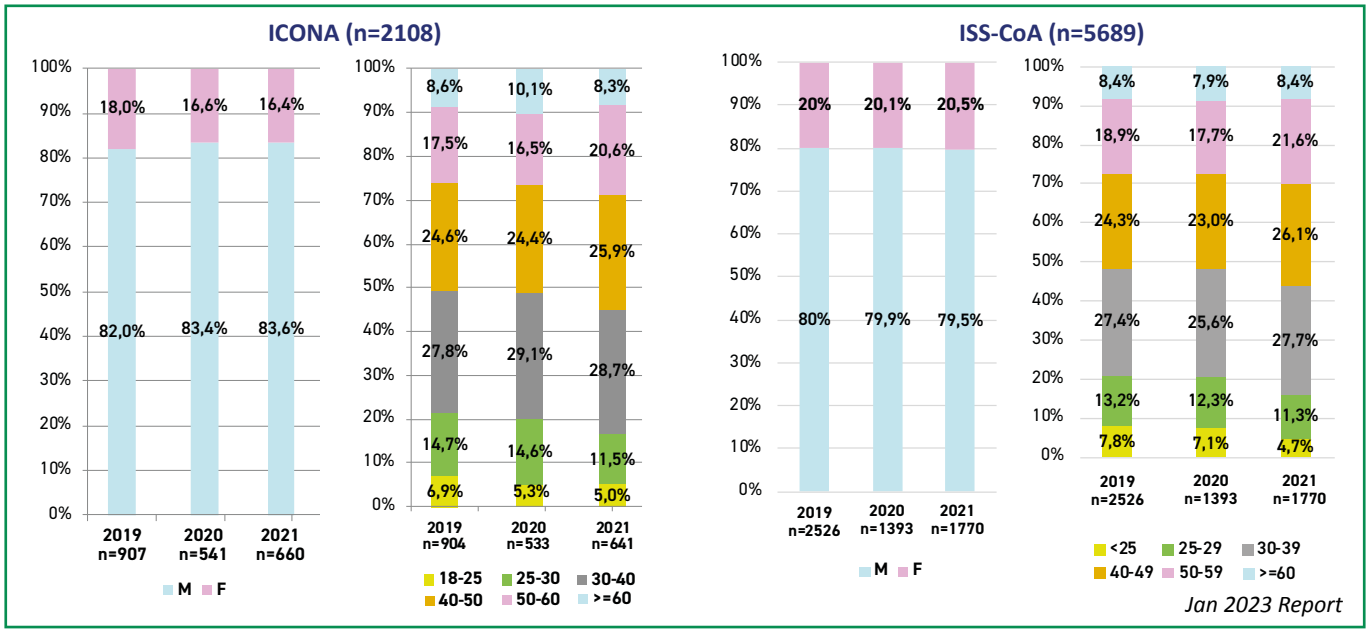
Data on median CD4 counts and CD4 strata at enrolment in ICONA (ART-naives)

Median CD4 counts at diagnosis continue to decrease in the cohort according to calendar year; the percentage of persons living with HIV (PLWHs) diagnosed with CD4 below 350/mmc (definition of late presenters) has increased from 38.9% in 1997-99 to 54.6% in 2020-22. PLWHs with CD4 below 200/mmc, i.e. with advanced HIV infection (diagnosis of AIDS according to CDC) represent 15% of new diagnoses in the last calendar years. These persons were presumably infected years ago and they are responsive of maintaining HIV infection and transmission within the population, being unaware to be HIV positive and thus viremic (as not in treatment) and with no safe-sex measures.



Le conte mediane di CD4 alla diagnosi continuano a diminuire negli anni, e la percentuale di persone con conte di CD4 <350/mmc (indicative di presentazione tardiva) è aumentata dal 38.9% negli anni 1997-99 al 54.6% nel 2020-22. Inoltre, persone con conte di CD4 inferiori a 200/mmc, con una diagnosi quindi di malattia da HIV in fase avanzata (diagnosi di AIDS per i CDC) rappresentano negli ultimi anni il 15% delle nuove diagnosi. Queste persone sono state presumibilmente infettate anni fa e sono la prima causa del mantenimento della circolazione del virus nella popolazione, essendo viremiche (in quanto non trattate) e inconsapevoli, quindi senza misure di protezione durante i rapporti sessuali.

Gender and age strata according to calendar year of enrolment (2019 to 2021): ICONA Cohort and ISS CoA Registry



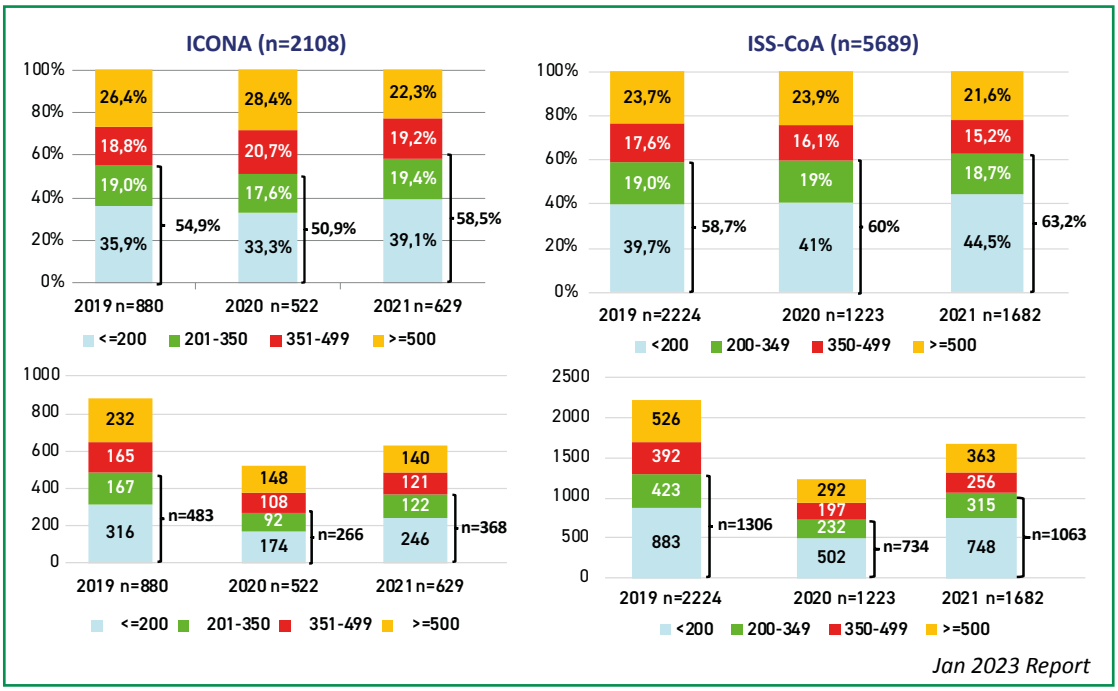
ICONA data are in agreement with the national registry of HIV diagnoses (ISS-COA Registry) showing, in a number around triple than patients enrolled in ICONA, similar sex and age representativity: in both settings women account for about 16-18% of new diagnoses and people over 50 years old for about 38% in 2021. We can thus state that ICONA well represents the Italian epidemiological scenario of new HIV diagnoses.

I dati raccolti dalla coorte ICONA sono in linea con i dati del Registro Nazionale delle nuove diagnosi di HIV, il registro ISS-COA. In entrambi i setting, le donne rappresentano circa il 16-18% delle nuove diagnosi, e le persone sopra i 50 anni circa il 30%.

Possiamo quindi affermare che ICONA ben rappresenta lo scenario epidemiologico italiano dell'infezione da HIV.

CD4 count strata according to calendar year of enrolment (2019 to 2021): ICONA Cohort and ISS CoA Registry

Looking at immunological data of new HIV diagnoses in ICONA and ISS-COA Registry, we confirmed the observation of increasing frequency of late and very late HIV diagnosis in the last three years. Both populations show in more that half of cases CD4 counts below 350/mmc at HIV diagnosis (indicative of late presentation) and in around 40% of cases their CD4 counts are below 200/mmc (indicative of advanced HIV disease).



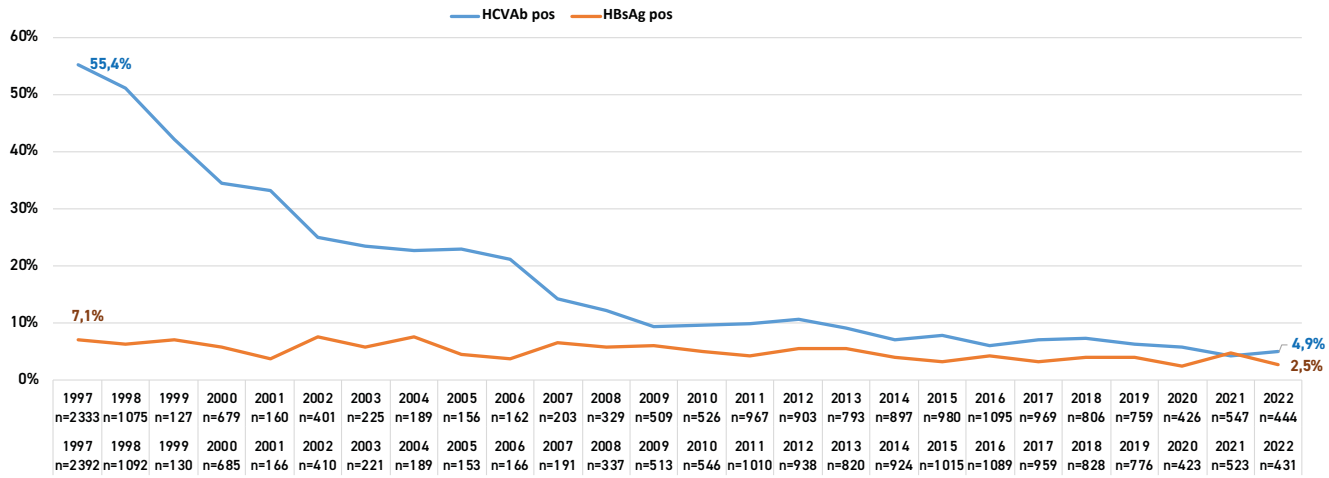
Even if this percentage of advanced naive has been stable

over the three considered calendar years, it is noteworthy that the absolute numbers of new HIV diagnoses is declining in both settings, by 30-35% from 2019 to 2021.

This finding might be related both to the effectiveness of extended use of ART and of use of PrEP in high risk groups, but also to a decrease of screening campaignes during COVID epidemics. Taken together, also in term of CD4 and new infections, ICONA well represents the overall Italian situation.

Analizzando i dati immunologici, i pazienti con nuova diagnosi di HIV arruolati nella coorte ICONA e nel registro ISS-COA negli anni 2019-2021 presentano in più della metà dei casi conte di CD4 < 350 cellule/mmc, indicative di presentazione tardiva, e nel 40% dei casi circa conte < 200 cellule/mmc, indicative di malattia in fase avanzata. È però importante evidenziare che il numero di nuove diagnosi di HIV si è ridotto negli ultimi tre anni, e nel 2021 i nuovi casi rappresentano il 70% dei casi diagnosticati nel 2019. Tale situazione può dipendere sia dall'efficacia dell'uso generalizzato della terapia antiretrovirale e dalla profilassi pre-esposizione PrEP nei gruppi a rischio, ma anche da una riduzione dello screening negli anni dell'epidemia da COVID. Nell'insieme, anche in termini di conte di CD4 alla diagnosi e di descrizione di nuovi casi, la coorte ICONA ben rappresenta la situazione italiana attuale.

Proportion of patients with HCVAb pos test and HbsAg pos test within 1 year from enrolment, according to calendar year of enrolment



Jan 2023 Report

The prevalence of HCV in people living with HIV (PLWHs) entering into care in Italy has progressively decreased over the last 25 years.

In 1997 more than half (55.4%) of the PLWHs enrolled in the ICONA cohort and tested for HCV-Ab, within 1 year, tested positive, while the prevalence of HCV-Ab positive is stable around 5% in more recent calendar years.

The observed decline was mainly explained by the changes in the modality of HIV transmission in Italy during the years of HIV epidemic, particularly the frequency of IDU.

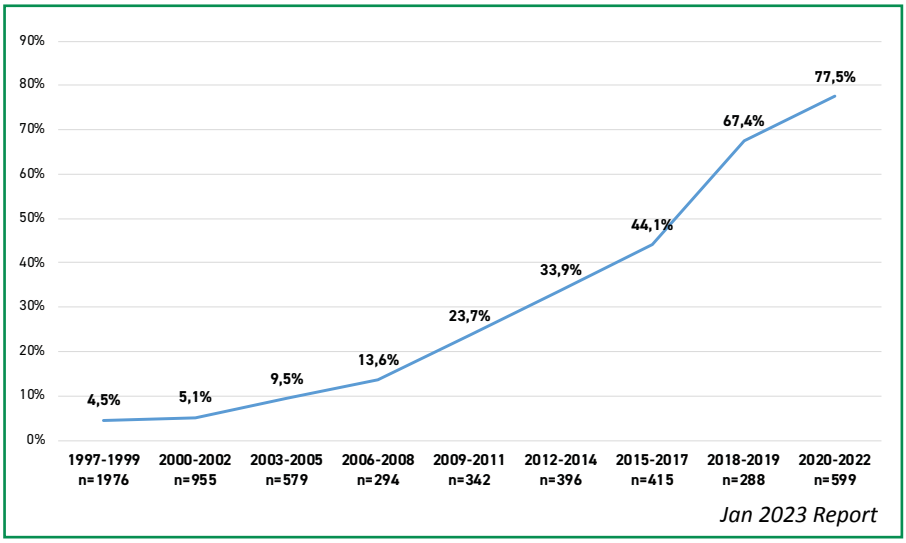
HBV prevalence has always been much lower in HIV population enrolled in ICONA, with a proportion of HBsAg positive PLWHs stably below 8%, now ranging around 2.5%-5.0% in recent years.

La prevalenza di HCV nelle persone che vivono con HIV (PLWH) che entrano in cura in italia è progressivamente diminuita negli ultimi 25 anni. Nel 1997 più della metà (55.4%) degli arruolati nella coorte ICONA, e testati per HCV entro un anno, sono risultati positivi per HCV-Ab, mentre negli anni più recenti la prevalenza è stabile intorno al 5%.

Questo andamento è in gran parte giustificabile con il cambiamento della modaltà di trasmissione di HIV osservato in Italia, in particolare per la diminuzione degli utlizzatori di sostanze per via iniettiva.

La prevalenza di HBV all'arruolamento nella coorte è invece sempre stata significativamente inferiore, con una proporzione di soggetti HBsAg-positivi stabilmente sotto l'8%, e attualmente intorno al 2.5%-5.0%.

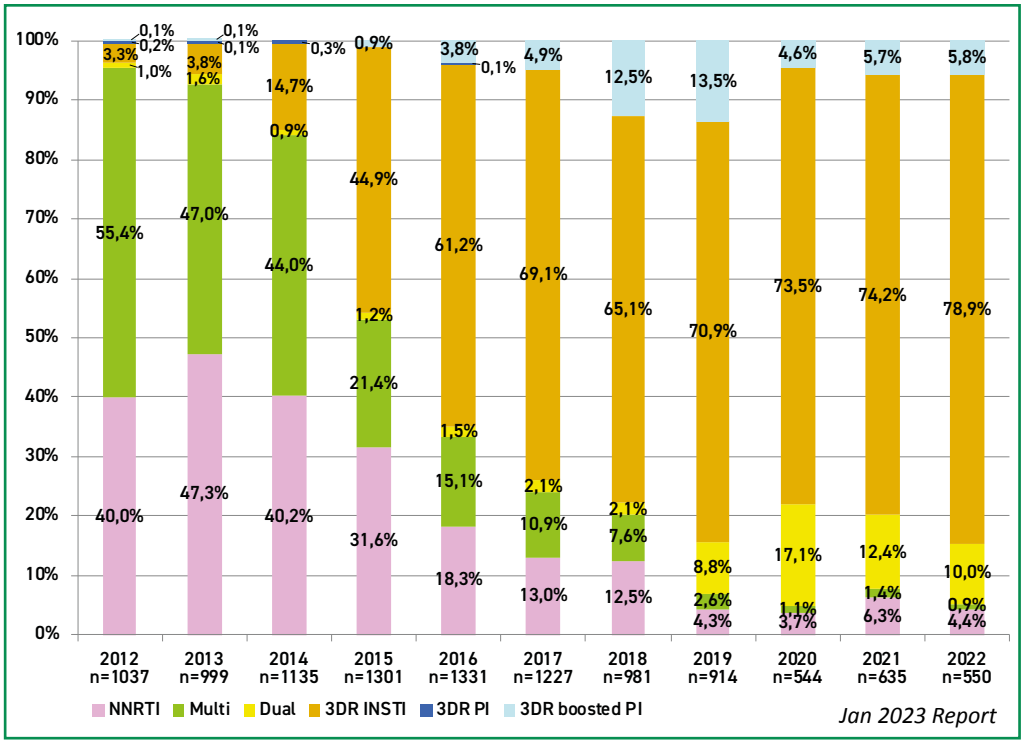
Prevalence of HCV-RNA negative in HCVAb pos patients according to calendar year of follow up in ICONA



A great increase of HIV/HCV subjects with negative HCV-RNA has been observed over the years reflecting the availability of anti-HCV therapy. In the first years, when essentially only the monotherapy with Interferon-α was available the prevalence of HCV viremic PLWHs was high (around 95% of HCVAb positive). Combination therapy with Peg-Interferon and Ribavirin led to an increase of the HCV-RNA negative proportion up to 33.9% in 2012-2014. The revolution of the Direct-Acting Antiviral (DAA) agents, changed the therapy of active HCV infection, with a proportion of cured HCV among PLWHs enrolled in ICONA that has grown significantly in the recent years (in 2020-2022 77.5% of HCVAb pos PLWHs tested for HCV-RNA were negative).

Possiamo osservare un notevole incremento negli anni di PLWH aviremici (HCV-RNA neg), il che riflette anche la differente disponibilità delle terapie anti-HCV: mentre nel primo periodo della coorte, dove i farmaci disponibili erano limitati alla monoterapia con Interferon-α, la prevalenza di PLWH viremici era elevata (95% degli HCVAb pos), nel successivo periodo l'introduzione della terapia con Peg-Interferone e Ribavirina ha portato ad un incremento della proporzione di soggetti HCV-RNA negativi fino al 33.9% nel 2012-2014, i DAA (antivirali ad azione diretta) hanno rivoluzionato la cura per l'epatite C, incrementando significativamente la proporzione di soggetti aviremici negli ultimi anni (fino al 77.5% di HCV-RNA neg del 2020-2022).

Proportion of usage of different ART classes as third drug in first line regimen according to calendar year of starting

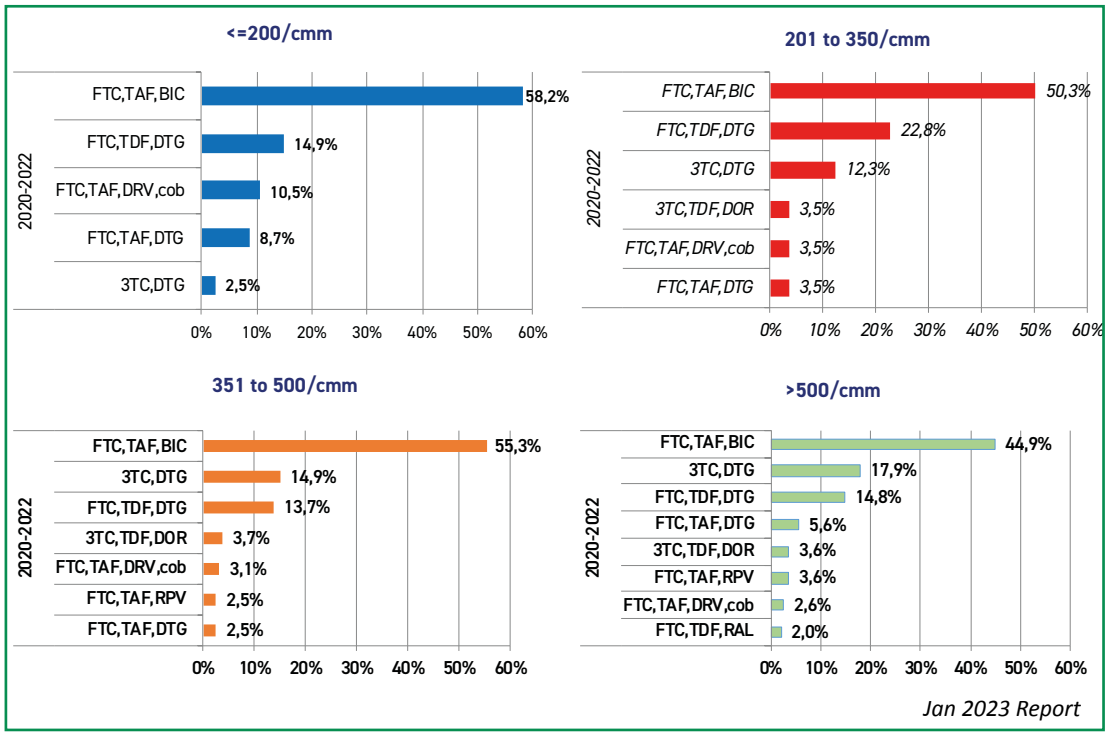


The graph shows the progressive increase, starting from 2015, in the use of integrase inhibitors which in recent years are present in about 90% of first-line regimens (including dual therapy with INSTI). In the last 4 years, the decline of first-line regimens containing NNRTIs and PI/b has corresponded to an increase in regimens with only 2 drugs (3TC+DTG) in conjunction with the recommendations of the main international guidelines.

L'analisi della prevalenza delle differenti classi di antiretrovirali, utilizzati come "terzo farmaco" in prima linea per anno di arruolamento, evidenzia il progressivo aumento, a partire dal 2015, dell'utilizzo degli inibitori dell'integrasi che negli ultimi anni sono presenti in circa il 90% dei regimi di prima linea (comprese le dual therapy con INSTI). Negli ultimi 4 anni al calo

dei regimi di prima linea contenenti NNRTI e PI/b è corrisposto un aumento dei regimi con 2 soli farmaci (3TC+DTG) in concomitanza con le raccomandazioni delle principali linee guida internazionali di terapia antiretrovirale.

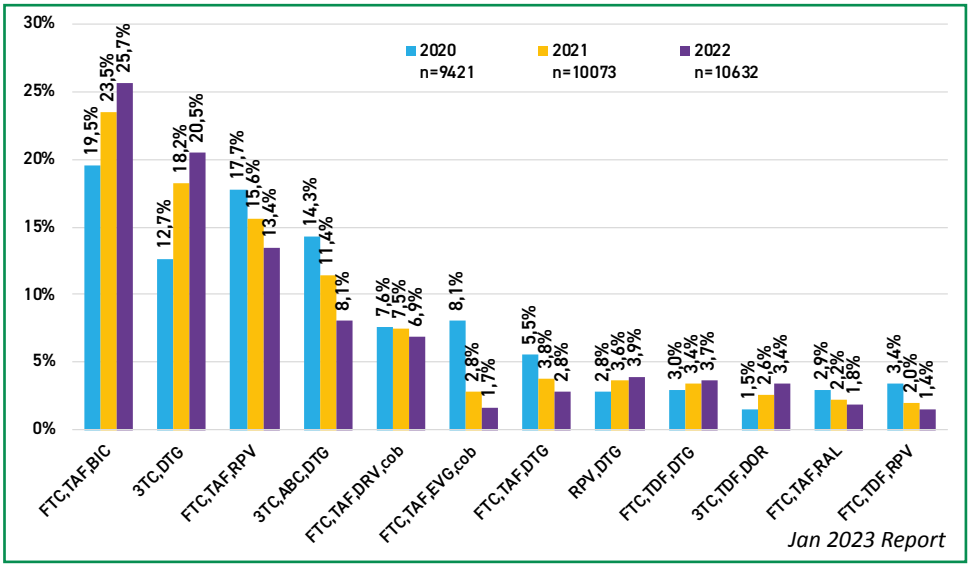
Distribution of first line regimens in patients starting ART according to CD4 count in 2020-2022



ICONA reports data on the main antiretroviral regimens used in the first line in relation to the baseline counts of CD4+ lymphocytes/mmc. There is a large use of regimens including second generation integrase inhibitors (BIC and DTG) associated with 2 NRTIs. The dual therapy regimen with 3TC/DTG tends to be used in a higher percentage in PLWHs displaying a higher count of CD4+/mmc. Regimens with DRV/c are used predominantly in patients with low CD4+/mmc while regimens containing DOR are used in low percentage but in patients with CD4+/mmc levels >200/mmc.

L'analisi dei principali regimi terapeutici utilizzati in prima linea in rapporto al valore basale di linfociti CD4+/mmc, mostra un largo utilizzo di regimi includenti inibitori dell'integrasi di seconda generazione (BIC e DTG) associati a 2 NRTI. Il regime dual therapy con 3TC/DTG tende ad essere utilizzato in una percentuale superiore di PLWH con un numero superiore di CD4+/mmc. I regimi con DRV/c sono utilizzati prevalentemente in pazienti con basso numero di CD4+/mmc mentre i regimi contenenti DOR sono utilizzati in bassa percentuale ma con livelli di CD4+ > 200/mmc.

Most used antiretroviral regimens in patients in follow up in 2020-2021-2022

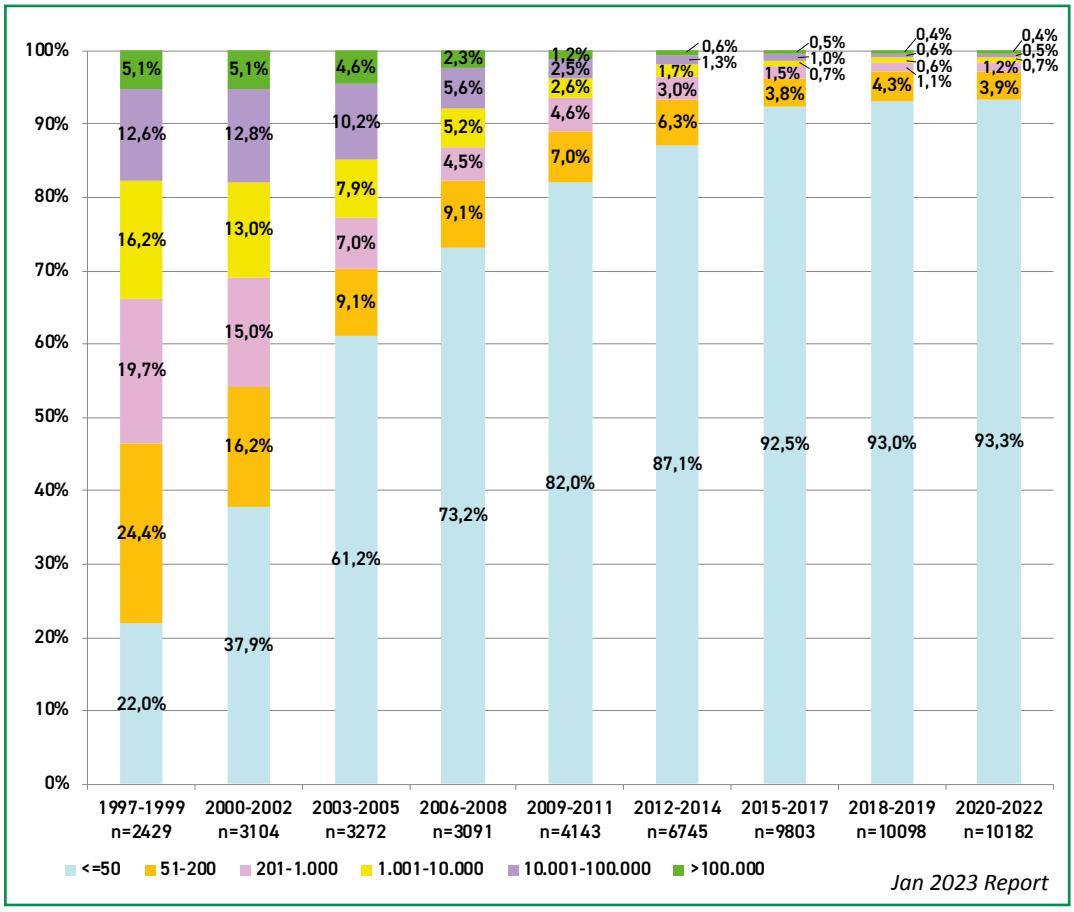


ICONA database analyzed the prevalence of PLWHs on different ART regimens who are in follow up in the last 3 years.
The data are related to all but the lines of regimens excluding the first 6 months of first line ART in care in the last year and illustrate the trend in the last 3 years of the most used antiretroviral regimens in patients in follow-up in the ICONA cohort including all therapeutic lines.
The percentage of PLWHs taking the most used STRs (Single Tablet Regimen) (FTC/TAF/BIC and 3TC/

DTG) is increasing. An important percentage of patients continues to take RPV in STR formulation with FTC/TAF. A relevant finding is that over 70% of patients currently on antiretroviral therapy take an STR regimen.

La coorte ICONA ha anallizzato l'andamento negli ultimi 3 anni dei regimi antiretrovirali più utilizzati nei pazienti in follow-up nella coorte ICONA includendo tutte le linee terapeutiche.
Si osserva un aumento dei due STR (Single Tablet Regimen) più utilizzati (FTC/TAF/BIC e 3TC/DTG).
Una percentuale importante di pazienti continua ad assumere RPV in formulazione STR con FTC/TAF. Un dato rilevante da sottolineare è quello che oltre il 70% dei pazienti attualmente in terapia antiretrovirale assume un regime STR.

HIV-RNA strata (copies/ml) in drug experienced patients, according to calendar period



Since 2015 the percentage of patients with undetectable viremia (<50 copies/ml) is stable well above 90%, showing the excellent efficacy of the new therapies.
A percentage of about 6-7% patients remains detectable: among these patients, more than half have very low level viremia (50-200 copies/ml), that in some guidelines is considered still a therapeutic success, while only about 1% has viremia >10,000.
Taken together, the data show a nearly complete control of virus replication and circulation among treated patients; this suggests a remarkable control of disease progression and, at the same time, a very limited transmission of drug resistant viruses, a situation of major concern in the recent past.
A limited number of patients failed therapy and still require new strategies able to keep the virus under control.

Dal 2015 a oggi, la percentuale di pazienti con viremia non rilevabile (<50 copie/ml) è stabile ben al di sopra del 90%, indicazione chiara dell'eccellente efficacia delle nuove terapie. Nello stesso tempo, una piccola percentuale di pazienti che è stabilmente con viremia rilevabile (6-7%).
Un'ulteriore analisi di tali pazienti mostra che più della metà di questo 6-7% ha una viremia rilevabile ma molto contenuta (50-200 copie), che in alcune linee guida internazionali è ancora considerata come successo terapeutico.
Circa l'1% dei pazienti ha viremia >10.000 copie/ml, indice di replicazione virale.
Nell'insieme, i dati mostrano un controllo massivo sia della replicazione virale, sia della circolazione/trasmissione del virus nei pazienti trattati. Ciò indica anche una limitata progressione della malattia, e un modestissimo rischio di trasmissione di virus resistente ai farmaci (problema non indifferente nel recente passato).
Una quota molto contenuta ma stabile di pazienti va incontro a fallimento terapeutico e necessita di nuove strategie terapeutiche mirate a controllare la replicazione del virus, spesso già resistente a farmaci.

03
Selected Papers published in 2021-22

03 | Papers published in 2021-22

2022

1. *A Cingolani, A Tavelli, GV Calvino, F Maggiolo, Girardi E, A Cozzi-Lepri, A Perziano, P Meli, A Camposeragna, S Mattioli, D Calzavara, R Gagliardini, S Nozza, A Antinori, A d'Arminio Monforte; for ICONA Foundation Study Group* **Awareness and perception of accuracy of the Undetectable=Untransmittable message (U=U) in Italy: results from a survey among PLWHA, infectious-diseases physicians and people having unprotected sex**. AIDS Care. 2022 May 17:1-11. doi: 10.1080/09540121.2022.2074960. Online ahead of print.PMID: 35579404

2. *A Cingolani, A Tavelli, F Maggiolo, A Perziano, A Saracino, F Vichi, M Cernuschi, G Guaraldi, E Quiros-Roldan, A Castagna, A Antinori, A d'Arminio Monforte, Icona Foundation Study Group* **Correlates of Treatment and Disease Burden in People Living with HIV (PLHIV) in Italy** J. Clin. Med. 2022, 11, 471

3. *P Rodari, F Tamarozzi, S Tais, M Degani, F Perandin, D Buonfrate, E Nicastri, L Lepore, ML Giancola, S Carrara, A Tavelli, A Cozzi-Lepri, A d'Arminio Monforte, R Silva, A Angheben* **Prevalence of Chagas disease and strongyloidiasis among HIV-infected Latin American immigrants in Italy - The CHILI study** Travel Med Infect Dis. 2022 Apr 1;48:102324. doi: 10.1016/j.tmaid.2022.102324

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6. *R Gagliardini, P Lorenzini, A Cozzi-Lepri, A Tavelli, V Borghi, L Galli, G Tagliaferri, F Maggiolo, C Mussini, A Castagna, A d'Arminio Monforte, A Antinori; Icona Foundation Study Group* **Real world efficacy of dolutegravir plus lamivudine in PLWH with undetectable viral load after previous failures**. J Glob Antimicrob Resist. 2022 Nov 16:S2213-7165(22)00256-9. doi: 10.1016/j.jgar.2022.11.010. Online ahead of print.PMID: 36402369

2021

1. *S Nozza, L Timelli , A Saracino, N Gianotti, C Lazzaretti, A Tavelli, M Puoti, S Lo Caputo, A Antinori, A d'Arminio Monforte, C Mussini, E Girardi* **Decrease in Incidence Rate of Hospitalizations Due to AIDS-Defining Conditions but Not to Non-AIDS Conditions in PLWHIV on cART in 2008-2018 in Italy** J Clin Med. 2021 Jul 30;10(15):3391. doi: 10.3390/jcm10153391

2. *R Gagliardini, N Gianotti, F Maggiolo, A Cozzi-Lepri, A Antinori, S Nozza, G Lapadula, A De Luca, C Mussini, A Gori, A Saracino, M Andreoni, A d'Arminio Monforte* **Durability of rilpivirine-based versus integrase inhibitor-based regimens in a large cohort of naïve HIV-infected patients starting antiretroviral therapy** Int J Antimicrob Agents. 2021 Jul 19:106406. doi: 10.1016/j.ijantimicag.2021.106406. Online ahead of print. PMID: 34293454

3. *M Spaziante, G Taliani, G Marchetti, A Tavelli, M Lichtner, A Cingolani, S Cicalini, E Biliotti, E Girardi, A Antinori, M Puoti, A d'Arminio Monforte, A Cozzi-Lepri* **Impact of HCV Eradication on Lipid Metabolism in HIV/HCV Coinfected Patients: Data from ICONA and HepaICONA Foundation Cohort Study** Viruses. 2021 Jul 19;13(7):1402. doi: 10.3390/v13071402

4. *E Merlini, A Cozzi-Lepri, A Castagna, A Costantini, S Lo Caputo, S Carrara, E Quiros Roldan, M Ursitti, A Antinori, A d'Arminio Monforte, G Marchetti* **Inflammation and microbial translocation measured prior to combination antiretroviral therapy (cART) and long-term probability of clinical progression in people living with HIV** BMC Infect Dis. 2021 Jun 12; 21(1):557. doi: 10.1186/s12879-021-06260-y

5. *C Mussini, P Lorenzini, A Cozzi-Lepri, A Mammone, G Guaraldi, G Marchetti, M Lichtner, G Lapadula, S Lo Caputo, A Antinori, A d'Arminio Monforte, E Girardi* **Determinants of loss to care and risk of clinical progression in PLWH who are re-engaged in care after a temporary loss** Sci Rep. 2021 May 5; 11(1):9632. doi: 10.1038/s41598-021-88367-5

6. *A Giacomelli, A Cozzi-Lepri, A Cingolani, A Tavelli, V Mazzotta, D Tesoro, M Bassetti, A Castagna, A Di Biagio, M Lichtner, A d'Arminio Monforte, S Rusconi* **Does syphilis increase the risk of HIV-RNA elevation >200 copies/mL in HIV positive patients under effective antiretroviral treatment? Data from the ICONA cohort** J Acquir Immune Defic Syndr. 2021 Jun 15. doi: 10.1097/QAI.0000000000002749

7. *A Bandera, P Lorenzini, L Taramasso, A Cozzi-Lepri, G Lapadula, C Mussini, A Saracino, F Ceccherini-Silberstein, M Puoti, E Quiros-Roldan, F Montagnani, A Antinori, A d'Arminio Monforte, A Gori* **The impact of DAA-mediated HCV eradication on CD4(+) and CD8(+) T lymphocyte trajectories in HIV/HCV coinfected patients: Data from the ICONA Foundation Cohort** J Viral Hepat. 2021 May;28(5):779-786. doi: 10.1111/jvh.13488. Epub 2021 Mar 11.PMID: 33600068

8. *G Madeddu, A De Vito, A Cozzi-Lepri, A Cingolani , F Maggiolo, CF Perno, R Gagliardini , G Marchetti, A Saracino, A d' Arminio Monforte, A Antinori, E Girardi* **Time spent with viral load 200 copies/mL in a cohort of people with HIV seen for care in Italy during the U=U prevention campaign era** AIDS. 2021 Jan 29. doi: 10.1097/QAD.0000000000002825. Online ahead of print.PMID: 33534204

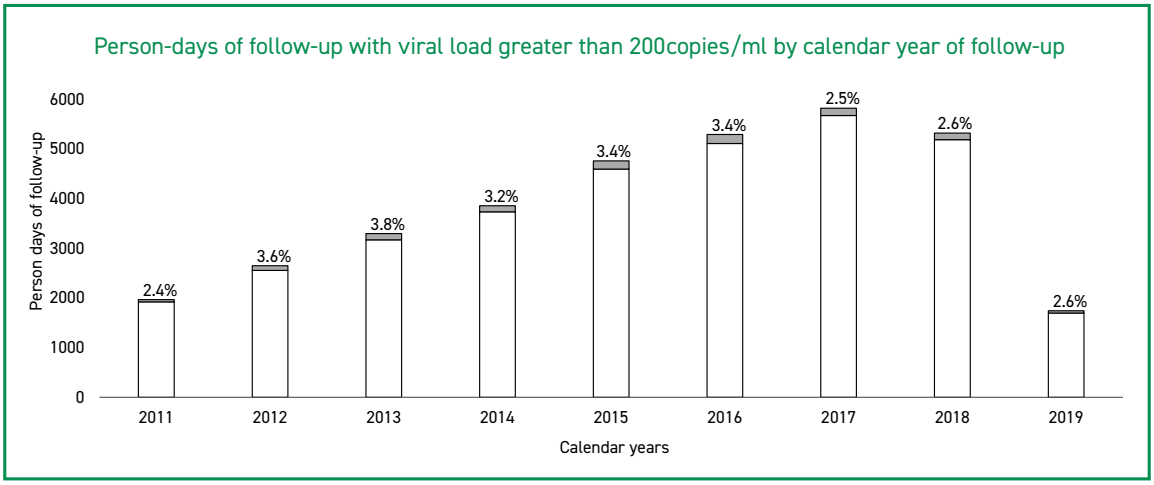
Selected papers in 2021-22

Time spent with HIV-RNA ≤ 200 copies/ml in a cohort of people with HIV during the U=U era

Giordano Madeddu[1], Andrea De Vito[1], Alessandro Cozzi-Lepri[2], Antonella Cingolani[3], Franco Maggiolo[4], Carlo Federico Perno[5], Roberta Gagliardini[6], Giulia Marchetti[7], Annalisa Saracino[8], Antonella d'Arminio Monforte[7], Andrea Antinori[6], Enrico Girardi[9]

Objective: Zero risk of linked HIV transmission in serodiscordant couples when the HIV-infected partner had viral load less than 200 copies/ml ('U status') was found in observational studies. We aimed at estimating the proportion of time in which 'U status' was maintained and identifying factors associated with the risk of losing it.
Design: Observational cohort study.
Methods: We included participants in the ICONA cohort who had reached an established 'U status' (viral load ≤200 copies/ml for >6 months) as of December 2010. The outcome was the number of person-days of follow-up (PDFU) above a viral load greater than 200 copies/ml, relative to the total number of PDFU observed. A logistic regression model was used to identify factors independently associated with the risk of losing 'U status'.
Results: Eight thousand, two hundred and forty-one persons living with HIV were included in the analysis who contributed 2 670 888 PDFU. Of these, 1648 (20%) were women, 768 (9%) were people who inject drugs (PWID), and 2066 (25%) were foreign-born. The median of viral load measurements was 9 (IQR: 4-15). Overall, only 3.1% of PDFU were observed when viral load was above 200 copies/ml. The proportion of PDFU with viral load more than 200 copies/ml was higher than average in women (5.3%), unemployed (5.4%), PWID (4.7%), and in people with more than three previous virologic failures (6.3%). These variables were significant predictors of losing 'U status' in the multivariable logistic regression.
Conclusion: Our results reinforce the validity of the U=U message in real-world setting. However, we identified subsets of our study population at higher risk of losing the 'U status' for whom additional efforts are needed.

AIDS 2021;**35**:1103-1112



TAKE HOME MESSAGE

U=U message, meaning that PLWHs on ART with undetectable HIVRNA do not transmit HIV by sexual route, is reinforced by this study, showing that the U=U condition is maintained over time with only less than 5% of patients with HIVRNA increasing above 200 copies/ml. Women and people who already displayed virological failure are at higher risk of losing the U status, requiring a closer follow-up.

BMC Infectious Diseases

RESEARCH Open Access

Inflammation and microbial translocation measured prior to combination antiretroviral therapy (cART) and long-term probability of clinical progression in people living with HIV

Esther Merlini[1], Alessandro Cozzi-Iepri[2], Antonella Castagna[3], Andrea Costantini[4], Sergio Lo Caputo[5], Stefania Carrara[6], Eugenia Quiros-Roldan[7], Maria A. Ursitti[8], Andrea Antinori[9], Antonella D'Arminio Monforte[1] and Giulia Marchetti[1*]

Abstract

Background: Despite the effectiveness of cART, people living with HIV still experience an increased risk of serious non-AIDS events, as compared to the HIV negative population. Whether pre-cART microbial translocation (MT) and systemic inflammation might predict morbidity/mortality during suppressive cART, independently of other known risk factors, is still unclear. Thus, we aimed to investigate the role of pre-cART inflammation and MT as predictors of clinical progression in HIV+ patients enrolled in the Icona Foundation Study Cohort.

Methods: We included Icona patients with ≥2 vials of plasma stored within 6 months before cART initiation and at least one CD4 count after therapy available. Circulating biomarker: LPS, sCD14, EndoCab, hs-CRP. Kaplan-Meier curves and Cox regression models were used. We defined the endpoint of clinical progression as the occurrence of a new AIDS-defining condition, severe non-AIDS condition (SNAEs) or death whichever occurred first. Follow-up accrued from the data of starting cART and was censored at the time of last available clinical visit. Biomarkers were evaluated as both binary (above/below median) and continuous variables (logescale).

Results: We studied 486 patients with 125 clinical events: 39 (31%) AIDS, 66 (53%) SNAEs and 20 (16%) deaths.

Among the analyzed MT and pro-inflammatory markers, hs-CRP seemed to be the only biomarker retaining some association with the endpoint of clinical progression (i.e. AIDS/SNAEs/death) after adjustment for confounders, both when the study population was stratified according to the median of the distribution (1.51 mg/L) and when the study population was stratified according to the 33% percentiles of the distribution (low 0.0–1.1 mg/L; intermediate 1.2–5.3 mg/L; high > 5.3 mg/L). In particular, the higher the hs-CRP values, the higher the risk of clinical progression (p = 0.056 for median-based model; p = 0.002 for 33% percentile-based model).

RH of clinical progression from fitting a Cox regression model

Crude and adjusted relative hazards of new AIDS or non-AIDS Severe Events (SNAEs) or death in total population

	Crude RH (95% CI)	p-value	Adjusted[a] RH (95% CI)	p-value	Adjusted[b] RH (95% CI)	p-value
(a) Biomarkers fitted as categorical variables						
LPS, pg/ml						
< =250.8	1.0		1.0		1.0	
> 250.8	0.85 (0.53, 1.36)	0.495	0.76 (0.46, 1.26)	0.292	0.88 (0.52, 1.49)	0.643
not measured	1.09 (0.72, 1.65)	0.681	1.11 (0.72, 1.73)	0.631	1.22 (0.77, 1.92)	0.400
sCD14, ug/ml						
< =2.83	1.0		1.0		1.0	
> 2.83	1.10 (0.77, 1.58)	0.586	0.95 (0.65, 1.39)	0.805	0.88 (0.59, 1.29)	0.504
not measured	1.26 (0.40, 4.03)	0.695	0.87 (0.26, 2.86)	0.819	1.44 (0.41, 5.02)	0.570
EndoCAb, MMU/ml						
< =36.5	1.0		1.0		1.0	
> 36.5	0.75 (0.52, 1.06)	0.107	0.82 (0.56, 1.19)	0.296	0.84 (0.57, 1.24)	0.378
not measured	0.22 (0.03, 1.56)	0.129	0.19 (0.03, 1.38)	0.100	0.18 (0.02, 1.40)	0.100
hs-CRP, mg/L						
< =1.51	1.0		1.0		1.0	
> 1.51	1.52 (1.01, 2.29)	0.044	1.47 (0.96, 2.26)	0.077	1.54 (0.99, 2.39)	0.056
not measured	1.19 (0.74, 1.93)	0.478	1.26 (0.76, 2.07)	0.369	1.28 (0.77, 2.13)	0.345
(b) Biomarkers fitted as continuous variables in the $\log_e$ scale						
LPS, pg/ml						
per $\log_e$ higher	0.99 (0.73, 1.35)	0.971	0.94 (0.68, 1.31)	0.729	0.72 (0.46, 1.12)	0.147
sCD14, ug/ml						
per $\log_e$ higher	1.17 (0.84, 1.63)	0.342	0.95 (0.64, 1.40)	0.798	0.79 (0.41, 1.51)	0.471
EndoCAb, MMU/ml						
per $\log_e$ higher	0.87 (0.70, 1.07)	0.195	0.94 (0.75, 1.17)	0.567	1.03 (0.70, 1.52)	0.874
hs-CRP, mg/L						
per $\log_e$ higher	1.12 (0.99, 1.27)	0.065	1.07 (0.94, 1.21)	0.334	1.06 (0.89, 1.25)	0.539

Note: SNAEs: cardiac decompensation, chronic renal insufficiency, liver diseases, myocardial infarction, malignancies, pneumonia, renal diseases and septic infections a All models (a separate one for each biomarker) adjusted for age, CD4, VL, HCV/HBV, years of cART, duration of HIV infection at starting cART, type of cART started bFurther mutually adjusted for all biomarkers

TAKE HOME MESSAGE

The study is aimed to verify whether inflammatory markers and microbial translocation at baseline (i.e. at ART initiation while naives) can be associated with clinical progression on ART, defined as occurrence of AIDS defining events or severe non AIDS diseases. A total of 486 PLWHs who developed 125 clinical events were studied. Plasma LPS, endo CAB, hsCRP and sCD14 were detected at baseline, of these, only hsCRP at baseline was found to be associated with clinical progression. As a consequence, more frequent clinical monitoring and disease-specific screening after cART initiation should be considered for PLWHs showing high levels of hs-CRP while still untreated.

JOURNAL OF VIRAL HEPATITIS
JVH

The impact of DAA-mediated HCV eradication on CD4+ and CD8+ T lymphocyte trajectories in HIV/HCV coinfected patients: Data from the ICONA Foundation Cohort

Alessandra Bandera[1,2] | Patrizia Lorenzini[3] | Lucia Taramasso[1,4] | Alessandro Cozzi-Lepri[5] | Giuseppe Lapadula[6] | Cristina Mussini[7] | Annalisa Saracino[8] | Francesca Ceccherini-Silberstein[9] | Massimo Puoti[10] | Eugenia Quiros-Roldan[11] | Francesca Montagnani[12] | Andrea Antinori[3] | A. d'Arminio Monforte[13] | Andrea Gori[1,2] | For the Icona Foundation Cohort

Abstract

HCV infection has been hypothesized as a contributor of poor CD4+ recovery in patients living with HIV (PLWHIV). Aim of this study was to evaluate CD4+, CD8+ cells and CD4/CD8 ratio trends before and after HCV treatment with direct acting agents (DAA) in PLWHIV. HIV/HCV patients enrolled in ICONA and HepaICONA cohorts with HIV-RNA≤ 50 copies/ml who achieved a sustained viral response after DAA treatment were studied. A linear regression model was used to investigate CD4+, CD8+ and CD4/CD8 changes 12 months before and after DAA treatment. A total of 939 HIV/HCV patients were included, 225 (24.0%) female, median age: 53 years (IQR 50–56).

At DAA initiation, CD4+ T cell count was <350 cells/mm3 in 164 patients (17.5%), and 246 patients (26.2%) had liver stiffness>12.5 kPa. Trends of CD4+ and CD4/CD8 ratio were similar before and after DAA in all study populations (CD4+ change +17.6 cells/mm3 (95%CI −33.5; 69.4, p = 0.494); CD4/CD8 change 0.013 (95%CI −0.061; 0.036, p = 0.611). However, patients treated with ribavirin (RBV)-free DAA showed a significant decrease in CD8+ cells (−204.3 cells/mm3, 95%CI −375.0;-33.4, p = 0.019), while patients treated with RBV experienced CD8+ cell increase (+141.2 cells/mm3, 95%CI 40.3; 242.1, p = 0.006). In conclusion, HCV eradication following DAA treatment does not seem to have an impact on CD4+ T cell recovery in PLWHIV. However, a fast decline of CD8+T cells has been observed in patients treated without RBV, suggesting a favourable effect of HCV clearance on the general state of immune activation.

Unadjusted and adjusted difference in the change of CD4, CD8, ratio and white cells by means of linear regression in the two strata of patients: a) treated with RBV and b) not treated

	Unadjusted difference in change		Adjusted[a] difference in change	
Biomarker	Variation Pre-Post DAA (95% CI)	p-value	Variation Pre-Post DAA (95% CI)	p-value
a. Patients treated with RBV, N = 332				
CD4				
Post-DAA vs. pre-DAA	36.2 (−5.7, 78.0)	0.090	33.9 (−13.6, 81.5)	0.161
CD8^				
Post-DAA vs. pre-DAA	119.0 (30.3, 207.7)	0.009	141.2 (40.3, 242.1)	0.006
Ratio				
Post-DAA vs. pre-DAA	−0.021 (−0.074, 0.033)	0.095	−0.022 (−0.083, 0.038)	0.470
White blood cells				
Post-DAA vs. pre-DAA	407 (99, 714)	0.010	279 (−162, 720)	0.214
b. Patients NOT treated with RBV, N = 607				
CD4				
Post-DAA vs. pre-DAA	7.2 (−69.5, 84.0)	0.853	−3.9 (−91.0, 83.2)	0.930
CD8^				
Post-DAA vs. pre-DAA	−173.7 (−324.8, −22.6)	0.024	−204.3 (−375.0, −33.4)	0.019
Ratio				
Post-DAA vs. pre-DAA	−0.009 (−0.080, 0.060)	0.783	−0.033 (−0.112, 0.047)	0.418
White blood cells				
Post-DAA vs. pre-DAA	734 (487, 982)	<0.001	710 (359, 1061)	<0.001

[a]Adjusted for time between measurements, age, stiffness and HCV genotype; ^the difference in change of CD8 is not adjusted for age.

TAKE HOME MESSAGE

Over 939 HCV co-infected PLWHs were treated with DAA in the ICONA/HepaICONA cohorts (26% with liver stiffness > 12.5 kPa). CD4 and CD8 counts were similar before and after DAA treatment, with a mean change of +17.6 CD4 cells/mmc and -68.1 CD8 cells/mmc. CD4/CD8 ratio change was −0.013 after 12 months from DAA initiation.

PLWHs treated with ribavirin had an increase in CD8 cell count (adjusted mean change +141 cells/mmc) while those treated with ribavirin-free DAA showed a decrease in CD8 cells (- 204 cells/mmc). No significant difference was seen according to RBV use in CD4 and CD4/CD8 ratio 1 year after DAA.

HCV eradication with DAA does not seem to impact on CD4 recovery in PLWHs. The decline of CD8 for RBV-free treatments suggests a favourable effect of HCV clearance on general state of immune activation.

Journal of *Clinical Medicine*

Article

Decrease in Incidence Rate of Hospitalizations Due to AIDS-Defining Conditions but Not to Non-AIDS Conditions in PLWHIV on cART in 2008–2018 in Italy

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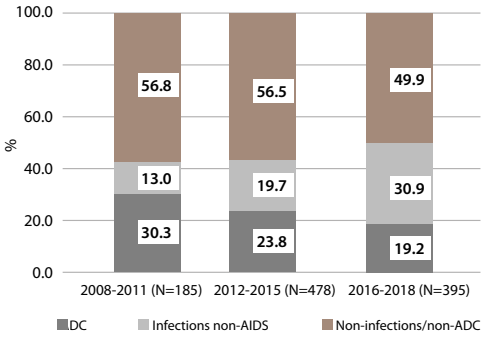
Abstract: Background: We aimed to describe the change in the incidence and causes of hospitalization between 2008 and 2018 among persons living with HIV (PLWHIV) who started antiretroviral therapy (ART) from 2008 onwards in Italy. Methods: We included participants in the ICONA (Italian Cohort Naïve Antiretrovirals) cohort who started ART in 2008. All the hospitalizations occurring during the first 30 days from the start of ART were excluded. Hospitalizations were classified as due to: AIDS-defining conditions (ADC), non-ADC infections and non-infections/non-ADC (i.e., cardiovascular, pulmonary, renal-genitourinary, cancers, gastrointestinal-liver, psychiatric and other diseases). Comparisons of rates across time were assessed using Poisson regression. The Poisson multivariable model evaluated risk factors for hospitalizations, including both demographic and clinical characteristics. Results: A total of 9524 PLWHIV were included; 6.8% were drug users, 48.9% men-who-have sex with men (MSM), 39.6% heterosexual contacts; 80.8% were males, 42.3% smokers, 16.6% coinfected with HCV and 6.8% with HBV (HBsAg-positive). During 36,157 person-years of follow-up (PYFU), there were 1058 hospitalizations in 747 (7.8%) persons; they had HIV-RNA >50 copies mL in 34.9% and CD4 < 200/mmc in 27%. Causes of hospitalization were 23% ADC, 22% non-ADC infections, 55% non-infections/non-ADC (11% cancers; 9% gastrointestinal-liver; 6% cardiovascular; 5% renal-genitourinary; 5% psychiatric; 4% pulmonary; 15% other). Over the study period, the incidence rate (IR) decreased significantly (from 5.8 per 100 PYFU in 2008–2011 to 2.21 per 100 PYFU in 2016–2018). Age > 50 years, intravenous drug use (IDU), family history of cardiovascular disease, HIV-RNA > 50, CD4 < 200, were associated with a higher hospitalization risk. Conclusions: In our population of PLWHIV, the rate of hospitalization decreased over time.

Hospitalization rate, overall and for grouping, per period

	TimeatRisk (Years)	Subjects	Numberof Hospitalizations	IR*100	95%CI		p-Value
					L	U	
Allhospitalizations							
2008–2011	3191	2187	185	5.80	5.02	6.70	ref
2012–2015	15,118	6400	478	3.16	2.89	3.46	<0.01
2016–2018	17,858	8687	395	2.21	2.00	2.44	<0.01
AIDS-definingconditions							
2008–2011	3191	2187	56	1.76	1.35	2.28	ref
2012–2015	15,118	6400	114	0.75	0.63	0.91	<0.01
2016–2018	17,858	8687	76	0.43	0.34	0.53	<0.01
Infectionsnon-ADC							
2008–2011	3191	2187	24	0.75	0.50	1.12	ref
2012–2015	15,118	6400	94	0.62	0.51	0.76	0.428
2016–2018	17,858	8687	122	0.68	0.57	0.82	0.68
Non-infections/non-ADC							
2008–2011	3191	2187	105	3.29	2.72	3.98	
2012–2015	15,118	6400	270	1.79	1.59	2.01	<0.01
2016–2018	17,858	8687	197	1.10	0.96	1.27	<0.01

Note:*p*-values were obtained from Log-rank test.

Overall crude rate of hospitalizations during the study period



TAKE HOME MESSAGE

The study is aimed to analyze the changes of incidence and causes of hospitalization among 9524 PLWHs enrolled in ICONA cohort who initiated ART in Italy in 2008-2018. The overall incidence rate decreased from 5.80/100 PYFU in 2008-11 to 2.21/100 PYFU in 2016-18. The decrease was related to AIDS, not to non-infectious/non AIDS-related causes, whose incidence remained stable over the calendar periods. The authors conclude that prevention strategies against non-communicable diseases and non-AIDS-defining infections are crucial to decrease hospitalization rate.

scientific reports

Determinants of loss to care and risk of clinical progression in PLWH who are re-engaged in care after a temporary loss

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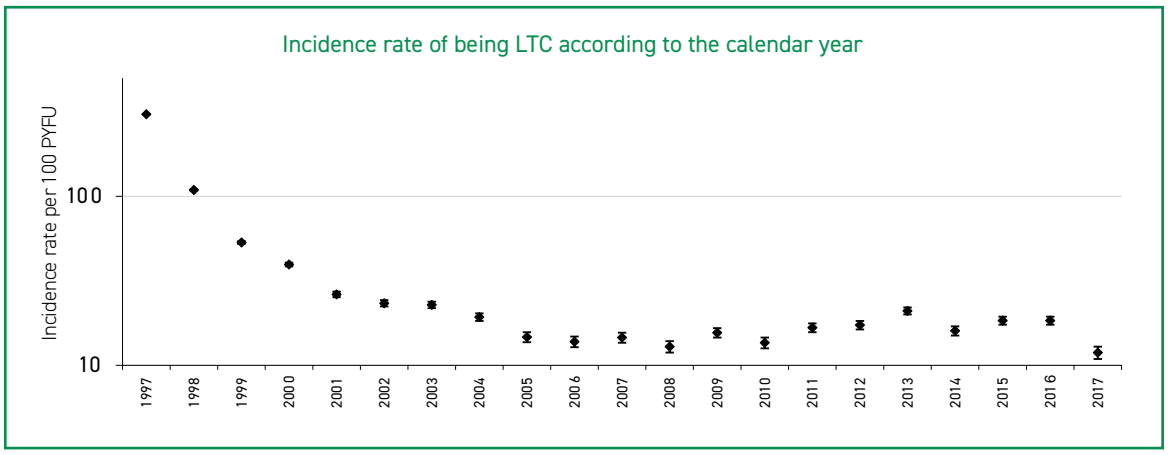
The risk of developing AIDS is elevated not only among those with a late HIV diagnosis but also among those lost to care (LTC). The aims were to address the risk of becoming LTC and of clinical progression in LTC patients who re-enter care. Patients were defined as LTC if they had no visit for ≥ 18 months. Of these, persons with subsequent visits were defined as re-engaged in care (RIC). Factors associated with becoming LTC and RIC were investigated. The risk of disease progression was estimated by comparing RIC with patients continuously followed. Over 11,285 individuals included, 3962 became LTC, and of these, 1062 were RIC. Older age, presentation with AIDS and with higher HIV-RNA were associated with a reduced risk of LTC. In contrast, lower education level, irregular job, being an immigrant and injecting-drug user were associated with an increased LTC probability. Moreover, RIC with HIV-RNA > 200 copies/mL at the re-entry had a higher risk of clinical progression, while those with HIV-RNA ≤ 200 copies/mL had a higher risk of only non-AIDS progression. Patients re-entering care after being LTC appeared to be at higher risk of clinical progression than those continuously in care. Active strategies for re-engagement in care should be promoted.



TAKE HOME MESSAGE

The yearly incidence rate of Loss to Care (LTC, defined as no visit for › 18 months) has decreased from the beginning of ICONA cohort in 1997 till 2005 with no major changes thereafter, over the subsequent 12 years (range 14-18 LTCU x 100 PYFU).

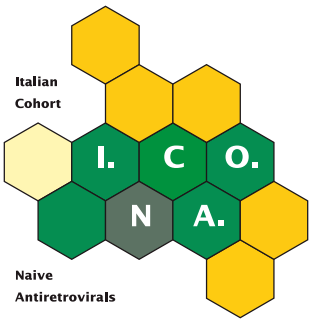
Older age, AIDS presentation and worse viro-immunological status at enrolment were independently associated with a reduced risk of becoming LTC.

Lower education level, irregular job at enrollment, being an immigrant and injecting drugs users were associated with a higher risk of becoming LTC.

26% of LTC re-entered in care, 54% with HIV-RNA > 200 at re-entry.

PLWHs who re-entered in care after a gap in care of at least 18 months had a significantly higher risk of clinical progression compared to those retained in care, with a stronger association for those with unsuppressed HIV-RNA (>200 copies/ml) at re-entry.

Active strategies for retention and re-engagement in care should be promoted.



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