

Management care improvement of people living with HIV: definition of a targeted clinical pathway in a University Hospital of South Italy

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Abstract. *Background and aim:* In the world 37,9 billions live with Human Immunodeficiency Virus and, despite the availability of retroviral therapy, they have an higher risk to acquire other infectious diseases and to develop severe complications. According to several guidelines their immunization is crucial but only some center have developed a specific scheduled pathway and vaccination coverage is very low. Aim of this study is: a) incentivize the active and free of charge offer of vaccines and increase of immunization coverage; b) application and implementation of a shared clinical pathway avoiding reluctance, embarrassment or shame by patients for their condition; d) instauration of an empathic relationship between doctor and patient; e) evaluation of side effects. *Methods:* A prospective study was conducted from October 2019 to February 2020 at the University Hospital G. Martino of Messina. Inclusion criteria were: age over 18; absence of other diseases; absence of immunization against HBV or HAV; CD4 count for live attenuated viral vaccines of 350/uL and for other vaccine 200/uL. A specific scheduled pathway was adopted for every patient. Statistical analysis was performed with Excel software. *Results:* 86 patients were enrolled (74.4% were males, 79.1% were Italian; mean age=40±13.3 SD). An increase in administration was observed between 2018 and 2019 (+164.3% for flu and for other vaccines +370%). The higher increase was observed for HPV one. No-one received DTpa, MMRV or Zoster vaccine. *Conclusions:* The undertook clinical pathway showed the relevance of specific management of these patients and the need to increase the vaccination offer. (www.actabiomedica.it)

Key words: people living with HIV, AIDS, vaccination, guidelines

Introduction

In the world 37,9 billions live with Human Immunodeficiency Virus (HIV).

The use of Highly Active Anti-Retroviral Therapy (HAART) has led to a decrease of the incidence of Acquired Immunodeficiency Syndrome (AIDS) over

time and, furthermore, the immune status of HIV-infected persons (1) is today improved compared to the past; finally, number of related deaths per year have fallen down from 1,7 billions in 2004 to 770.000 in 2018 (2).

The immunodeficiency of seropositive patients leads to a higher risk of acquiring an infectious disease

respect to general population and they may develop severe clinical complications (3).

According to Center of Disease Control (CDC) of Atlanta recommendations, Italian Society of Infectious and Tropical Diseases (SIMIT), and according to Italian National Plan 2020-2025 they must be immunized against certain pathogen, especially for the most frequent ones such as capsulated microorganism, flu and Human Papilloma Virus (HPV) (4-6).

The control of infectious diseases is of paramount importance for Public Health, especially in this emergency period in which the availability of an efficacy vaccination is crucial (7).

Furthermore, due to the circulation of Severe Acute Respiratory Syndrome- Coronavirus -2 (SARS-CoV-2) CDC highlighted PLWHA as a population at heightened risk for severe physical health illness that could be implemented by the presence of comorbidity (8).

Until to date, only some center have developed a specific scheduled pathway and no indications are present in Italian National Plan 2020-2025 (9).

However, this plan suggested some vaccinations for at risk categories and in people with certain clinical conditions such as cardiovascular, respiratory, metabolic diseases or immunosuppression because of the higher risk of acquire an infectious disease and to develop severe complications (5).

Furthermore, SIMIT suggested the same vaccinations for People Living with HIV-AIDS (PLWHA).

In general, the control of infectious disease is very important in the world and today more efforts are necessary to increase vaccination coverage; many studies described safety vaccination in PLWHA (10,11) but, despite this national and international literature data describe low rates of immunization for this category (12).

This could be consequence of several factors: first of most vaccines are not offered free of charge and PLWHA often do not get vaccine; second, by patients' beliefs and attitudes toward vaccines and lastly the reluctance to declare their pathological condition to healthcare workers (13).

Moreover, sometimes also physicians and infectious disease specialists are doubtful about the use of vaccines in this category (14).

In a study conducted in Greek on a cohort of patients of vaccination coverage remained insufficient

for all vaccine-preventable infections investigated (15). The authors concluded that determinants for vaccination were largely not evidence-based, and efforts should be focused on improving physicians' knowledge about guidelines (16).

Similarly, Gagneux-Brunon et al found a lower vaccination coverage against Hepatitis A Virus, Hepatitis B Virus, and Invasive Pneumococcal Disease (IPD). Vaccination coverage against seasonal influenza was quite similar. According to the authors, this difference in vaccine coverage in PLWHA between Greece and France are not explained by different guidelines or costs, but

mistrust; in fact, France is the leading country for vaccine hesitancy, and more than 40 % of the French people consider doubtful the safety of vaccines. Secondly, in Greece, vaccines to PLWHA are provided free of charge by the hospital, in France, vaccines are also provided free of charge for PLWH, but patients should take vaccines in a pharmacy and administered by a physician. This discrepancy between the two systems suggests that active offer of vaccinations in HIV clinics may improve vaccine coverage (17).

In other studies, the main reasons for the low vaccination coverage seem to be at first the diffidence and doubt on the safety (18).

However, different results could be related to active offer of vaccinations in HIV clinics. In Italy Sticchi et al investigated seroprotection/seropositivity rates and coverage against the common vaccine preventable disease in a sample of patients with vertically transmitted HIV-1 infection and they detected satisfactory coverage for polio and HBV, suboptimal for diphtheria and tetanus and low immunization rates for other agents (19)

These results are in line with the poor vaccination coverage described in Italy in a sample of children with different chronic diseases, specifically type 1 diabetes, cystic fibrosis, Down syndrome, neurological diseases, and HIV infection (19). Children affected by HIV infection were most likely to face delays in routine immunizations and to complete DTP, polio and HBV vaccination course (20)

Moreover, the main route of transmission of HIV infection is the sexually one and men having sex with men (MSM) have a higher risk of acquiring other sexually transmitted diseases (STDs). In fact, as reported

by European Center of Disease Control sex between men remains the predominant mode of HIV transmission reported in the EU/EEA, accounting for 39% of all new HIV diagnoses in 2019. Among those with known route of HIV transmission, sex between men accounted for more than 60% of new HIV diagnoses in 10 countries (21).

Furthermore, the Relative Risk (RR) of acquiring especially infections depends on sexually intercourse type people having receptive anal intercourse have the higher risk(22).

HAV vaccination is crucial in patients with HIV; in fact, from 2016 several outbreaks were observed in Europe, as reported by ECDC (23) and this infection mostly affect MSM. In Italy its incidence is increasing and only in the period August 2016–November 2018 4014 cases were detected by Integrated epidemiological system of acute viral hepatitis of Italy (24)

Similarly, PLWHA have an increase risk to acquire other STDs respect to other people and in this optic primary prevention is important (25).

These patients must be guided by their own physicians to avoid at risk behaviors and to get vaccine as soon as possible for communicable diseases passible of acquired immunizations such as HBV and HPV. In Italy mandatory HBV was introduced in 1991 for new-born with the catch-up of people who turned twelve years of age, and for this reason many PLWHA were not immunized (26).

Moreover, HPV vaccination is offered free and actively to girls in their twelfth year of life

(eleven years old) in all Italian Regions and Autonomous Provinces since 2007/2008 (27).

In addition, some Regions had extended the active offer of vaccination to girls of other age groups. Subsequently, three Regions (Sicily, Puglia, Molise) have introduced, as early as 2015, the anti-HPV vaccination also for males in the twelfth year of life and others (Calabria, Liguria, Friuli Venezia Giulia and Veneto), did so for cohort 2004 in 2016. In addition, the Emilia-Romagna and Friuli Venezia Giulia regions also offer the vaccine to HIV positive individuals, males, and females (28) .

Finally, in the Sicily Region a “Vaccinal Calendar for Life of the Sicily Region” is available, representing one of the most updated and complete in the world as regards the active and free offer of vaccinations for

all ages of life, guaranteeing a preventive and public health offer to the offer to Sicilian population (29–31).

In Sicily, vaccinations are offered free of charge for age of for some at risk categories; i.e., HPV vaccination is offered free of charge in children from 12 years of age of both sex and from 26 years old to 45 (in copayment); furthermore, the vaccination is offered free of charge according after medical prescription by a specialist.

In general, any vaccination is offered free of charge and at any age for subjects considered at high-risk after risk assessment and vaccination recommendation by own medical practitioner (29–31).

In Messina province incidence of HIV was 4.9/100.000 in 2013 and grow-up until to 11.6/100.000 in 2019. The 40% was diagnosed at late stage of infection (32).

In this scenario immunization of PLWHA is very difficult for the several reasons discussed before.

The aims of this study are:

- a.) incentivize the active and free of charge offer of vaccines in PLWHA and the increase in vaccination coverage of this patients
- b.) the application and implementation of a shared clinical pathway between the Immunization Center of Hospital Hygiene and the HIV/AIDS Disease Prevention, Diagnosis and Treatment Center of Infectious Diseases that could guide every physician
- c.) offer an immunization program to PLWHA, avoid every reluctance, embarrassment or shame for their own condition
- d.) the instauration of an empathic relationship between doctor and patient
- e.) the evaluation of side effects in this category

Materials and methods

A prospective study was conducted from October 2019 to February 2020 at the University Hospital G. Martino of Messina.

Infectious Diseases hospital ward of University Hospital G. Martino follows a total of 250 patients affected by HIV infection

We chose the patients to include in our study in accordance with inclusion criteria:

1. Men or women over 18 years old of age able to understand the informed consent
2. Absence of other diseases
3. Absence of immunization against HBV (HbsAb <10 IU / ml) or HAV
4. Absence of natural immunization against HBV (HbsAg < 0.05 IU/mL) or HAV (Ab>1.10 and IgM <0.9)
5. CD4 count for live attenuated viral vaccines of 350/uL and for other vaccine 200/uL

After the initial evaluation 138 patients (55.2%) met the inclusion criteria but only 62% was enrolled (n=86). The other patients did not accept to be involved in the study. The project began in 2019 and it is still in progress. No drop out was observed.

Following the acquisition of informed consent, we collected socio-anagraphical data and we started the free administration of vaccines by providing an hoc

calendar in the Immunization Centre of the Operative Unit of Hospital Hygiene. We collected socio-anagraphical data and serum blood samples for the evaluation of the immunization status. Statistical analysis was performed with Excel platform.

Schedule calendar

We used the described guidelines and RCP of the vaccines to make an hoc calendar for every patient. In Table 1 we report the main indications for every vaccine until to date and in figure 1 a prototype of calendar in a patient previously not immunized.

Results

Of the 138 patients followed by the HIV/AIDS Disease Prevention, Diagnosis and Treatment Center 62.31% (n=86) were enrolled in our study and they were addressed to the Immunization Centre of Hospital Hygiene. The project began in 2019 and

Table 1. Main indications for every vaccine

Vaccine	CD4 count <200/mm ³	CD4 count >200/mm ³
<i>DTpa</i>	1 booster dose dT(pa) every 10 years	
<i>Pneumococcal vaccine</i>	2 doses of PCV13 at least 8 weeks apart, followed by 1 dose of PPV23 6-12 months apart	- Pneumococcal vaccination naive subjects: 1 dose of PCV13 followed by a dose of PPV23 6-12 months later - Subjects previously vaccinated with PPV23: 1 dose of PCV13 at least 1 year after the previous dose of PPV23. In the event that only one dose of PPV23 has been administered, a further dose of PPV23 is recommended at least 5 years after the previous dose of PPV23 and at least 6 months after the administration of PCV13
<i>MMR vaccine</i>	Controindications	2 doses (0, 4-8 weeks) (more indicated with count over 400-500/ μ L)
<i>Meningococcal ACWY vaccine</i>	One dose	
<i>Meningococcal B vaccine</i>	Men B 2 doses, until to 50 years of age	
<i>Chickenpox</i>	Controindications	2 doses (0, 4-8 weeks)
<i>HPV 9</i>	3 doses (until to 26 years for males and 45 for females) with CD4 count over 350/ μ L	
<i>HAV</i>	2 doses (0, 6-12 months)	
<i>HBV</i>	3 doses (0,1, 6 months)	3 doses (0,1, 6 mesi) 3, 4, 5
<i>Hib</i>	1 dose	
<i>Influenza</i>	1 dose every year	

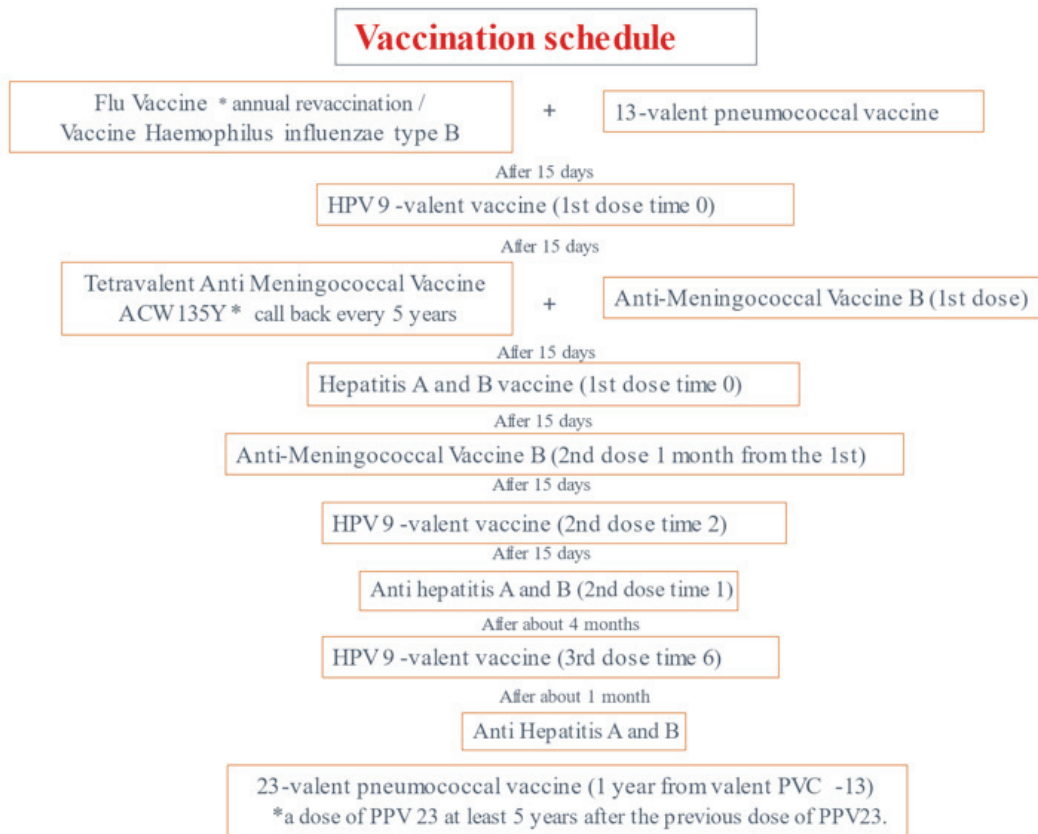


Figure 1. An example of scheduled calendar in naive subjects previously immunized for DTpa

it is still in progress and until to date no drop-out was observed. Of the 86 patients 74.4% were males, 79.1% were Italian.

The two classes of age more represented were 29-38 and 39-48 (mean age was 40 ± 13.63 ; 41 ± 13.63 for females and 41 ± 13.53 for males).

Socio-anagraphical characteristics of the sample are represented in the Table 2.

After evaluation of serological status and CD4 count we administered the required vaccines. CD4 count was in every patient over $200/\mu\text{L}$ (mean 695.1 ± 303.3 SD).

Until today we administered 102 doses for flu (+164.3%) and for other vaccines a total of doses (+370%). In Table 3 we described the number of doses administered for every vaccination. An increase in administration was observed between 2018 and 2019 as showed by Figure 2.

As reported in Figure 1 HAV vaccination coverage has increased by 28% in 2018 to 42% in 2019.

Similarly, an increase of vaccination coverages for other disease was observed as indicated by Figure 1. The higher increase was observed for HPV vaccination as described in Table 3

No-one received DTpa vaccination (all immunized) and MMRV or Zoster vaccination (although CD4 count allow this vaccine in our cohort we delegated it in a later moment, see discussion section).

Furthermore, we are currently administering the relative vaccination doses against H. influenzae type b.

Discussion and conclusion

Low vaccination coverage rates may be attributed to many reasons: first, PLWHA represents a population sometimes difficult to reach; second, the vaccination hesitancy arising from healthcare workers' doubts about the effectiveness and the safety of vaccines, the duration of immunization, the fear of side effects (19).

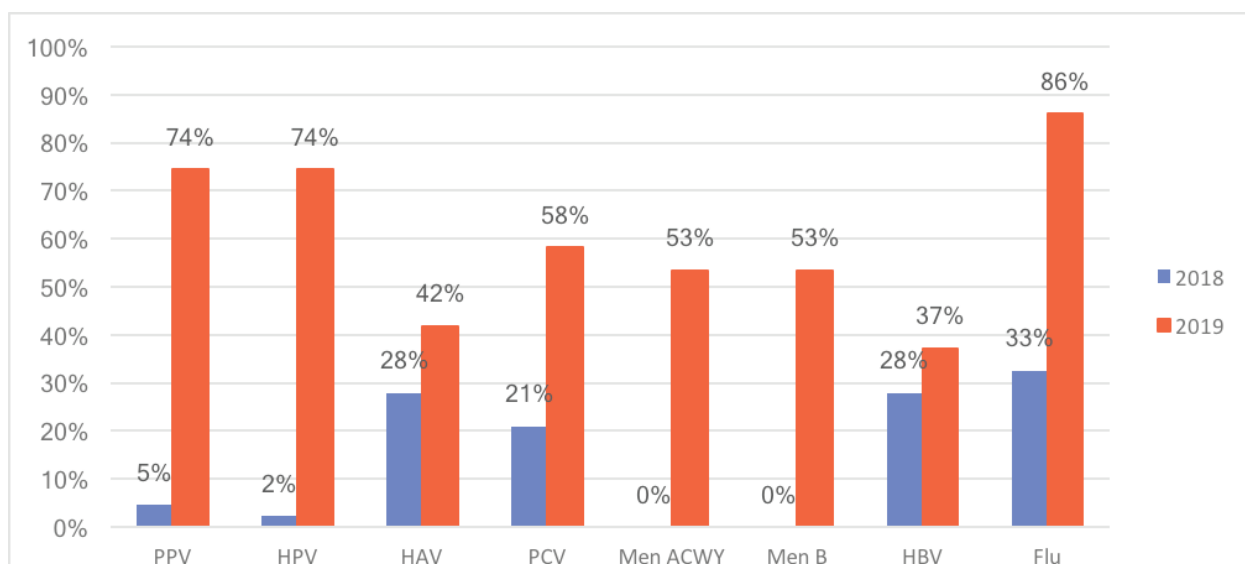
Table 1. Socio-anagraphical characteristics of the sample

Gender	N	(%)
Males	64	74.4
Females	22	25.6
Nationality		
Italians	68	79.1
Foreigners	18	20.9
Age		
18-28	20	23.3
29-38	24	27.9
39-48	24	27.9
49-58	10	11.6
59-68	2	2.3
>69	6	7.0

Table 3. Total doses administered in 2018-2019 (n, %) and percentage increase

Vaccine	Doses administered in 2018-2019 (n, %)	Percentage increase
Flu	102	+164%
HAV*	60 (24%)	+50%
HBV*	56 (22.4%)	+33.3%
HPV9	66(26.4%)	(+3100%)
MenACWY	46 (18.4%)	+46,5%
MenB	46 (18.4%)	+46,5%
PCV13	68 (27.2%)	+66,6%
PPV23	68 (27.2%)	(+1600%)
Total	250	+370%

* based on immunological status we administered HAV or HBV or HAV-HBV vaccine)

**Figure 2.** Percentage of immunized patients on total sample by years

Points of weakness of immunization in these patients are: little awareness of the frailty condition, general lack of awareness of the importance of vaccination as a prevention tool for infectious diseases, little knowledge about the safety and efficacy of vaccines, complexity of the fragile population which requires specific and articulated vaccination programs, poor knowledge of vaccination programs (33).

On the other hand, strengths of our project were: advantage of accessing a Vaccination Center located in the same hospital where patients are followed (greater

privacy), better knowledge about the infectious disease, better knowledge of the phase of immunosuppression / vaccine response, more frequent opportunity for vaccination start and booster (occasion of first visit, follow-up visits), protected environment, opportunity to verify the antibody titre, possible application of vaccination programs customized (e.g. HBV booster) through integration between clinical, vaccination and laboratory data.

In general, as indicated by SIMIT guidelines (4) the recommendations relating to vaccination in PLWHA did not differ in general from those reserved

for other categories of patients; however, in these patients for immunosuppression status the vaccine response could be altered and less protective than in the immunocompetent ones, needing additional doses or shorter times for revaccinations or boosters (34).

In our cohort an increase of vaccination coverages for all vaccines was observed, as previously described.

The higher increase was observed for HPV vaccination and this assumed great importance due to increase risk to acquire other STDs respect to other people; in this optic primary prevention is of paramount importance give to limited prevention offered by condom for some STDs such as HPV, HSV2 and syphilis.

On the other hand, in this category other vaccines have an important role, such as the one against HAV.

However, in our cohort CD 4 count was over 200/ μ L, We chose do not administer anti-measles and anti-chickenpox because of reported risk of complications such as pneumonia and encephalitis.

Furthermore, the use of the combined quadrivalent vaccine (measles, mumps, rubella, varicella-MPRV) is contraindicated in people with severe deficiency of the immune system and according to Committee for Medicinal Products for Human Use (CHMP) of the 2013 EMA review.

MPRV vaccination may be considered in patients with less severe immune system deficiencies if the benefits outweigh the risks. Even more it is more indicated with CD4 count over 400-500/ μ L (35).

Although a higher frequency of episodes is documented for Herpes Zoster and an increased incidence in PLWHA is described, several data showed that the live attenuated vaccine is safe and immunogenic in these patients with CD4 + counts over 200 cells / μ L, the indications of the main international guidelines do not agree in indicating its use in this category (36).

Recently, Canada and the United States have approved the use of an inactivated, recombinant adjuvanted vaccine for the prevention in people aged ≥ 50 . Probably the future availability of this vaccine also in our country could give the possibility to immunize these patients avoiding several problems related to live attenuated vaccine (37).

However, the data currently available do not allow to evaluate its use in people with HIV infection.

Finally, during the health emergency, due to Covid-19, the remodelling of the calendars, with the guarantee of safe access, allowed the recovery of the vaccine doses to be administered. Furthermore, the current availability of Covid-19 vaccines give other opportunities to enrol other patients in our centre and so to catch-up vaccination coverage in this category. On the other hand, despite the accessibility of these vaccines for the future phase of vaccination campaign in Italy until to date no data are available to establish efficacy, effectiveness and vaccine safety. However, the dangers of no vaccination in these patients are high due to the increased risk for severe COVID-19 especially when CD4 count is under 350/ μ L; they must be immunized after reliable data about vaccine safety profile and effectiveness in immunocompromised populations (38,39). Finally, the future availability of new vaccines based on different platform strategies could impact the immunization rate across some at risk categories, such as HIV patients and probably fight vaccine hesitancy also among healthcare workers (40-46).

Conclusion

Immunization in PLWHA is essential to reduce the risk of contracting infectious diseases. It is important to implement a shared clinical path to increase vaccination rates for these patients.

In our realty the application of the protocol had a strong impact on patients' compliance with vaccination, also due to the possibility of accessing the service in a comfortable environment suitable for protecting their privacy.

Conflict of interest: each author declares that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article".

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Received: 6 March 2021

Accepted: 20 May 2021

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