

## REVIEW

# Nine ideas to improve the clinical management of HIV infected patients during the COVID-19 pandemic

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## Keywords

HIV • COVID-19 • PLHIV • Italy • Antiretroviral therapy

## Summary

*Globally, in 2019, HIV infection was still responsible for 1.7 million new infections and for 690,000 deaths in the same year. Tailored and new antiretroviral therapy (ART) regimens, individualised follow-up and new technologies to support data-sharing between health-care professional caring for people living with HIV (PLHIV) and to deliver ART to patients are desperately needed to reach the 90-90-90-90 ambitious goals. The severe*

*acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, responsible for the Coronavirus-19 (COVID-19) pandemic that spread globally in 2020, posed a huge challenge for PLHIV and HIV physicians worldwide in terms of continuum of care. In this paper we encourage “up-to-date patient-centred HIV medicine” and we give nine ideas to improve HIV management in clinical practice during the COVID-19 pandemic.*

## Introduction

Globally, in 2019, HIV infection was still responsible for 1.7 million new infections (range: 1.2 million - 2.2 million) and for 690,000 (range: 500,000-970,000) deaths in the same year [1].

In Italy, in 2018, 2,847 new HIV infections were reported and, despite the continuous progress in terms of screening, 661 new cases of AIDS were notified [2]. The median age of new HIV diagnoses is 39 years for males and 38 years for females, with a higher incidence between 25 and 39 years [2]. Antiretroviral therapy (ART) and pre-exposure prophylaxis (PrEP) have the potential to massively decrease the global burden of HIV new infections; however, no “one size fits all” approach can reach the ambitious goal of HIV eradication [3]. Moreover, in time of health-care system disruption due to the Coronavirus-19 (COVID-19) pandemics, dedicated integrated service for people living with HIV (PLHIV) should be ensured to maintain retention to care and avoid loss to follow-up due to the fear of COVID-19 [4, 5]. Tailored ART, individualised follow-up and new technologies to support data-sharing between health-care professional caring for PLHIV and to deliver ART to patients are desperately needed [6, 7]. Again, from the Italian epidemiological picture, it is clear how aging of new infected patients should be a main concern, effectively addressing multi-morbidity, poly-pharmacy, co-infections; thus, HIV-care is constantly

becoming a sub-specialization of Infectious Diseases that needs continuous updating and that embraces other medical specializations (e.g. Internal Medicine, pharmacology, Geriatric, Public Health) [8].

Aim of this paper, in a view of “up-to-date patient-centred medicine”, is to give nine ideas to improve HIV management in clinical practice during the COVID-19 pandemic.

## Methods

The text of this nine-point manuscript was ultimately organised in the following major paragraphs: i) HIV-tailored follow-up; ii) integrated HIV outpatient service; iii) HIV online-consultation; iv) ART-delivering; v) ART-monitoring; vi) inter-regional clinical data sharing; vii) pro-active screening; viii) HIV-dedicated wards; ix) HIV-physician training; x) future challenges and conclusion. Every paragraphs highlights how to implement the subject within the clinical practice.

### HIV-TAILORED FOLLOW-UP

Thanks to ART, sustained viral suppression (viral load < 50 copies/ml) and prompt immune stability (CD4+ cell count > 500 cell/mm<sup>3</sup>) can be achieved, ensuring immunovirological benefits to our patients [9, 10]. However, art became a life-long treatment that requires

laboratory monitoring, clinical follow-up visits, tailored regimens adjustments according to patient needs, side effects, drug-drug interactions (ddi), comorbidities, co-infections, and availability of drugs, in order to preserve efficacy, safety and, ultimately, adherence to treatment and retention to care [11, 12].

Substantial time and costs for patients and healthcare systems are deployed to standard check-up, while individualised visits and laboratory monitoring should be tailored on patients' profile, enhancing patients' quality of life and decreasing healthcare costs [9].

In the setting of acute infection, late presenter, and in any case in which patients need to start art, prompt antiviral treatment should be initiated.

For instance, in case of virological suppression, immunological recovery, good psychological and clinical condition, no comorbidities, no risk-factors for co-infections, well tolerated art regimens, good adherence to treatment, and no complains by the patient, laboratory monitoring, co-infection screening, and clinical check-up could be delayed every 6-8 months [13]. Vice-versa, if a patient displays risky behaviours for co-infections, immunovirological goals are not met, art regimen is leading to intolerance and/or ddis and/or scarce adherence to treatment, follow-up visits should be anticipated, even monthly, in order to offer counselling, timely screening, and treatment simplification to improve patients' quality of life [14, 15].

#### **INTEGRATED HIV OUTPATIENT SERVICE**

Hiv-outpatients service should be "patients-centered", offering clinical answers to patient both for hiv related issues and non-hiv complications resulting from art, co-infections and/or aging, as well as prep and post-exposure prophylaxis (pep) [16, 17]. Scheduled follow-up visits with the possibility of specialists' consultation other than infectious diseases specialists (namely: pulmonologist, gastroenterologist, cardiologist, gynecologist, gerontologist, immunologist, pycologist, psychiatric, hospital pharmacist, cultural mediator as well as peer-patients meetings) can improve patients retention to care, creating an unique environment to pursue the goal of hiv-care. This integration can be done by a group of hospital in confined area.

#### **HIV-ONLINE CONSULTATION**

When disruption of normal health-care system procedures prevents access to care or when it is not feasible for the patient reaching her/his hiv-dedicated outpatient service, retention to care should be still ensured [18]. Telemedicine, with free online video-call and text-message reminders for appointment and art delivery, could overcome the problem created by interrupted hiv-services, avoiding exposure to pathogens in time of pandemics, offering continuum to care to our patients [19]. However this consultation does not replace the face-to-face visit, but constitutes a new way of relating.

#### **ART DELIVERING**

Again, if normal follow-up of PLWH is not possible or risky due to external conditions or patients' inability,

technology-supported ART delivery should be considered [20].

In sub-Saharan Africa, drone delivery of HIV test and ART has been found feasible as well as mobile fully-equipped ART clinics; this switching the paradigm from "patients go to ART" to "ART goes to patient" [20]. Strategic placement of electronic pick-up machines, where registered patients can receive tailored treatment refill, coupled with text-message reminders on patients' mobile phone, is another example of how ART delivering could be made more efficiently and safer for patients. Moreover, ART delivering shouldn't be offered monthly, but according to patient's peculiarity (adherence to treatment, effective presence at online tele-consultations), it can be delivered for the following 2-3 months, reducing costs.

#### **ART MONITORING**

To fulfil the UNAIDS third "90" (viral suppression) ambitious goals, ART monitoring can be enhanced through periodic text reminder for ART administration, portable point-of-care HIV-viral load self-testing with results live-delivered to health care providers, in order to timely decide possible clinical visit, further laboratory test (e.g. resistance testing, CD4+ cell count) and treatment changes [21, 22]. Indeed, treatment-as-prevention (TasP) can be achieved only if our patients are constantly virologically suppressed, highlighting how even the first two "90" of the UNAIDS strategy are linked to effective ART monitoring. ART monitoring includes for the HIV physician to be updated with new antiviral agents in commerce, possible side effects, DDIs, and with national and international guidelines, to promote best patients' care [23].

#### **INTER-REGIONAL DATA SHARING**

To convey and uniform clinical data, clinical practices, monitoring patients' laboratory exams and treatment' history, discuss challenging cases among HIV physicians, and to share data to perform trial, an online inter-regional platform should be implemented between HIV-referral centres across the nation [24]. The experience of the "Rete Ligure", in the Ligurian Region of Italy (extended to other infectious diseases such as tuberculosis), which enables physicians to track and monitor patients' progress, retention to care, and HIV historical genotype as well as ART history, is an example of how health care providers can deliver a better service to patients and reduce ART related expenditure thanks to an interconnected health care system [25-27].

#### **PRO-ACTIVE SCREENING**

HIV screening, with opt-out strategy, should be part of daily clinical activity in Infectious Diseases wards, pregnant woman, outpatients service for sexually-transmitted infections, patients undergoing immunosuppressive treatment (e.g. oncology, haemato-oncology), and before surgical procedures [28]. Moreover, person at risk should be offered HIV periodically-scheduled screening in dedicated outpatient services or at home with self-testing with immediate linkage to care if resulted positive [28].

However, “pro-active screening” does not involve just HIV-testing in at risk population, but regularly screening viral hepatitis (hepatitis A, hepatitis B, hepatitis C, hepatitis D), tuberculosis, human papilloma virus (HPV), opportunistic infections, sexually transmitted diseases, and, when actively circulating, virus-responsible for pandemic in PLHIV [29, 30]. Active vaccination of vaccine-preventable infections should be promoted.

#### HIV-DEDICATED WARDS

Viruses with pandemic potential are emerging faster causing exponential growth of infected patients, reallocation of health-care resources, disruption of ambulatory services and fear of health-care settings [18, 31]. However, preparedness to avoid to stop or to reduce HIV routine care should be prioritized, as well as the creation of HIV dedicated wards for patients that require hospitalization, with properly trained staff (doctors, pharmacists, nurses and other health care professions), screening for pandemic viruses prior-to-admission and linkage to HIV-outpatient service after discharge.

#### HIV-PHYSICIAN TRAINING

HIV care is evolving quickly and, to provide comprehensive primary health care services to PLHIV, it is necessary for young Infectious Diseases specialists to own a solid background in infectious diseases, internal medicine, and epidemiology. Moreover, HIV-specialists need to be updated on new drugs available, DDIs, comorbidities, PrEP, PEP, and psychological counselling at diagnosis and during follow-up [32]. HIV-related continuing medical education should be encouraged and periodically done to awake and answer to intellectual challenges encountered by HIV physicians in daily practice (e.g. drug interactions between new ART regimens) and to care for the whole person rather than just to achieve viral suppression [33].

#### Future challenges and conclusion

Currently, online consultation, via email, in the Ligurian Region has been implemented, giving the chance to all patients to consult ID specialists even during lockdown. In the next future, pro-active HIV screening should be encouraged among General Practice doctors, through dedicated courses by ID specialists, in order to implement the path to linkage to care. Moreover, annual inter-regional or national post-graduated course for ID specialist, willing to take care of PLWH, should be promoted. Finally, inter-regional data sharing through dedicated online platform should be implemented.

The over-mentioned goals may represent the first steps to improve HIV management in clinical practice to keep delivering to our patient the best possible care.

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#### Authors' contributions

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#### References

- [1] <https://www.unaids.org/en/resources/fact-sheet>
- [2] <https://www.epicentro.iss.it/aids/epidemiologia-italia>
- [3] Velloza J, Delany-Moretlwe S, Baeten JM. Comprehensive HIV risk reduction interventions for 2020 and beyond: product choices and effective service-delivery platforms for individual needs and population-level impact. *Curr Opin HIV AIDS* 2019;14:423-32. <https://doi.org/10.1097/COH.0000000000000567>
- [4] Pinto RM, Park S. COVID-19 Pandemic disrupts HIV continuum of care and prevention: implications for research and practice concerning community-based organizations and frontline providers. *AIDS Behav* 2020;24:2486-9. <https://doi.org/10.1007/s10461-020-02893-3>
- [5] Mantica G, Riccardi N, Terrone C, Gratarola A. Non-COVID-19 visits to emergency departments during the pandemic: the impact of fear. *Public Health* 2020;183:40-1. <https://doi.org/10.1016/j.puhe.2020.04.046>
- [6] Giannini B, Riccardi N, Cenderello G, Di Biagio A, Dentone C, Giacomini M. From Liguria HIV web to Liguria infectious diseases network: how a digital platform improved doctors' work and patients' care. *AIDS Res Hum Retroviruses* 2018;34:239-40. <https://doi.org/10.1089/aid.2017.0064>
- [7] Ford N, Geng E, Ellman T, Orrell C, Ehrenkranz P, Sikazwe I, Jahn A, Rabkin M, Ayisi Addo S, Anna Grimsrud, Rosen S, Zulu I, Reidy W, Lejone T, Tsitsi A, Charles Holmes C, Kolling AF, Phate Lesihla R, Nguyen HH, Bakashaba B, Chitembo L, Tiriste G, Doherty M, Bygrave H. Emerging priorities for HIV service delivery. *PLoS Med* 2020;17:e1003028. <https://doi.org/10.1371/journal.pmed.1003028>
- [8] High KP, Brennan-Ing M, Clifford DB, Cohen MH, Currier J, Deeks SG, Deren S, Effros RB, Gebo K, Goronzy JJ, Justice AC, Landay A, Levin J, Miotti PG, Munk RJ, Nass H, Rinaldo CR Jr, Shlipak MG, Tracy R, Valcour V, Vance DE, Walston JD, Volberding P; OAR Working Group on HIV and Aging. HIV and aging: state of knowledge and areas of critical need for research. A report to the NIH Office of AIDS Research by the HIV and Aging Working Group. *J Acquir Immune Defic Syndr* 2012;60(Suppl. 1):S1-S18. <https://doi.org/10.1097/QAI.0b013e31825a3668>
- [9] [http://www.salute.gov.it/imgs/C\\_17\\_pubblicazioni\\_2655 Allegato.pdf](http://www.salute.gov.it/imgs/C_17_pubblicazioni_2655 Allegato.pdf)
- [10] d'Arminio Monforte A, Tavelli A, Cozzi-Lepri A, Castagna A, Passerini S, Francisci D, Saracino A, Maggiolo F, Lapadula G, Girardi E, Perno CF, Antinori A; Icona Foundation Study Group. Virological response and retention in care according to time of starting ART in Italy: data from the Icona Foundation Study cohort. *J Antimicrob Chemother* 2020;75:681-9. <https://doi.org/10.1093/jac/dkz512>
- [11] Jose S, Delpech V, Howarth A, Burns F, Hill T, Porter K, Sabin CA; UK CHIC Study Steering Committee. A continuum

- of HIV care describing mortality and loss to follow-up: a longitudinal cohort study. *Lancet HIV* 2018;5:e301-8. [https://doi.org/10.1016/S2352-3018\(18\)30048-1](https://doi.org/10.1016/S2352-3018(18)30048-1)
- [12] Prinapori R, Giannini B, Riccardi N, Bovis F, Giacomini M, Setti M, Viscoli C, Artioli S, Di Biagio A. Predictors of retention in care in HIV-infected patients in a large hospital cohort in Italy. *Epidemiol Infect* 2018;146:606-11. <https://doi.org/10.1017/S0950268817003107>
- [13] Saag MS, Gandhi RT, Hoy JF, Landovitz RJ, Thompson MA, Sax PE, Smith DM, Benson CA, Buchbinder SP, Del Rio C, Eron JJ Jr, Fätkenheuer G, Günthard HF, Molina JM, Jacobsen DM, Volberding PA. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2020 recommendations of the International Antiviral Society–USA Panel. *JAMA* 2020. <https://doi.org/110.1001/jama.2020.17025>
- [14] Ford N, Flexner C, Vella S, Ripin D, Vitoria M. Optimization and simplification of antiretroviral therapy for adults and children. *Curr Opin HIV AIDS* 2013;8:591-9. <https://doi.org/10.1097/COH.000000000000010>
- [15] Nachega JB, Mugavero MJ, Zeier M, Vitória M, Gallant JE. Treatment simplification in HIV-infected adults as a strategy to prevent toxicity, improve adherence, quality of life and decrease healthcare costs. *Patient Prefer Adherence* 2011;5:357-67. <https://doi.org/110.2147/PPA.S22771>
- [16] Di Carlo P, Immordino P, Mazzola G, Di Carlo P, Immordino P, Mazzola G, Colletti P, Alongi I, Mineo M, Scognamiglio M, Vitale F, Casuccio A. Determinants of HIV outpatient service utilization according to HIV parameters. *J Int AIDS Soc* 2014;17(Suppl. 3):19611. <https://doi.org/110.7448/IAS.17.4.19611>
- [17] Di Biagio A, Riccardi N, Signori A, Maserati R, Nozza S, Gori A, Bonora S, Borderi M, Ripamonti D, Rossi MC, Orofino G, Quirino T, Nunnari G, Celestia BM, Martini S, Sagnelli C, Mazzola G, Colletti P, Bartolozzi D, Bini T, Ladisa N, Castelnuovo F, Saracino A, Lo Caputo S. PrEP in Italy: the time may be ripe but who's paying the bill? A nationwide survey on physicians' attitudes towards using antiretrovirals to prevent HIV infection. *PLoS One* 2017;12:e0181433. <https://doi.org/110.1371/journal.pone.0181433>
- [18] Santos GM, Ackerman B, Rao A, Wallach S, Ayala G, Lamontagne E, Garner A, Holloway IW, Arreola S, Silenzio V, Ström-dahl S, Yu L, Strong C, Adamson T, Yakusik A, Doan TT, Huang P, Cerasuolo D, Bishop A, Noori T, Pharris A, Aung M, Dara M, Chung SY, Hanley M, Baral S, Beyrer C, Howell S. Economic, Mental Health, HIV Prevention and HIV Treatment Impacts of COVID-19 and the COVID-19 Response on a Global Sample of Cisgender Gay Men and Other Men Who Have Sex with Men. *AIDS Behav*. 2021;25:311-21. <https://doi.org/10.1007/s10461-020-02969-0>. PMID: 32654021; PMCID: PMC7352092
- [19] Jacomet C, Linard F, Prouteau J, Lambert C, Ologeanu-Taddei R, Bastiani P, Dellamonica P. E-health. Patterns of use and perceived benefits and barriers among people living with HIV (PLHIV) and their physicians - Part 3: Telemedicine and collection of computerized personal information. *Med Mal Infect* 2020;50:590-6. <https://doi.org/10.1016/j.medmal.2020.04.009>. Epub 2020 Apr 19.
- [20] Bulstra CA, Hontelez JA, Ogbuoji O, Bärnighausen T. Which delivery model innovations can support sustainable HIV treatment? *African Journal of AIDS Research* 2019;18:315-23.
- [21] [https://www.unaids.org/sites/default/files/media\\_asset/90-90-90\\_en.pdf](https://www.unaids.org/sites/default/files/media_asset/90-90-90_en.pdf)
- [22] Dorward J, Drain PK, Garrett N. Point-of-care viral load testing and differentiated HIV care. *Lancet HIV* 2018;5:e8-e9. [https://doi.org/10.1016/S2352-3018\(17\)30211-4](https://doi.org/10.1016/S2352-3018(17)30211-4)
- [23] <https://www.eacsociety.org/files/guidelines-10.1.finalsept2020.pdf>
- [24] Giannini B, Riccardi N, Cenderello G, Di Biagio A, Dentone C, Giacomini M. From Liguria HIV Web to Liguria Infectious Diseases Network: How a Digital Platform Improved Doctors' Work and Patients' Care. *AIDS Res Hum Retroviruses* 2018;34:239-40. <https://doi.org/10.1089/aid.2017.0064>
- [25] Taramasso L, Dentone C, Alessandrini A, Bruzzzone B, Icardi G, Garraffo R, De Macina I, Viscoli C, Di Biagio A; HIV/HCV Collaborative Liguria Group. Successful anti-retroviral therapy by using unusual antiretroviral combinations in heavily pre-treated patients: two case reports. *Int J STD AIDS* 2015;26:831-4.
- [26] Cenderello G, Fanizza C, Marengo S, Nicolini LA, Artioli S, Baldissarro I, Dentone C, De Leo P, Di Biagio A. Cost per care of the first year of direct antiviral agents in the Liguria Region: a multicenter analysis. *Clinicoecon Outcomes Res* 2017;9:281-93. <https://doi.org/10.2147/CEOR.S129859>
- [27] Riccardi N, Giannini B, Borghesi ML, Taramasso L, Cattaneo E, Cenderello G, Toscanini F, Giacomini M, Pontali E, Cassola G, Viscoli C, Di Biagio A. Time to change the single-centre approach to management of patients with tuberculosis: a novel network platform with automatic data import and data sharing. *ERJ Open Res* 2018;4:00108-2017. <https://doi.org/10.1183/23120541.00108-2017>. PMID: 29410957; PMCID: PMC5795190
- [28] <https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5514a1.htm>
- [29] Martínez-Sanz J, Vivancos MJ, Sánchez-Conde M, Gómez-Ayerbe C, Polo L, Labrador C, González P, Mesa A, Muriel A, Chamorro C, de la Fuente Y, Pérez Elías P, Uranga A, Herrero M, Ares S, Barea R, Moreno S, Pérez-Elías MJ. Hepatitis C and HIV combined screening in primary care: A cluster randomized trial. *J Viral Hepat*.2021;28:345-352. <https://doi.org/10.1111/jvh.13413>. Epub 2020 Oct 7. PMID: 32979880
- [30] Petruccioli E, Chiacchio T, Navarra A, Vanini V, Cuzzi G, Cimaglia C, Codecasa LR, Pinnetti C, Riccardi N, Palmieri F, Antinori A, Goletti D. Effect of HIV-infection on QuantiFERON-plus accuracy in patients with active tuberculosis and latent infection. *J Infect* 2020;80:536-46. <https://doi.org/10.1016/j.jinf.2020.02.009>
- [31] Madhav N, Oppenheim B, Gallivan M, Mulembakani P, Rubin E, Wolfe N. Pandemics: risks, impacts, and mitigation. In: Jamison DT, Gelband H, Horton S, et al. (eds.). *Disease control priorities: improving health and reducing poverty*. 3rd edition. Washington (DC): The International Bank for Reconstruction and Development / The World Bank 2017, Chapter 17.
- [32] Landon BE, Wilson IB, Wenger NS, Cohn SE, Fichtenbaum CJ, Bozzette SA, Shapiro MF, Cleary PD. Specialty training and specialization among physicians who treat HIV/AIDS in the United States. *J Gen Intern Med* 2002;17:12-22. <https://doi.org/10.1046/j.1525-1497.2002.10401.x>
- [33] Green M. A letter to a young HIV doctor. *AIDS* 2020;34:1991-2. <https://doi.org/10.1097/QAD.0000000000002670>

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