

## Early initiation of antiretroviral treatment: Challenges in the Middle East and North Africa

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**Author contributions:** Sardashti S and SeyedAlinaghi SA made substantial contributions to conception and design of the study, review of the literature, interpretation of findings, and drafting the article; Samaei M, Firouzeh MM, Mirshahvalad SA and Pahlaviani FG contributed to integration of findings through literature review and drafting of the manuscript; Sardashti S made critical revisions; SeyedAlinaghi SA made the final approval.

**Conflict-of-interest:** The authors certify that they have no affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript.

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Received: October 28, 2014

Peer-review started: October 30, 2014

First decision: November 27, 2014

Revised: January 30, 2015

Accepted: February 9, 2015

Article in press: February 11, 2015

Published online: May 12, 2015

### Abstract

New World Health Organization guidelines recommend the initiation of antiretroviral treatment (ART) for asymptomatic patients with CD4+ T-cell counts of  $\leq 500$  cells/mm<sup>3</sup>. Substantial reduction of human immunodeficiency virus (HIV) transmission is addressed as a major public health outcome of this new approach. Middle East and North Africa (MENA), known as the area of controversies in terms of availability of comprehensive data, has shown concentrated epidemics among most of its at risk population groups. Serious challenges impede the applicability of new guidelines in the MENA Region. Insufficient resources restrict ART coverage to less than 14%, while only one fourth of the countries had reportable data on patients' CD4 counts at the time of diagnosis. Clinical guidelines need to be significantly modified to reach practical utility, and surveillance systems have not yet been developed in many countries of MENA. Based on available evidence in several countries people who inject drugs and men who have sex with men are increasingly vulnerable to HIV and viral hepatitis, while their sexual partners - either female sex workers or women in monogamous relationships with high-risk men - are potential bridging populations that are not appropriately addressed by regional programs. Research to monitor the response to ART among the mentioned groups are seriously lacking, while drug resistant HIV strains and limited information on adherence patterns to treatment regimens require urgent recognition by health policymakers. Commitment to defined goals in the fight against HIV, development of innovative methods to improve registration and reporting systems, monitoring and evaluation of current programs followed by cost-effective modifications are proposed as effective steps to be acknowledged by National AIDS Programs of the countries of MENA Region.

**Key words:** Antiretroviral agents; HIV; CD4 counts; Co-infections; Regional health planning

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**Core tip:** The main purpose of the present review was to investigate the feasibility of new World Health Organization guidelines on earlier initiation of antiretroviral treatment in resource-limited settings, specifically in the Middle East and North Africa region.

Sardashti S, Samaei M, Firouzeh MM, Mirshahvalad SA, Pahlaviani FG, SeyedAlinaghi SA. Early initiation of antiretroviral treatment: Challenges in the Middle East and North Africa. *World J Virol* 2015; 4(2): 134-141 Available from: URL: <http://www.wjgnet.com/2220-3249/full/v4/i2/134.htm> DOI: <http://dx.doi.org/10.5501/wjv.v4.i2.134>

## INTRODUCTION

In 2013, recommendations regarding the early initiation of antiretroviral treatment (ART) were published by World Health Organization (WHO) in consolidated HIV treatment and prevention guidelines. Initiation of ART among asymptomatic adults and adolescents with CD4+ T-cell counts of  $\leq 500$  cells/mm<sup>3</sup>, regardless of clinical stage is strongly recommended in this guideline<sup>[1]</sup>.

Previous guidelines (2010) suggested that treatment be initiated for patients with CD4 counts of  $\leq 350$  cells/mm<sup>3</sup><sup>[2]</sup>. Several recent studies provide evidence of substantially reduced risks of HIV transmission among serodiscordant couples, if ART is initiated when CD4 counts range from 350 to 550 cells/mm<sup>3</sup><sup>[3]</sup>. Hence new recommendations have a greater focus on public health issues concerning HIV transmission.

Although the new guidelines delineate the earlier initiation of ART as "highly cost-effective", adaptation of these recommendations is a significant challenge for many countries including those in the Middle East and North Africa (MENA). Evidence from most of the 23 countries of MENA has indicated a significant increase in HIV incidence and AIDS-related deaths in the recent decade; nonetheless, antiretroviral coverage was reported to be less than 14% by the end of 2011<sup>[1-4]</sup>.

From a social perspective, the cultural context that prohibits HIV related high-risk behaviors encourages ubiquitous stigma that affects access to available services in the MENA countries<sup>[4-7]</sup>. Availability and allocation of resources, on the other hand, has been threatened by ongoing conflicts and high rates of migration<sup>[8-12]</sup>. From a public health perspective, in many countries of the MENA lack of integrated data on HIV incidence rates and disease progression among known patients requires to be increased<sup>[8]</sup>. In addition, scarcity of gender-sensitive programs and lack of systematic approach in development of national guidelines hinder

enactment of new treatment strategies in MENA<sup>[4,5,13,14]</sup>. HIV epidemic is characterized by rising incidence and prevalence rates among key at-risk populations, specifically among people who inject drugs (PWIDs)<sup>[12]</sup>.

Hence the co-infections that are diagnosed more commonly among these population groups require particular attention in the implementation of the ART guidelines<sup>[15,16]</sup>. Additionally, in many countries of the region where cost-effective tests for viral load and CD4+ T-cell counts are not available and retention in care is not well understood, monitoring of response to ART and disease progression inherits location-specific challenges in adapting ART guidelines<sup>[17]</sup>.

Previous studies that have investigated the quality of clinical practice guidelines in the region indicate that serious gaps; including outdated or inconsistent clinical contents, weak methodology in tailoring recommendations, and insufficient applicability<sup>[13]</sup>.

The development of HIV treatment protocols that are coordinated with international standards requires better knowledge of the epidemiological and clinical characteristics of patient populations in the region<sup>[13,18]</sup>. Hence, we highlight the available evidence-based information that may benefit research scientists, clinicians, and health authorities of the region in their attempts at scaling up of HIV/AIDS programs including ART coverage.

## RESEARCH

To conduct the present study, we searched PubMed, Embase, and local databases for all relevant articles published from the MENA region. Also, published results of incomplete cohorts and other related studies that investigated early initiation of antiretroviral regimens or initiation among at-risk populations, including articles not available before June 2013 were accessed through PubMed and Google search engines; online library of the International AIDS Society and Research Gate were also screened for possible research works. Publications with findings that are important in the context of HIV/AIDS responses among low and middle income countries in other parts of the world were also used for the review.

Major search key words and phrases included, but were not limited to, the following: "early antiretroviral initiation + 2013-14", "ART and HIV-Hepatitis C (HCV)", "ART and HIV-hepatitis B (HBV)", "ART and HIV-tuberculosis (TB)", "ART cost-effectiveness", "HIV retention in care", "HIV antiretroviral adherence", "HIV and drug resistance", "HIV-HCV PWIDs", "HIV/AIDS MENA region", "PWIDs in MENA", "Men who have sex with men (MSM), Female sex workers (FSWs) in MENA region"; all the keywords were specifically searched for in publications from countries of the MENA region.

## ART INITIATION BASED ON CD4 + T-CELL COUNTS

Available antiretroviral drugs are prescribed to delay

immunologic failure and control HIV-related diseases rather than to eradicate the virus<sup>[19]</sup>. CD4+ T-cell counts are the most utilized, and probably available, immunologic marker for clinicians to decide for initiation of ART<sup>[20]</sup>. This test also serves as a predictor of rates of AIDS and non-AIDS related causes of death<sup>[21,22]</sup>. However, many resource-limited settings still depend on the WHO clinical staging system for decision-making<sup>[17]</sup>.

According to a recent short report, only six of the countries in MENA had reportable data on patients' initial CD4 counts at the time of diagnosis in 2011, and eight countries had provided similar data in 2009. In most countries over 50% of the patients were ART eligible meaning they had CD4 counts of  $\leq 350$  cells/mm<sup>3</sup> at the time of diagnosis<sup>[5,18]</sup>. Development or improvement of standard and organized surveillance systems in settings where CD4 measurements are available seems a priority in the region<sup>[18,23]</sup>. In resource-limited countries, WHO clinical staging if carefully adapted in practice should provide as an accurate substitute to accelerate response in these areas<sup>[17]</sup>.

## IMPLEMENTING ART UPTAKE AMONG AT-RISK POPULATIONS

Concentrated HIV epidemics have been reported among at least one of the high-risk population groups (PWIDs, female/male sex workers, MSM) in all countries of the region<sup>[11]</sup>. However, at least in ten countries out of 23, HIV surveillance is not available among most at risk groups and sample size estimations of most at risk groups using primary data acquisition has been established only in Pakistan<sup>[18]</sup>. Overall, HIV prevalence, and concurrent high-risk behaviors of injecting drug users have been widely investigated within MENA countries<sup>[24,25]</sup>. MSM and FSWs are the two other major groups; in recent years their HIV risk behaviors have been better understood in several countries of the region<sup>[11]</sup>. Evidence also suggests that the disproportionate prevalence of HIV among men is related to unknown sexual behaviors and drug use as overlapping high-risk activities<sup>[5]</sup>. Nevertheless, no studies are available concerning response to ART or patterns of treatment adherence among HIV infected patients who are affiliated with these high-risk groups; nor is there sufficient evidence from the other countries regarding improved outcomes due to the early initiation of ART among PWIDs and other high risk groups<sup>[20]</sup>.

### PWIDs

From 13 MENA countries that have published evidence-based data on PWIDs, epidemics are reported as being concentrated in Pakistan, Iran, Afghanistan, Egypt, Morocco and Libya<sup>[26]</sup>. While increasing trends are reported in Pakistan, Iran and Egypt, Libya has recently been facing the highest HIV prevalence (87%) among

PWIDs in the region<sup>[27]</sup>.

The burden of disease related to blood-borne infections among PWIDs remains high and raises global concerns<sup>[4,11,28]</sup>. The MENA region is no exception, and expansion of harm reduction programs is essential for effectively fighting HIV. HCV and HBV are also not targeted appropriately despite higher transmission rates compared to HIV<sup>[26]</sup>.

Management of HBV or HCV co-infections in HIV patients has been a matter of controversy for years<sup>[20]</sup>. Although ART regimens have shown benefits in several studies, despite moderate levels of liver toxicity among non-injectors<sup>[23,29]</sup>, serious hepatic complications impede initiation of ART among PWIDs<sup>[24]</sup>. Study of a large cohort of more than 60 thousand people living with HIV/AIDS in Europe and North America has led to the proposal that liver-related causes of death, including hepatitis and liver failure, are the most common causes of mortality among PWIDs during and after the first year of ART initiation<sup>[15]</sup>. For example, Nevirapine-based regimens may lead to elevated CD4 levels in HIV-HBV co-infected patients<sup>[29]</sup>, however, the very complicated immunopathology of viral hepatitis co-infections in these patients requires evidence-based decisions that are suitable for the epidemic in the MENA Region<sup>[24]</sup>. We underscore the HIV and hepatitis co-infection prevalence among general and high-risk populations in various MENA countries in Table 1.

### Bridging populations

New guidelines also suggest that ART should be initiated among HIV patients who are in serodiscordant relationships, to reduce risk of transmission<sup>[1]</sup>. This recommendation is based on recent findings that indicate substantial decrease (89%) in virus transmission from infected patients to their uninfected partners, who were prescribed ART with CD4 counts of 350 to 550 cells/mm<sup>3</sup> of blood<sup>[3]</sup>. A recent study from Iran provides valuable data on potential concentrated epidemics among the non-injecting sexual partners of PWIDs<sup>[7,30]</sup>; this study provides insights into the possibility of overlapping transmission between high-risk groups such as PWIDs and FSWs; considering the disproportionately high male-to-female prevalence and the lack of confirmatory surveys in the region, we cannot rule out the possibility of current or future hidden sub-epidemics among FSWs and MSM in certain countries of the region<sup>[18,30,31]</sup>. The existing gap between identified and estimated numbers of people infected with HIV may potentially feed the increasing vertical transmission of the virus in the near future<sup>[4,5,32]</sup>.

Women in monogamous relationships with PWIDs or MSM, are perceived to have low rates of high-risk activities, but are at high risk of transmitting HIV, and probably also HBV and HCV to their newborns<sup>[26,30]</sup>. On the contrary these women do not have consistent access to HIV counseling and lack the willingness to test for HIV<sup>[4,33]</sup>. Hence, HIV awareness should be developed

**Table 1 Evidence-based prevalence rates of human immunodeficiency virus, hepatitis B and C co-infections in 13 countries of the Middle East and North Africa region**

Country - city names (yr)	Target population (n) <sup>1</sup>	HIV prevalence	Methodology	HCV <sup>2</sup> (Isolated or co-infection prevalence)	HBV <sup>2</sup> (Isolated or co-infection prevalence)
Afghanistan - three cities (2009) <sup>[56,56]</sup>	FSWs (n = 520)	0.19%	Cross-sectional	Isolated: 1.92%	Isolated: 6.54% (range: 3% to 17.5%) Isolated: 7.1%
	PWIDs	7.1% (1% to 18.4%)	Cross-sectional	Isolated: 40.3% Co-infection: 94.9%	
Bahrain - Bahrain (2002-2006) <sup>[57]</sup>	HCV infected patients (n = 183)	0.5%	Retrospective cohort	HCV-HBV co-infection: 3.3%	-
Egypt - Cairo (2010) <sup>[58]</sup>	Blood donors-family members (n = 15017)	0.01%	Cross-sectional	Isolated: 4.3%	Isolated: 1.7%
Iraq - Karbala (2009) <sup>[59]</sup>	Healthcare workers (n = 124)	0	Cross-sectional	0	0
Iran - Tehran (2007) <sup>[60]</sup>	PWIDs (n = 899)	10.7%	Cross-sectional	Isolated: 34.5% Co-infection: 80.6%	Isolated: 50.7% Co-infection: 7.8%
Jordan (2009) <sup>[61]</sup>	Blood donors (n = 8190)	0	Cross-sectional	Isolated: 0.9%	Isolated: 1.4%
Lebanon - Beirut (2008) <sup>[62]</sup>	Inmates (n = 580)	0.17%	Cross-sectional	Isolated: 3.43%	Isolated: 2.4%
Libya - Tripoli (2013) <sup>[27]</sup>	PWIDs (n = 328)	87%	Respondent-driven sampling	Co-infection: 83%	Co-infection: 4%
Morocco - Casablanca (2006-2010) <sup>[63]</sup>	HIV infected patients of a referral clinic (n = 504)	All patients were infected.	Cohort	5.4%	Co-infection: 5.2%
Pakistan - Lahore (2011) <sup>[64]</sup>	Inmates (n = 4915)	2.01%	Cross-sectional	Co-infection: 73.74%	0.01% (HBV/HCV Co-infections: 77.78%)
Saudi Arabia (2009) <sup>[65]</sup> (2012) <sup>[66]</sup>	PWIDs (n = 344) Rehab center inmates-drug users (n = 115)	Not checked 4%	Cross-sectional Cross-sectional	Isolated: 38% (HBV-HCV: 3.5%) -	Isolated: 12% (HBV DNA) Isolated: 4%
Tunisia (2007) <sup>[67]</sup>	HIV infected patients (n = 362)	Not applicable	Cross-sectional	Co-infection: 39.7% (For PWIDs: 87.4%)	-
Yemen - Hodeidah (2010) <sup>[68]</sup>	Blood donors (n = 1483)	0.14%	Cross-sectional	Isolated: 0.79%	Isolated: 2.35%

<sup>1</sup>Sample size; <sup>2</sup>Lab evaluations: Anti-HIV antibody (enzymatic immunoassay or western blot); Anti-HCV antibody; HBs antigen (enzymatic immunoassay). HCV: Hepatitis C virus; HBV: Hepatitis B virus; FSWs: Female sex workers; PWIDs: People who inject drugs.

in parallel with HIV testing facilities to successfully implement HIV clinical guidelines in MENA region.

FSWs that also comprise a proportion of sexual partners of both PWIDs and men with same-sex behaviors are also a potential bridging population in transmitting HIV to the general population in MENA<sup>[11,30,34]</sup>. Notably rates of syphilis (weighted prevalence: 7.2%) in Iran<sup>[35]</sup>, and of viral hepatitis reported among non-injecting FSWs in Afghanistan is relatively high<sup>[36]</sup>.

## HIV AND TB IN MENA REGION

Latest WHO estimates of the burden of disease caused by TB in the Eastern Mediterranean Region indicate a stable trend in TB mortality, prevalence, and incidence; these estimates introduce the region as a medium-burden area. Since 2010, New incidence of TB among HIV-infected patients in the region has remained steady [11 (10-12) thousand in 2012], however, no improvements are evident in case detection rates during this same period. In addition, lack of detection and surveillance systems suggests that these estimates

may not fully capture actual incidence<sup>[37]</sup>.

On the other hand, the number of reported patients with multi-drug resistant TB (MDR-TB) has tripled from 2007 to 2010 globally. Estimates show that 56% these MDR-TB patients have been successfully treated in the Eastern Mediterranean Region, and despite better outcomes compared to other regions, this number is much lower than WHO's defined goal of 75% for 2015<sup>[37]</sup>. Country-specific studies highlight the urgent need for addressing MDR-TB, specifically among patients who are re-treated with anti-TB drugs<sup>[38-40]</sup>. The situation is becoming especially critical in Saudi Arabia due to high influence of travelers and migrating laborers from TB endemic areas, and also in Somalia which reports the highest prevalence of MDR-TB in the region<sup>[41,42]</sup>. Similar situations cannot be precluded in other countries, where sufficient measures have not been taken into account.

New guideline recommends initiation of ART among all patients with active TB regardless of CD4 counts or clinical stage<sup>[1]</sup>. Comparison of migrant and non-migrant patients by the Antiretroviral Therapy Cohort Collaboration revealed different AIDS-defining events

in the two groups, with migrants from MENA displaying significantly higher rates of TB in the first year after initiation of ART<sup>[15]</sup>. Immune response to tuberculosis is blunted following ART initiation, and this suppression persists for years due to decreased alveolar macrophage activity and specific cellular responses<sup>[43]</sup>. Hence, patients that receive ART remain susceptible to TB, a challenge that requires further attention in TB endemic countries of MENA.

Simultaneous treatment of HIV and TB, as recommended by WHO, remains controversial because of patients who develop immune reconstitution syndrome (IRIS) after ART initiation, and show higher mortality rates. The reason why IRIS affects certain patients is not thoroughly understood, but may be linked to monocyte-derived responses<sup>[44]</sup>. Our expanding knowledge about human leukocyte antigens associations observed among non-seroconverting partners of HIV patients should uncover a role for genetic factors in the future<sup>[45]</sup>. Context-specific decisions on the timing for initiation of ART among TB-infected patients are highly dependent on future findings of large cohorts among different high-risk groups from various ethnic backgrounds. Meanwhile, a scaling up of HIV testing and counseling and of efforts at detecting cases with MDR-TB should be considered a priority<sup>[36,46]</sup>.

## ADHERENCE AND DRUG RESISTANCE

Our knowledge about adherence to ART in MENA is limited to a few studies<sup>[47,48]</sup>, which show that the role of stigma and discrimination, specifically among female patients, poses a major barrier to adherence<sup>[47]</sup>. A cross-sectional study conducted in Iran shows adherence rates of 65.5% (self-report) and 60.4% (pill count) during a three month follow-up; however, the short term follow-up and the limited number of patients evaluated in a single center setting limit our ability to generalize these findings. Results of this study indicate that living with family members, shifting to new ART regimens, and the stage of the disease are major correlates of higher adherence rates<sup>[48]</sup>.

Although most evidence on the antiretroviral resistance profiles of ART-naïve and ART-treated patients is limited to a few studies<sup>[47-50]</sup>, the critically high rates of resistance to antiretroviral regimens requires immediate attention in the countries of the region, with the goal of increasing availability of viral load tests and modification of ART regimens, based on genotype sequencing<sup>[51]</sup>. Policymakers should consider the cost-effectiveness of early ART initiation compared to scaling up of educational programs that target ART adherence, or to reaching out for the new and cheaper means of viral load measurement<sup>[52]</sup>.

Studies conducted in resource poor settings emphasize that documentation of ART adherence through patient self-reports derived from administration of standard questionnaires, is not costly and helps

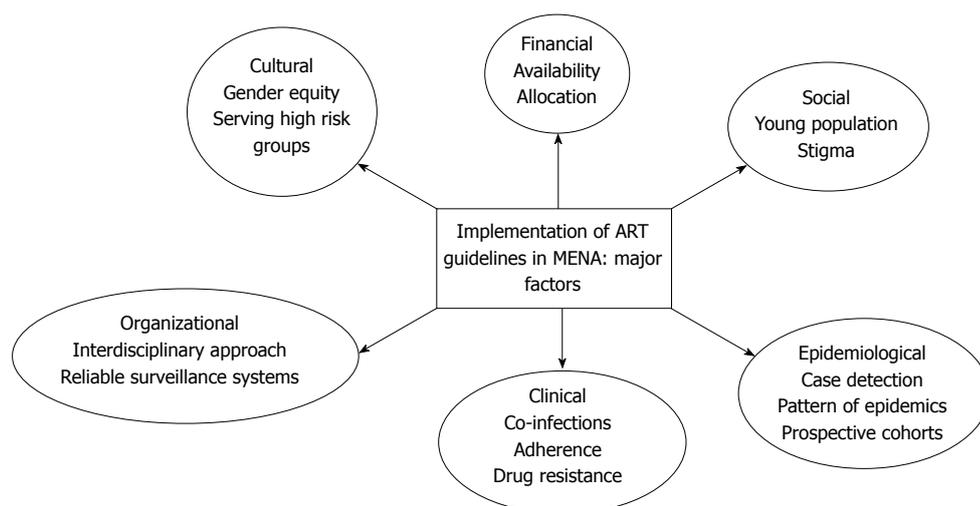
to improve clinical outcomes (CD4 and viral load). Healthcare managers can also monitor ART distribution, availability of services, and counseling practices by utilizing metrics from these screenings<sup>[53]</sup>. Documentation about adherence is helpful in decreasing transmitted drug resistance, which in-turn may require inevitable high expenditure in the future in these countries.

## CONCLUSION

Serious challenges need to be tackled before adapting new clinical guidelines in current healthcare settings in MENA countries. The general response of MENA countries to HIV epidemics although effective has not been proportionate to the increasing needs. Insufficient human and financial resources, presence of punitive laws and social stigma are barriers for implementation of prevention, treatment or care programs in this region. Additionally, the lack of consistent documentation, registration and reporting systems that is required for monitoring and evaluating the present situation of HIV impedes appropriate response.

We recommend the following as major areas requiring action by health authorities in MENA countries for successful adaptation of ART guidelines: (1) To manage registration of HIV prevalence and incidence, and to design innovative data registry systems where necessary; (2) To investigate and monitor the genetic sequence of the most common HIV strains, and drug resistance profiles of infected patients (*e.g.*, among different high-risk groups); (3) To conduct cohort studies to investigate clinical outcomes among large groups of patients to empower health policymakers and clinicians with relevant data; (4) To develop standard adherence measurement tools to promote adherence and to document findings required for proper resource allocation; (5) To design disease databases for prevalent HIV co-infections to help in potential revisions required in national guidelines based on local patient needs; and (6) To recognize the concomitant role of social stigma and access to illicit drugs (opiates or stimulants) in the future pattern of HIV epidemic in the region.

Figure 1 summarizes the major areas that we suggest they need to be targeted by healthcare systems for development of new HIV treatment guidelines. We also suggest original research and implementation projects can be of prominent help in MENA. Based on computational models early initiation of ART could be of high impact in reducing immunologic failure<sup>[54]</sup>. In MENA region such innovative models could be of assistance among the networks of infected people to make size estimations and map distribution where the majority also has high-risk activities<sup>[32]</sup>. A practical approach could be to strengthen case detection systems through finding vulnerable people in each patient's network to reduce the time to diagnosis in newly identified patients. This will reduce the probability of transmitting



**Figure 1** Major challenge for development of human immunodeficiency virus treatment guidelines in Middle East and North Africa. MENA: Middle East and North Africa; ART: Antiretroviral treatment.

drug-resistant strains which could be a major concern in coming years. Recent clinical trials are also suggesting new treatment protocols; as an example alternating regimens that provide patients with intermittent combinations of antiretroviral agents are supposed to reduce the probability of multi-drug resistance<sup>[55]</sup>. These new protocols may be of prominent significance in the future of HIV epidemic in MENA region; however, their feasibility is yet to be established in settings with limited access to ART.

## ACKNOWLEDGMENTS

We thank the Iranian Research Center for HIV/AIDS, UNAIDS-Iran, and Dana-Farber Cancer Institute for supporting the interactive scientific writing workshop at which this manuscript was edited. The editor was Dr. Sonal Jhaveri and the workshop was funded by an award to Dr. Madani from ViiV Healthcare.

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P- Reviewer: Arriagada GL, Farzin R, Qiu HJ S- Editor: Ji FF

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