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WHY A UNIVERSAL ANTIRETROVIRAL REGIMEN?

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In 2015, with its "Treat all" recommendation, World Health Organization (WHO) removed all restrictions on eligibility for antiretroviral treatment (ART) among HIV positive people. WHO estimates that by the end of 2018, 20 million people worldwide will be receiving combination ART. An additional 15–17 million will be in need of ART but unable to access or afford it [1]. Most of the existing supply of antiretrovirals (ARVs) is provided through international agencies, such as PEPFAR and the Global Fund, or governments of low- and middle-income countries (LMICs), all of which face stable or shrinking health care budgets.

The economic challenges facing global provision of ARVs alone represent an overwhelming barrier to full treatment access. When combined with the logistical and implementation barriers, civil unrest, increasing ARV drug resistance worldwide, and continued issues with stigma in many parts of the world, it is hard to imagine how the treatment needs of all people with HIV can be met with existing programs and resources.

It is now quite clear that effective ART not only benefits the individual through immune reconstitution and elimination of the risk of opportunistic diseases, but also protects individuals at risk of acquiring HIV through sexual contact or intravenous drug use [2]. In theory, a strategy that places everyone with HIV on suppressive ART for a generation would substantially – and perhaps permanently – reduce the risk of HIV infection worldwide. The challenge then is to develop a strategy with the highest likelihood of meeting this goal.

When examining past epidemics brought under control by antimicrobial drugs or vaccines, several themes emerge. First, and foremost is a concerted and coordinated global effort to provide access to protection, perhaps best illustrated by the global campaign to eradicate smallpox. But equally important is the availability of a simple, easy to deliver intervention that is inexpensive to manufacture and distribute, completely or nearly completely effective, is very safe, and is practical within the care context. Is such an intervention possible for HIV? That will be the topic addressed by this issue of *Current Opinions*.

The advantages of identifying a “universal” ART regimen are numerous. Health care benefits include simplicity of prescribing. Logistic benefits include simplicity of distribution and delivery, avoiding many of the concerns related to “stock-outs” in situations where multiple formulations and regimens need to be available. Economic benefits include simplicity of manufacturing and the possibility of negotiating down prices with large volumes and multiple competing generic suppliers. Although this one-size-fits-all approach may seem inelegant, in reality if the treatment meets standards of universality, then this is the ultimate in precision public health.

Of course, it is easy to imagine problems with such an approach. First are the special populations – infants, children, pregnant women, those co-infected with tuberculosis and other diseases – for whom the potential disadvantages of the regimen might not meet the same standards of universality, be that related to dosing, formulation, teratogenicity or pharmacokinetic drug interactions. Because most drugs are developed based on a tradeoff between pharmacologic properties and economic ones, it is hard to find any antimicrobial agents that meet all the features of a target product profile for global use as part of the only primary treatment for an infectious disease. Finally, we need to ask: how much data on safety and efficacy are required before a regimen receives the “universal” designation?

One possible objective in this endeavor might be to try and identify a flawless ART regimen. Although the availability of effective, safe, and easy to take ARVs is greatly improved today compared to past decades, we could argue that we are still quite some way from accessing a perfect regimen. That is, one with uniform safety, tolerability, convenience, effectiveness, and low cost. On the other hand, previous global campaigns to control epidemics such as smallpox, rinderpest (in livestock), polio and TB suggest that an effective intervention need not be perfect, especially when it comes to adverse effects. If toxicity is rare and reversible, and if an alternative regimen could be accessed by those who for whatever reason cannot tolerate the primary regimen, the net outcome for individuals and populations is still overwhelmingly positive.

What possible ART regimens in existence today meet the standards of universality? There is great interest in, and ongoing studies of, the combination of a well-tolerated once daily integrase strand transfer inhibitor (InSTI) with two nucleoside or nucleotide analogs. Dolutegravir is the leading InSTI candidate today, because it is already widely used and has demonstrated excellent efficacy, a high barrier to resistance, and long-term tolerability. Trials to generate evidence for its use in LMIC – where populations include more pregnant women and people coinfecting with TB, for whom data are not usually available after registrational trials for high-income countries – are underway, several of which are described in this issue of *Current Opinion*.^[3]

However, recent reports of unexplained CNS toxicity with dolutegravir and an unexpectedly high discontinuation rate compared to raltegravir and elvitegravir warrant further investigation.^[4] There are also concerns about the risk of TB IRIS, but this is likely a class effect with all INSTI. [5, 6] Bictegravir, a new once daily InSTI that also does not require pharmacokinetic enhancement and has a compact daily dose of 50 mg QD might be a

promising alternative to dolutegravir. But there are currently even more evidence gaps regarding this drug, particularly with regards to populations common in LMIC. [7]

In the nucleoside/nucleotide arena, tenofovir alafenamide (TAF) has the advantages of compact dosing, as well as excellent, and improved tolerability compared to tenofovir disoproxil fumarate. Lamivudine and emtricitabine have been deemed therapeutically equivalent by the WHO [8] both embody nearly ideal properties of safety and efficacy that has now been documented in tens of thousands of recipients.

The combination of dolutegravir, TAF, and emtricitabine or lamivudine is currently being studied in populations in sub Saharan Africa. [3] This combination has the advantage of a low relative daily dose (275–375 mg total in the regimen, as compared to 1100–1200 mg in the popular efavirenz, emtricitabine or lamivudine, and TDF regimen), possibility of co-formulation, and high evidence for efficacy, tolerability, and long-term safety. Of course, other regimens are possible as candidates for the Universal Antiretroviral Regimen, and are evaluated in the following pages. In addition, alternative formulations and routes of delivery, such as injections or implants, could meet future standards of universality.

This edition of *Current Opinion* takes a broad look at the many intricacies involved in gathering evidence for, recommending and procuring a universal ART regimen. Cahn describes what is known (and where the evidence gaps lie) for dolutegravir, which fits many of the requirements to be considered as the anchor drug for a universal first-line regimen [9] Likewise, Gothan et al examine the evidence to date for TAF, and consider it in comparison with TDF [10] Ford et al compare lamivudine to emtricitabine, [8] and Boffito et al summarize the current position of efavirenz 400 mg. [11] Venter et al describe the novel history of ADVANCE, a large ongoing clinical trial testing new first-line ART regimens [3] Maartens et al [12], Slogrove et al [13] and Penazzato et al [14] examine the respective research needed to ensure that new ART regimens can be recommended for people with TB coinfection, in pregnant and breastfeeding women, as well as in pediatric populations. Seden et al discuss drug-drug interactions with ART that need to be considered for LMICs [15]. Looking ahead, Jacobsen and Flexner discuss future alternatives to daily oral ART [16].

Ripin and Prabu show how the introduction of new ARVs could not only offer clinical benefits but could reduce costs to cover more patients at the same funding level [17]. Amole et al [18], Harris et al [19] and Malati [20] et al describe the role of generic manufacturers, donors, and supply chain management in the successful introduction of promising new drugs and regimens to LMICs. Geffen looks at how treatment literate HIV activists have campaigned for and supported access to ART regimens. [21] Finally, Vitoria et al ask when could the new ARVs described in these pages be recommended as part of a universal regimen for LMIC [22]

Although nothing is guaranteed, a gathering confluence of evidence indicates that a universal ART regimen may be the best way to control the HIV epidemic. Many hurdles remain to making this a reality. But, when considered alongside the search for an effective HIV vaccine and pharmacologic HIV cure, the availability of a single universally acceptable

ART regimen is one of the three most important approaches to controlling this infection, and may be the most practical and the most feasible for many years to come.

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