HIV and Critical Care Delivery in Resource-Constrained Settings

A Public Health Perspective

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The international acquired immunodeficiency syndrome (AIDS) community has largely focused its political, financial, and advocacy efforts on expanding early antiretroviral treatment to eligible individuals and preventing new infections in high-risk populations [1,2]. In resource-constrained settings, relatively little attention has been paid to the opposite side of the disease spectrum: the hospitalized human immunodeficiency virus (HIV) patient with advanced disease. Yet, despite progress in enrolling millions of people living with HIV (PLWH) into care in Sub-Saharan Africa, most individuals present with advanced disease [3]. Although the pursuit of an AIDS-free generation is essential, there remains an important parallel need to foster and maintain expertise in the clinical care of PLWH presenting with coinfections, including those requiring critical care. This paper reviews 3 important issues related to development of an acute care infrastructure for PLWH in resource-constrained settings from a public health perspective: 1) What are the priorities for improving critical care services for PLWH? 2) How will the evolving HIV epidemic—and particularly the increased burden of cardiovascular disease in this population—affect the future of critical care delivery in these settings? And, 3) what can the past 30 years of public health response to HIV teach us about developing a critical care health infrastructure in resource-constrained settings?

Although estimates of HIV prevalence in intensive care units in resource-constrained settings are lacking, general medical and surgical inpatient wards in Sub-Saharan Africa often report prevalence rates >50% [4,5], underscoring the need for high-quality inpatient HIV services in the region. Because management of HIV begins with an HIV diagnosis, among the greatest priorities is fostering a culture of provider-initiated testing for all inpatients [6]. Inpatient testing and linkage to outpatient care has been shown to be acceptable and feasible [7], whereas missed opportunities for testing undermine the quality of inpatient care and contribute to delays in outpatient treatment. Moreover, less than one-half of PLWH in Sub-Saharan Africa are aware of their status [8], so every medical encounter should be considered an opportunity to begin the cascade of linkage into care.

For those with a diagnosis, the impact of HIV infection on critical care is broad, and, though beyond the scope of this article, has been reviewed extensively elsewhere (Table 1) [9]. Key features of HIV-related critical care pertaining specifically to resource-limited settings include: optimizing the timing of antiretroviral therapy (ART) initiation, diagnosing and treating coinfections properly and promptly, and effective management of specialized AIDS-related clinical scenarios, including severe sepsis (from disseminated staphylococcal and streptococcal infections), intracranial hypertension (from cryptococcal meningitis), and respiratory failure (most commonly from *Pneumocystis jeroveci*, streptococcus, and tuberculosis infections). All of these conditions require advanced diagnostics, supportive care, and treatment, which may not be readily available in resource-constrained settings.

The complex nature of critical care of PLWH also requires multidisciplinary health professional expertise. In addition to physicians, expertise in nursing, pharmacy, physical therapy, and social work are essential to adequately monitor patients, manage dosing and drug-drug interactions, and ensure adequate attention to rehabilitation and end-of-life care. Importantly, with this package of multidisciplinary intensive care expertise, clinical outcomes for PLWH are similar to that of uninfected individuals [10,11]. These data support advocacy for acutely ill PLWH, to ensure that no patient is barred entry from an intensive care unit based on their HIV serostatus alone.

To ensure access to ART for acutely ill patients, collaborative relationships with outpatient providers, who are generally assigned responsibility to distribute ART medicines, should be developed and maintained. Data now strongly support early initiation of ART for the majority of PLWH, including those with most coinfections [12,13], and those receiving intensive care at the time of diagnosis [14]. Based on this evidence, intensive care units and other acute care settings should be empowered to initiate or restart ART for eligible patients. Building relationships between inpatient hospital providers and outpatient HIV clinics will be a prerequisite to coordinate and achieve this goal.

To best prioritize the resources for inpatient management of the 30 million PLWH worldwide, the evolution of the HIV epidemic must also be considered. Whereas opportunistic infections are currently the most common indication for hospitalization, continued successful expansion of ART is expected to spur an epidemiologic shift toward chronic disease. Evidence of this trend is already evident. Recent estimates in Sub-Saharan Africa, have demonstrated similar life expectancies for PLWH on ART and HIV-uninfected populations [15,16]. In

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TABLE 1. Considerations for critical care management of people living with HIV

Examples	HIV Coinfections	Noncommunicable Diseases
Diagnostics		
Basic laboratory testing	Metabolic disarray from sepsis, respiratory failure, acute hepatitis, drug toxicity; complete blood count testing for cytopenias, anemia, thrombocytopenia, and other hematologic abnormalities	Diabetic complications, cardiac ischemia, complications of malignancy (e.g., tumor lysis syndrome)
CD4+ T-lymphocyte testing by point-of-care or flow cytometry, HIV viral load and resistance testing	Coinfection risk, treatment monitoring, ART options	Malignancy risk, treatment monitoring
Gram stain and culture	*Staphylococcal*, *Streptococcal,* and other bacterial infections	N/A
Fungal stain and culture	Histoplasmosis, coccidiomycosis, cryptococcosis, and others	N/A
Cryptococcal antigen detection	Cryptococcal disease	N/A
Specialized staining	PCP testing	N/A
Viral PCR and culture	Herpes simplex virus, Varicella zoster virus, and others	N/A
Mycobacterial testing including molecular (e.g., Gene Xpert) and culture methods	Tuberculosis and nontuberculous mycobacterial infections (MAC)	N/A
Serologic testing	Viral hepatitis and other viral infections, toxoplasmosis	N/A
Stool testing	Soil transmitted helminths, cryptosporidium, microsporidium, and others	N/A
Imaging modalities, with preferential availability of ultrasound, x-ray, computed tomography with capability for angiography, and magnetic resonance imaging	Respiratory infections, intracranial infections	Myocardial infarction, congestive heart failure, cerebrovascular disease, diagnosis and complications of malignancy
Pathology	Multiple, including lymph node, bronchiolar lavage, lung, brain and other diagnostic biopsies	Malignancy diagnosis
Specialized clinical care		
Ventilator and respiratory failure management	Pneumonia most commonly from streptococcal infections, tuberculosis, PCP infections	Congestive heart failure, chronic obstructive pulmonary disease, asthma, and other forms of chronic lung disease
Shock	Most commonly streptococcal and staphylococcal-related sepsis	Cardiogenic shock
Neurologic intensive care	Cryptococcal meningitis, tuberculous meningitis	Cerebrovascular disease
Renal replacement therapy	Acute renal failure related to sepsis or drug toxicity	Acute and chronic renal failure from diabetes and hypertension complications
Liver failure management	Acute and chronic viral hepatitis, drug toxicity	Chronic liver disease related to alcohol use and nonalcoholic steatohepatitis
Ancillary services		
Pharmacy	Initiation, maintenance and discontinuation of appropriate ART regimens, drug-drug interactions most commonly from protease inhibitors, oral and intravenous administration routes, drug toxicity	Pharmacologic management of acute stroke and myocardial infarction
Nutrition	Critical care feeding, malnourishment management, drug-nutrition interactions	Diabetes, congestive heart failure, renal failure, liver failure, and other chronic disease nutrition issues
Occupational and physical rehabilitation care	Recovery from prolonged hospitalization, neurologic rehabilitation after meningitis or other intracranial infections	Recovery from automobile and other accidents, recovery from stroke, heart failure, and other
End-of-life care and hospice	Multiple	Multiple

ART, antiretroviral therapy; HIV, human immunodeficiency virus; MAC, mycobacterium avium-intracellulare complex; N/A, not applicable; PCP, *Pneumocystis jiroveci* pneumonia; PCR, polymerase chain reaction.

resource-rich settings, PLWH also have increased rates of atherosclerosis, stroke, and myocardial infarction [17—19]. Whereas ART mitigates a portion of this risk, even those with durable virologic suppression, compared with uninfected populations, have increased inflammation and atherosclerosis risk [20,21]. Attention must also be paid to the diagnosis, treatment, and complication management of HIV-associated malignancies. Cancer risk remains significantly elevated for PLWH in the ART era and is now estimated to be the leading cause of death for PLWH in resource-rich settings [22].

To adapt to these changes and optimize hospital-based care for PLWH globally, we must seek answers to 2 important public health questions: 1) How will local influences, including host genetics, endemic chronic infections, and both cardiovascular and cancer risk factors, differentially alter the epidemiology of disease among the aging HIV population in these settings? And 2) how can the healthcare infrastructure in resource-constrained settings best confront this epidemiologic shift? Currently, few medical centers in Sub-Saharan Africa are prepared to diagnose and manage the burgeoning epidemic of cardiovascular-, cerebrovascular-, and cancer-related morbidity. It remains unclear whether strategies used to manage acute presentations of chronic disease in resource-rich settings, including widespread availability of magnetic resonance imaging and cardiac catheterization, will be equitable and appropriate for resource-poor settings. More locally feasible and scalable interventions will likely be needed, appropriate for local epidemiology, as well as financial and human resource capabilities. Most importantly, resource-constrained settings will need to foster a greater reliance on disease prevention, creating new models for chronic disease detection, diagnosis, and management. The development of the HIV care infrastructure in Sub-Saharan Africa, which established an outpatient medical care platform with clinical evaluations, laboratory monitoring, and pharmacy dispensing for many millions of people, has demonstrated that chronic, well-care is feasible in this setting. Leveraging this infrastructure to include preventative and chronic care for PLWH and those uninfected alike is a stated priority [23] and deserves further attention.

As health systems experts consider and plan for the next generation of acute care delivery in resource-constrained settings, they would be remiss not to take lessons from the massive, 30-year international effort to building HIV care delivery systems. The US President's Emergency Plan for AIDS Relief (PEPFAR) alone has contributed over US$50 billion globally to the AIDS epidemic [24]. Much has been implemented well. PEPFAR funds have been executed through a remarkable collaboration of multinational donors, national ministries of health, and local nongovernmental organizations. Designers and developers of inpatient health systems should seek to replicate similar relationships, which rely on catalyzing a mix of local programming and international expertise. Among the many secondary gains from these international partnerships has been formation of a collective voice advocating for the global PLWH community. These advocacy efforts were instrumental in bringing about equitable ART drug pricing and expanded access to HIV care, and similar efforts could lead to improved access to acute care management in the region as well.

Another important lesson from expansion of HIV care services in Sub-Saharan Africa has been that non-physician-delivered care can be both cost-effective and of high quality [7]. Although acute hospital care is inherently complex, similar task-shifting and task-sharing approaches to maximize human resources should be evaluated. Finally, PEPFAR has, from its inception, prioritized monitoring and evaluation of its programs, and it can act as a model for other systems seeking to build capacity. The benefits of this strategy are innumerable, and include quality assurance, efficient resource allocation, implementation evaluation, and fostering of academic partnerships.

Finally, there are many features of the response to the HIV epidemic that can be improved on in the next generation of inpatient and intensive care unit development. HIV has suffered from a silo effect—where HIV services have often been delivered in isolation. Acute and intensive care are inherently multidisciplinary and will require improved partnerships to optimize care provision and transitions from the inpatient to outpatient setting. Provision of HIV testing and treatment services has largely been driven by an "if you build it they will come" philosophy. Yet, too often, the patients do not come, or if they do, they often do not remain engaged in care. The factors responsible for poor linkage and retention are largely patient-centered and include a complex array of economic and social forces [25—29]. Similar factors will likely contribute to the success and failure of acute care delivery services in resource-constrained settings. We can demonstrate these lessons were not forgotten by creating an affordable, high-quality, multidisciplinary acute care health infrastructure in the next round of health systems building for acute HIV care in resource-constrained settings.

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