



## Rostrum

# Cervical cancer screening opportunities for Guinea-Bissau



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## ABSTRACT

Guinea-Bissau is a severely resource constrained country, in search of political stability and development in every sector of public life. International aid is permanent and healthcare is one of the most targeted fields, focusing mostly on infectious diseases, maternity, infant malnutrition, access to healthcare and gender inequality in health. As in the rest of Sub-Saharan Africa, cervical cancer is gathering increasing attention from the community and ruling officers. The potential of screening for control of cervical cancer raised the interest of adapting screening methods to low-resource settings. This started the search for the best resource-adapted strategies, which promoted several trials that currently shape the development of screening programs in these countries. Prevention and control strategies are also being adapted taking into account the availability of human Papillomavirus vaccination. Nonetheless, several barriers are still in place for widespread vaccination programs, and cervical cancer screening and treatment remain central in the control of cervical cancer in low-resource settings.

We intend to discuss current cervical cancer screening approaches in low-resource countries and opportunities for their implementation in Guinea-Bissau.

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## Cervical cancer

Cervical cancer is the third most frequent cancer in women worldwide, after breast and colorectal cancers, with an estimated 527,624 new cases in 2012, corresponding to an age standardized incidence rate – world reference population (ASIR-W) of 14 per 100,000 women. It is also responsible for a high mortality rate, accounting for an estimated 266,000 deaths (age standardized mortality rate – world reference population [ASMR-W]: 6.8/100,000).<sup>1</sup> In Sub-Saharan Africa, cervical cancer is the most frequent cancer, accounting for an estimated 57,381 deaths in 2012 (ASMR-W: 22.5/100,000) corresponding to 22% of the number of deaths due to cervical cancer worldwide.<sup>1</sup>

*Abbreviations:* ASIR-W, age standardized incidence rate – world reference population; ASMR-W, age standardized mortality rate – world reference population; HPV, human Papillomavirus; HIV, human immunodeficiency virus; AIDS, acquired immune deficiency syndrome; Pap test, Papanicolaou test; VIA, visual inspection with acetic acid; LEEP, loop electrosurgical excision procedure; CIN2, cervical intraepithelial neoplasia grade 2.

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Infection with human papillomavirus (HPV) infection is central in the epidemiology of cervical cancer and development of strategies for its prevention and control. On the one hand, HPV is estimated to cause nearly all cases of cervical cancer,<sup>2–4</sup> making vaccination against HPV a tool of paramount importance for the prevention of cervical cancer. On the other hand, persistent HPV infections (approximately 10% of all infections) are estimated to take ten or more years to develop into cervical cancer, which allows for early detection, through screening, of highly curable lesions caused by the infection.<sup>5</sup>

Cervical cancer is considered to be a defining disease of acquired immune deficiency syndrome (AIDS).<sup>6</sup> Human immunodeficiency virus (HIV)-positive women have a greater incidence of HPV infection, overall and with multiple HPV types, and present a faster progression to cervical cancer, as well as a higher risk of recurrence after treatment.<sup>7</sup> Since time from infection to cancer can be considerably shorter among HIV-positive women, more frequent screening is very important to detect and cure early lesions.<sup>8</sup>

## Screening

The development of effective HPV vaccines brought a new paradigm for prevention of cervical cancer.<sup>9</sup> However, in developing countries, scarce resources and failure to complete full dosage

schemes constitute barriers to the implementation of effective vaccination programs.<sup>10</sup> Therefore, screening will expectedly remain an essential tool for the prevention and control of cervical cancer in the next decades.<sup>11</sup>

For the last 60 years and mostly since the implementation of organized screening programs based on cytology with the Papanicolaou test (Pap test), cervical cancer mortality has been largely reduced in developed countries.<sup>12</sup> However, screening programs are lacking in most low-income countries, which results in a large proportion of the patients presenting with large invasive tumours, who frequently need multimodal treatments including surgery, chemotherapy and radiotherapy.<sup>13,14</sup> Many developing countries do not have the capability for complex surgery, radiation therapy or chemotherapy, and often have shortage of chemotherapy agents, which highlights the importance of screening in these settings to identify lesions at stages amenable to more effective treatment, and with lower risks and costs.<sup>15</sup>

Screening programs based on the Pap test showed a high effectiveness, decreasing by 80% cervical cancer mortality in some countries.<sup>12</sup> However, this is a costly method requiring highly trained professionals and the ability to obtain, store and transport samples, which are not easily available in many developing settings.<sup>16</sup> Moreover, screening with the Pap test requires a follow-up visit for treatment of patients with lesions. In some studies conducted in developing countries, one-third or more of women did not return for test results, rendering this screening method ineffective.<sup>8</sup> Therefore, “test & treat” strategies were developed to overcome these shortcomings, and are currently proposed by World Health Organization for the screening and treatment of cervical pre-invasive lesions in low-income settings.<sup>17</sup>

#### *Test & treat*

Test & treat involves screening and treatment in the same visit.<sup>17</sup> It is usually based on visual inspection with acetic acid (VIA) followed by cryotherapy. These procedures are easy to learn, may be performed by non-physicians, are less dependable on well-equipped facilities and therefore have a high potential for widespread use even in settings where human resources are scarce.<sup>18</sup> The loop electrosurgical excision procedure (LEEP) can be used if the eligibility criteria for cryotherapy are not met.<sup>17</sup> Several countries use this approach and in Zambia, for instance, a national scale-up program was possible using test & treat.<sup>19,20</sup>

#### *Test – VIA*

VIA uses acetic acid to highlight intraepithelial cervical lesions (pre-invasive lesions) caused by HPV infection.<sup>17</sup> The specificity and sensitivity of VIA for the detection of cervical intraepithelial neoplasia grade 2 or worse (CIN2+) have been evaluated in several studies in low resource settings and VIA showed a higher sensitivity for CIN2+ lesions when compared to the Pap test.<sup>21–23</sup> In a pooled analysis of the accuracy of five cervical cancer screening tests assessed in eleven studies in Africa and India, sensitivity and specificity estimates of VIA for CIN2+ were 79.2% (95% confidence interval [95%CI]: 73.3–94.9) and 84.7% (95%CI: 80.7–88.8), respectively. On the other hand, the pooled sensitivity and specificity estimates of the Pap test were 57.0% (95%CI: 37.6–76.3) and 92.8% (95%CI: 88.7–96.8), respectively.<sup>24</sup>

#### *Test – digital cervicography*

VIA can be combined with digital cervicography to increase its accuracy. Cervicography uses a magnified photograph of the cervix to evaluate abnormalities in detail.<sup>25</sup> Cervicographs may be shown to women for active education, while reassuring them about the results. It also makes quality assurance possible by reviewing photos with the providers.<sup>26,27</sup> Cervicography is currently used

for screening in some countries, including Zambia, Botswana and Ethiopia.<sup>19,28,29</sup>

One study in Zambia evaluated different point-of-care screening methods showing a sensitivity and specificity of 59% (95%CI: 41–76) and 88% (95%CI: 82–93), respectively, for digital cervicography, while for VIA alone, the corresponding figures were 48% (95%CI: 30–67) and 92% (95%CI: 86–95).<sup>30</sup> However, other studies have not shown improved results in terms of accuracy when compared to VIA.<sup>31</sup>

#### *Test – HPV test*

HPV detection can be used for screening. In western countries, HPV testing is now part of screening programs because of its high sensitivity, over 90%, for the detection of CIN2+ lesions.<sup>32</sup> However, it has a suboptimal specificity, ranging from 85% to 90%, which results in a high proportion of women being unnecessarily referred for colposcopy.<sup>33</sup> In addition, women younger than 30 years have a higher rate of transient HPV infections that do not evolve to pre-invasive lesions. This decreases specificity even more, limiting the usefulness of the test in this age group.<sup>34</sup> HPV testing is currently being evaluated for cervical cancer screening in low-income settings. It can be combined with other tests, such as VIA, to increase specificity while still using a resource-adapted, same-day visit methodology.<sup>35</sup> HPV testing is evolving to be a fully resource-adapted screening method: rapid point-of-care tests that do not need to be performed in a lab and do not require complex training are already available<sup>36</sup>; different methods for sample collection that do not need to be performed by a health provider such as self-sampling or based on urine samples are being evaluated.<sup>37</sup> However, HPV tests are not yet ready for a widespread use, namely due to their high cost.<sup>11</sup>

#### *Treat – cryotherapy*

Cryotherapy is the most frequently used treatment procedure in the test & treat approach. It relies on the destruction of cervical lesions by frost, using pressured carbon dioxide or nitrogen dioxide. It is very fast and easy to learn, requiring simple equipment that can be used by non-medical personnel and serious side effects are very rare. In addition, cryotherapy showed a high acceptability in low-income settings.<sup>35,38</sup> In eligible lesions, cryotherapy produces similar results to electrosurgical procedures in terms of lesion destruction<sup>39</sup>; however, it destroys cervical tissue and samples will become unavailable for histopathological evaluation to confirm complete excision.<sup>17</sup> Finally, it requires a supply of pressured gas, which can be challenging in some settings.<sup>40</sup>

#### *Treat – LEEP*

Electrosurgical removal of the transformation zone is one of the most effective procedures for treatment of cervical lesions. However, it is technically challenging when compared with cryotherapy, must be performed by a trained doctor, is expensive and relies on electricity. In the test & treat approach, patients should be referred for LEEP when lesions are ineligible for cryotherapy.<sup>17,41</sup>

### **Guinea-Bissau**

The Republic of Guinea-Bissau is a small country located in the west coast of the African continent. It has 36,125 km<sup>2</sup> and an estimated population of 1,520,830 inhabitants according to the 2009 census.<sup>42</sup> It is a severely resource constrained country with considerable economic difficulties and 44% of the inhabitants live with less than a dollar per day. Development is threatened by a persistent political fragility that arises from the innumerable coups in the past. According to the Human Development Index, Guinea-Bissau ranks 178th out of 188 countries, having an average life expectancy

at birth of 54 years and an infant mortality of 81 per 1000 live births.<sup>43,44</sup>

Guinea-Bissau is composed of eight regions and an independent sector, Bissau. These sectors are made of a central city that names the region and multiple communities surrounding it, called *tabancas*, which are sometimes very small and usually very poor. It is often difficult to access distant *tabancas* due to bad maintenance of roads, which are flooded seasonally. Houses are frequently built with dry clay, with only one room for multiple family members and animals often live in these rooms. Electricity is mainly available in Bissau and there is no functioning electrical network throughout the country. Running water is scarce and sewage is unavailable. Poverty and isolation increase with increasing distance from the capital city. Social organization in Guinea-Bissau varies according to ethnicity, but is mostly patriarchal and polygamous.<sup>45,46</sup>

### Health statistics

In 2015, the estimated most frequent causes of death in Guinea-Bissau were lower respiratory infections (120 deaths per 100,000 inhabitants), followed by HIV infection (95 deaths per 100,000 inhabitants) and diarrheal diseases (91 deaths per 100,000 inhabitants).<sup>47</sup> HIV has an estimated prevalence of 3.9% among adults (15–49 years) as of 2012 and 41,000 people, of all ages, are estimated to currently live with HIV.<sup>48</sup> Epidemiological data about cancer in Guinea-Bissau is scarce. Nevertheless, cancer was estimated to account for approximately 600 deaths per year in 2012, corresponding to an ASMR-W of 67.5/100,000 inhabitants. Cervical cancer was estimated to be the most frequent cancer in women, with 149 new cases per 100,000 inhabitants (ASIR-W of 29.8/100,000), and 104 deaths per 100,000 (ASMR-W of 21.6/100,000).<sup>1</sup>

### Healthcare

In Guinea-Bissau, healthcare relies on several infrastructures with poor technical conditions and scarce human resources. The *Hospital Nacional Simão Mendes*, the central hospital in Bissau, is the most comprehensive in the country from the standpoint of diagnostic capability, medical and surgical care, and perinatal services. It is a referral centre for other hospitals. However, some patients still need to be evacuated for treatment abroad due to limitations in its diagnostic and treatment capability. There are five regional hospitals and several community healthcare clinics spread throughout the territory that are frequently ill-equipped. There are also scarce private healthcare services, mainly in Bissau. Some of them are managed by religious institutions; the largest is the *Hospital de Cumura* that is established in Cumura, near Bissau. Even so, existing hospitals and clinics are mainly located in the largest population centres of each region or community, and services are frequently expensive. Therefore, access to healthcare remains limited for the farthest communities and also due to costs. Competing services such as animism and wizardry also reduce the use of the health system.<sup>45,46,49</sup>

There are multiple foreign and national organizations trying to improve healthcare through education, health planning, drugs and food distribution, and sporadic screening programs, mainly focusing on infectious diseases.<sup>50,51</sup>

### Cervical cancer screening

The National Reproductive Health Service (*Serviço Nacional de Saúde Reprodutiva*) is currently responsible for coordinating the development of reproductive health programs, including cervical cancer screening. From 2009 to 2014, with the help of a Spanish non-governmental organization (*Mujer y Madre*) and other local

institutions, more than 10,000 women were screened using the Pap test in several screening campaigns throughout the country. These campaigns had two different moments: first, collecting cervical samples to be evaluated in Spain, and second, some months after, returning for treatment of lesions identified by positive Pap tests. This program also ensured training on cervical cancer screening, including cytology evaluation, sample collection and treatment of pre-invasive lesions. However, barriers to screening implementation with the Pap test in Guinea-Bissau were similar to the observed in other developing countries, including difficult logistics regarding transport of samples; technical complexity of cytological evaluation with respect to local available training; high costs; low return rate for treatment after the Pap test result. These campaigns are currently suspended.<sup>52</sup>

### Opportunities for cervical cancer screening in Guinea-Bissau

Several aspects must be considered for the development of a cervical cancer screening program in Guinea-Bissau: 1 – screening programs in similar settings, past screening campaigns in Guinea-Bissau, and the evolution of screening and treatment techniques; 2 – the existing infrastructure network; 3 – the cultural and social specificities; 4 – the possibility for treatment of advanced disease.

1. Cytology-based screening is being increasingly surpassed by test & treat approaches. Evidence from similar settings and the experience acquired in past screening campaigns in Guinea-Bissau prove the difficulty of implementing cytology with delayed treatment. On the other hand, test & treat with VIA and cryotherapy were shown to be feasible in low-income countries, with a high acceptance of the screening procedures by women. Most of the resources required for VIA, except the speculum, can be acquired at any local market, including vinegar, containers and cotton. However, cryotherapy systems and maintenance must be acquired abroad and carbon dioxide is available in a neighbouring country, Senegal. Screening strategies including the rapid HPV test and digital cervicography have been shown to be feasible and effective, and may be used in Guinea-Bissau.
2. Despite the difficult access to healthcare in Guinea-Bissau, there is a network of infrastructures in place that include regional hospitals and small healthcare clinics that may provide support for a screening program. Based on past experiences in Guinea-Bissau, participation of women in cervical cancer screening was high. However, for each region, the procedures were centred in a single clinic or hospital, with remote communities being underserved. The use of mobile units to cover a large number of communities while using fewer trained technicians may allow a wider coverage of the general population, whereas screening based on regional teams requires a larger number of workers for the same level of coverage. Another option is the use of already existing logistics for HIV programs, established throughout the country, to screen only those at a higher risk for cervical cancer due to HIV infection.<sup>19,53,54</sup>
3. Guinea-Bissau has several ethnicities with different cultural and religious backgrounds. This could pose as a threat for screening due to the intimate nature of cervical observation. However, based on our previous field experience, women greatly value their reproductive health and fertility, are open to being educated, and available to undergo medical examination. Furthermore, past screening campaigns showed that most women found no objections towards observation by a male or female practitioner (personal communication). Since the general literacy level is low, education is essential for women to understand cancer and screening, while improving the uptake of the latter,<sup>55</sup> and the development of educational sessions must take part in the screening program.

4. The treatment of invasive lesions requires complex multimodal treatment, including radical surgery, radiotherapy, chemotherapy or palliative medicine. For developing countries, there are guidelines to adjust treatment strategies due to the lack of most of these methods. They devise four different settings according to the availability of resources (basic, limited, enhanced or maximal) and suggest adapted treatment methods for each, reinforcing palliative medicine as central to the treatment of cervical cancer patients.<sup>13</sup> Guinea-Bissau currently has the capacity to perform cervical cancer surgery and palliative care. While other resources are being developed, such as the ability to perform chemotherapy, referral abroad provides a temporary solution for invasive lesions.

#### Recent developments

Cancer is becoming a matter of debate in Guinea-Bissau and socially active citizens are promoting the development of oncology services. Recently, a patient advocacy organization, *Liga Guineense de Luta Contra o Cancro*, has been established, and is working to educate and stimulate social and political interest in cancer.

Amidst this wave of development, a research project addressing different screening procedures is being undertaken by Portuguese and Guinea institutions. During the initial undertaking of the project, several stakeholders have committed to the development of cervical cancer screening in Guinea-Bissau, namely the National Reproductive Health Service, the Cabinet of the First Lady, the Maternity Department of the Central Hospital, local hospitals responsible for women's health and HIV care such as Cumura Hospital, patient's advocates such as the *Liga Guineense de Luta Contra o Cancro*, the National Department of Referrals of the Ministry of Health, among others. All of these partners have shown their lively interest and have already cooperated in the implementation of this project. The main objective of this enterprise is to search for the best and the most adapted strategy among several procedures for cervical cancer screening in Guinea-Bissau. One of its specific objectives is to evaluate the feasibility, acceptability, safety and costs of the test & treat approach using rapid HPV test, digital cervicography, VIA, cryotherapy and LEEP. To meet this objective, a large cohort of women in Biombo Region will be invited for screening using all the described procedures and providing treatment as necessary. This will allow the assessment of the applicability and feasibility of each procedure, while evaluating their performance in a point-of care perspective. It will also provide information on the distribution of HPV subtypes for the first time in Guinea-Bissau. Moreover, it intends to test and adapt a training course on cervical cancer screening and treatment for local practitioners, attempting to prepare future screening programs. This study will have the help of local health agents, healthcare providers, other individuals interested in cervical cancer and national institutions, not only for logistics but also for strategy development. It will start with a pilot study aiming to evaluate the applicability of all the procedures, including logistical aspects and the acceptability of the methods. For this, a small group of women in a community of the Biombo Region will be invited to participate. Upon good results, it is expected to evolve into a region-wide evaluation. Thus, this study will try to enlighten the best way to implement a screening program with the best applicability, ensuring local motivation and engagement, while stimulating the development of a national strategy for oncology in Guinea-Bissau, as it is the major expectation of all involved stakeholders.

In conclusion, taking into account the local specificities and available resources, there are several opportunities for cervical cancer screening in Guinea-Bissau and some are already in place. Social pressure and political interest will make the difference in building the future of oncology in the near future.

#### Author's contribution

Ivo Julião: The author extensively reviewed the available literature, designed and drafted the article, interpreted data and critically reviewed the final article and approved the version to be submitted.

Joana Savva-Bordalo: The author contributed for the Conception of the article, cooperated in the acquisition of data and evidence, critically reviewed the contents and approved the version to be submitted.

Nuno Lunet: The author supported and contributed for the design of the article, worked the available evidence, critically reviewed the content and approved the version to be submitted.

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#### Conflicts of interest

The authors declare no conflicts of interest.

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